PROTOCOL RA0098 AMENDMENT 2

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

PHASE 3

IND Number: 011197

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SERIOUS ADVERSE EVENT AND PRODUCT QUALITY COMPLAINTS REPORTING

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Product Quality Complaints Reporting (24h)	
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LIST OF ABBREVIATIONS

ADE	adverse device effect
AE	adverse event
AS	ankylosing spondylitis
ASADE	anticipated serious adverse device effect
ASI	Assessment of Self Injection
BP	blood pressure
CD	Crohn's disease
CDMS	clinical data management system
CI	confidence interval
CPM	Clinical Project Manager
CPMP	Committee for Proprietary Medicinal Products
CRO	contract research organization
CZP	certolizumab pegol
DMARD	disease-modifying antirheumatic drug
ECG	Electrocardiogram
eCRF	electronic Case Report form
EudraCT	European Union Drug Regulating Authorities Clinical Trials
FAS	Full Analysis Set
FDA	Food and Drug Administration
GCP	Good Clinical Practice
HCP	healthcare provider
ICH	International Council for Harmonisation
IEC	Independent Ethics Committee
IFU	Instructions for Use
IMP	investigational medicinal product
IRB	Institutional Review Board
IXRS	interactive response technology
LTB	latent tuberculosis
PFS	pre-filled syringe
PS	Patient Safety
PsA	psoriatic arthritis

Q2W	every 2 weeks
Q4W	every 4 weeks
RA	rheumatoid arthritis
RR	respiratory rate
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
TNFα	tumor necrosis factor alpha
UADE	unanticipated adverse device effect
USADE	unanticipated serious adverse device effect
VAS	Visual Analog Scale

1 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 on 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.

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 CZP using the e-Device.

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

During self-injection, if the skin sensor at the injection port loses contact with the skin, the e-Device will withdraw the needle and stop administration of CZP. If less than five minutes have elapsed since loss of contact with skin, the subject can reposition the e-Device on a new clean injection site and resume and complete the self-injection. If the subject is unable to complete the self-injection and deliver the entire dose of medication (ie, the device indicates incomplete

administration and the CZP-cassette is not seen to be empty), the HCP evaluating the self-injection will document the incomplete self-injection, note the reason why the complete dose was not administered, and using his/her best medical judgment, advise the subject regarding any further dosing.

For subjects on the Q4W dosing regimen who will self-inject twice (2×200mg 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.

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 INTRODUCTION

Cimzia (certolizumab pegol [CZP]) is an anti-TNFα humanized PEGylated Fab' fragment of a monoclonal antibody. Certolizumab pegol has demonstrated a high affinity for TNFα which has been shown to have a central role in the pathogenesis of RA, AS, PsA, and CD. Certolizumab pegol has received market authorization in the US for the treatment of moderate and severe active RA, active PsA, active AS, and moderately to severely active CD. Certolizumab pegol may be used as monotherapy or in combination with disease-modifying antirheumatic drugs (DMARDs). It is available for subcutaneous (sc) injection as a 200mg lyophilized powder for reconstitution (with 1 mL of sterile water for injection) in a single use vial or as 200mg/mL solution in a single-use 1mL PFS in the US.

The availability and convenience of the PFS device provide subjects with chronic diseases such as RA, AS, PsA, or CD with the option to manually self-inject their medication.

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 described in the Instructions for Use (IFU) supplied with the e-Device. Eligible subjects with RA, PsA, or AS will perform CZP self-administration on a Q2W or 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.

Impaired hand function is seen in patients with RA (Durmus et al, 2013), to a lesser extent in patients with PsA (Gottieb et al, 2008), and is uncommon in patients with AS (Tam et al, 2010) or CD (Lossos et al, 1995). Since prompt treatment can reduce inflammation and the level of functional impairment seen in patients with RA or PsA (Goossens et al, 2000), it is not possible to accurately predict the proportion of patients treated with CZP who will have impaired hand

function or how easy or difficult it may be to recruit such patients. In a recently published simulated injection study, the author notes that the investigators had difficulties in recruiting patients with high (Cochin score ≥20) versus low (Cochin score <20) hand disability so much so that they decided to stop the recruitment process when only 12 out of 15 subjects with high hand disability were enrolled (Hundry et al, 2017). This suggests that recruiting patients with impaired hand function may be challenging. Given these considerations, this study will recruit a minimum of 10 patients with impaired hand function. Impaired hand function will be measured using the Cochin scale (Poiraudeau 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 STUDY OBJECTIVES

3.1 Primary objective

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 CZP using the e-Device at Visit 2.

3.2 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.

3.3 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 with training cassette)
- Subject experience of self-injection as assessed by the Pain Visual Analog Scale (VAS) and Assessment of Self Injection (ASI).
- Subject preference for e-Device vs PFS using a self-administered Self-Injection Preference Questionnaire

3.4 Safety objective

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

4 STUDY VARIABLES

4.1 Study outcome variables

4.1.1 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 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

During self-injection, if the skin sensor at the injection port loses contact with the skin, the e-Device will withdraw the needle and stop administration of CZP. If less than five minutes have elapsed since loss of contact with skin, the subject can reposition the e-Device on a new clean injection site and resume and complete the self-injection. If the subject is unable to complete the self-injection and deliver the entire dose of medication (ie, the device indicates incomplete administration and the CZP-cassette is not seen to be empty), the HCP evaluating the self-injection will document the incomplete self-injection, note the reason why the complete dose was not administered, and using his/her best medical judgment, advise the subject regarding any further dosing.

For subjects on the Q4W dosing regimen who will self-inject twice (2×200mg 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.

4.1.2 Secondary outcome variables

The secondary outcome 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

  During self-injection, if the skin sensor at the injection port loses contact with the skin, the e-Device will withdraw the needle and stop administration of CZP. If less than five minutes have elapsed since loss of contact with skin, the subject can reposition the e-Device on a new clean injection site and resume and complete the self-injection. If the subject is unable to complete the self-injection and deliver the entire dose of medication (ie, the device indicates incomplete administration and the CZP-cassette is not seen to be empty), the HCP evaluating the self-injection will document the incomplete self-injection, note the reason why the complete dose was not administered, and using his/her best medical judgment, advise the subject regarding any further dosing.

  For subjects on the Q4W dosing regimen who will self-inject twice (2×200mg 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.
- 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)

4.1.3 Other outcome 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 the e-Device

  Subjects on the Q4W dosing regimen who will self-inject twice (2×200mg 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 preinjection ASI at Visit 1
- Responses to the postinjection ASI by visit at all visits after self-injection using the e-Device

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

4.2 Safety variables

The safety variables are:

- Occurrence of AEs and ADEs
- Vital signs

5 STUDY DESIGN

5.1 Study description

In this Phase 3, open-label study of the e-Device, subjects diagnosed with RA, PsA, or AS (treated on 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 (Poiraudeau 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.

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, 1×200mg 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, 2×200mg 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 (IMP and investigational device) and pregnancy are outlined in Section 10.1.3, Section 10.2.3, and Section 10.3, respectively. 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.

At both study visits, subjects may be provided with a brochure that summarizes an independent post-RA0098 market research study to be conducted by an independent external third party vendor. The market research study will evaluate the patient's experience with the e-Device and the pre and postinjection questionnaire. If interested in the post-RA0098 market research study, the brochure will ask that patients contact the external third party vendor.

5.1.1 Study duration per subject

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

5.1.2 Planned number of subjects and sites

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 at approximately 45 sites. 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 (Poiraudeau 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.

5.1.3 Anticipated regions and countries

The study is planned to be conducted in the US.

5.2 Schedule of study assessments

Table 5–1: 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	
Assessment of structural integrity for CZP-cassette		X	X	
In vitro functional evaluation of e-Device			X	
Subject completes Self-Injection Preference Questionnaire			X	

Table 5–1: 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		
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 5–2: 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	
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 5–2: 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.

5.3 Rationale for study design and selection of dose

UCB has developed a reusable e-Device for the self-administration of a sc dose of CZP. The e-Device provides subjects with another option to self-inject their medication. 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, and an electronic log of the injection history. A production version of the e-Device will be utilized for the purpose of this study.

Impaired hand function is seen in patients with RA (Durmus et al, 2013), to a lesser extent in patients with PsA (Gottieb et al, 2008), and is uncommon in patients with AS (Tam et al, 2010) or CD (Lossos et al, 1995). Since prompt treatment can reduce inflammation and the level of functional impairment seen in patients with RA or PsA (Goossens et al, 2000), it is not possible to accurately predict the proportion of patients treated with CZP who will have impaired hand function or how easy or difficult it may be to recruit such patients. In a recently published simulated injection study, the author notes that the investigators had difficulties in recruiting patients with high (Cochin score ≥20) versus low (Cochin score <20) hand disability so much so that they decided to stop the recruitment process when only 12 out of 15 subjects with high hand disability were enrolled (Hundry et al, 2017). This suggests that recruiting patients with impaired hand function may be challenging. Given these considerations, this study will recruit a minimum of 10 patients with impaired hand function. Impaired hand function will be measured using the Cochin scale (Poiraudeau 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.

The study will be open-label. All eligible subjects should be currently treated with commercial CZP, on a stable dosing regimen for the prior 3 months, and self-administering CZP using the PFS on a Q2W (RA, PsA, or AS) or Q4W (RA, PsA, AS, or CD) dosing regimen, as appropriate.

6 SELECTION AND WITHDRAWAL OF SUBJECTS

6.1 Inclusion criteria

To be eligible to participate in this study, all of the following criteria must be met:

1. An Institutional Review Board (IRB)/Independent Ethics Committee (IEC) approved written Informed Consent form is signed and dated by the subject.
2. Subject is considered reliable and capable of adhering to the protocol (eg, able to understand and complete questionnaires, able to use investigational device according to the Instructions for Use [IFU], visit schedule, or medication intake via self-administration) according to the judgment of the Investigator.
3. Subject is male or female and must be at least 18 years old at Visit 1.
4. Subject must have been diagnosed at least 6 months prior to Visit 1 with documented moderate to severe active RA, active PsA, active AS (in US), or moderately to severely active CD (in US).

5. A minimum of 10 subjects will have impaired hand function. Impaired hand function will be measured using the Cochin scale (Duruöz et al, 1996; Poiraudeau et al, 2000) and impaired hand function will be defined as patients who have a Cochin score ≥13.5 at baseline.
6. Subjects must have been prescribed CZP and must have been self-injecting CZP using the PFS for at least 3 months prior to Visit 1. Subjects with RA, PsA, or AS must have been on a stable Q2W or Q4W CZP dosing regimen for at least 3 months prior to Screening. Subjects with CD must have been on a stable Q4W CZP dosing regimen for at least 3 months prior to Visit 1.
7. Subjects must have been screened according to the applicable national tuberculosis (TB) screening guidelines (to be documented) or provide a documented TB screening activity (TB questionnaire, IGRA test, or chest x-ray) within the past 12 months prior to Visit 1.
8. Female subjects of childbearing potential should have a negative pregnancy test at Visit 1 and should be using a medically accepted method of contraception during the entire duration of the study. Medically accepted methods of contraception are: hormonal contraception for at least 2 cycles prior to screening, intrauterine device, implant device, diaphragm with spermicide, bilateral tubal ligation, monogamous relationship with vasectomized partner (for at least 2 months prior to screening), or using condoms with spermicide gel. Abstinence is not an acceptable method of contraception for the study. Female subjects who are postmenopausal for at least 2 years or have undergone a complete hysterectomy, bilateral tubal ligation, and/or bilateral oophorectomy, or have a congenital sterility are considered not of childbearing potential.

6.2 Exclusion criteria

Subjects are not permitted to enroll in the study if any of the following criteria is met:

1. Subject is <18 years of age at Visit 1.
2. Subject has participated in another study of an investigational medicinal product (IMP) or an investigational device) within the previous 3 months or is currently participating in another study of an IMP or an investigational device.
3. Subject has a history of chronic alcohol or drug abuse within the previous 6 months.
4. Female subjects who are breastfeeding, pregnant, or plan to become pregnant during the study or <6 months of the last study CZP dose.
5. Subject has a history of significant cardiovascular, respiratory, gastrointestinal, hepatic, endocrine, renal, dermatological, neurological, psychiatric, hematological, or bleeding disorders.
6. Subjects with known TB infection and at high risk of acquiring TB infection. Subjects with latent TB (LTB) who have not completed the prophylactic treatment regimen for LTB 3 months prior to enrollment.
    a. Known TB infection whether present or past is defined as:
        i) Active TB infection or clinical signs and symptoms suspicious for TB (pulmonary or extra pulmonary)

ii) History of active TB infection involving any organ system or findings in other organ systems consistent with TB infection

iii) Any evidence by radiography or other imaging modalities consistent with previously active TB infection that is not reported in the subject's medical history.

b. High risk of acquiring TB infection is defined as:

i) Known exposure to another person with active TB infection within the 3 months prior to Screening

ii) Time spent in a healthcare delivery setting or institution where individuals infected with TB are housed and where the risk of transmission of infection is high.

c. Latent TB infection (unless appropriate prophylaxis is completed 3 months prior to study enrollment. Subjects must have completed the full course of LTB prophylaxis treatment).

7. Subject has an active chronic/latent infection including but not limited to TB (untreated latent or active), hepatitis virus (HV), hepatitis C virus (HCV), or human immunodeficiency virus (HIV).
8. Subject has a current malignancy or a history of malignancy. Subjects with less than 3 completely excised basal cell carcinomas or with cervical carcinoma in situ successfully treated surgically more than 5 years prior to Screening may be included.
9. Subject is in a situation or has any condition which in the opinion of the Investigator or Sponsor, may interfere with the optimal participation in the study or produce a significant risk to the subject.
10. Subject has had major surgery (including joint surgery) within 8 weeks prior to Visit 1, or has a scheduled surgery during the study.

6.3 Withdrawal criteria

Subjects are free to withdraw from the study at any time, without prejudice to their continued care. Subjects should be withdrawn from the study if any of the following events occur:

1. Subject develops an illness that would interfere with his/her continued participation.
2. Subject is noncompliant with the study procedures or medications in the opinion of the Investigator.
3. Subject withdraws his/her consent.
4. There is confirmation of a pregnancy during the study, as evidenced by a positive pregnancy test.
5. The Sponsor or a regulatory agency requests withdrawal of the subject.
6. Subject undergoes surgery related to an exacerbation of their disease.
7. The Investigator is of the opinion that the subject's continued participation in the study is not in the best interest of the subject.

8. Subject experiences a severe or serious injection site reaction (eg, bleeding, bruising, or pain) or a serious adverse event (SAE) that would, in the opinion of the Investigator, preclude the subject's further participation in the study.

Investigators should attempt to obtain information on subjects in the case of withdrawal or discontinuation. For subjects considered as lost to follow up, the Investigator should make an effort (at least 1 phone call and 1 written message to the subject), and document his/her effort (date and summary of the phone call and copy of the written message in the source documents), to complete the final evaluation. All results of these evaluations and observations, together with a narrative description of the reason(s) for removing the subject, must be recorded in the source documents. The electronic Case Report form (eCRF) must document the primary reason for withdrawal or discontinuation.

Investigators should contact the Medical Monitor in advance, whenever possible, to discuss the withdrawal of a subject.

7 IMP AND INVESTIGATIONAL DEVICE

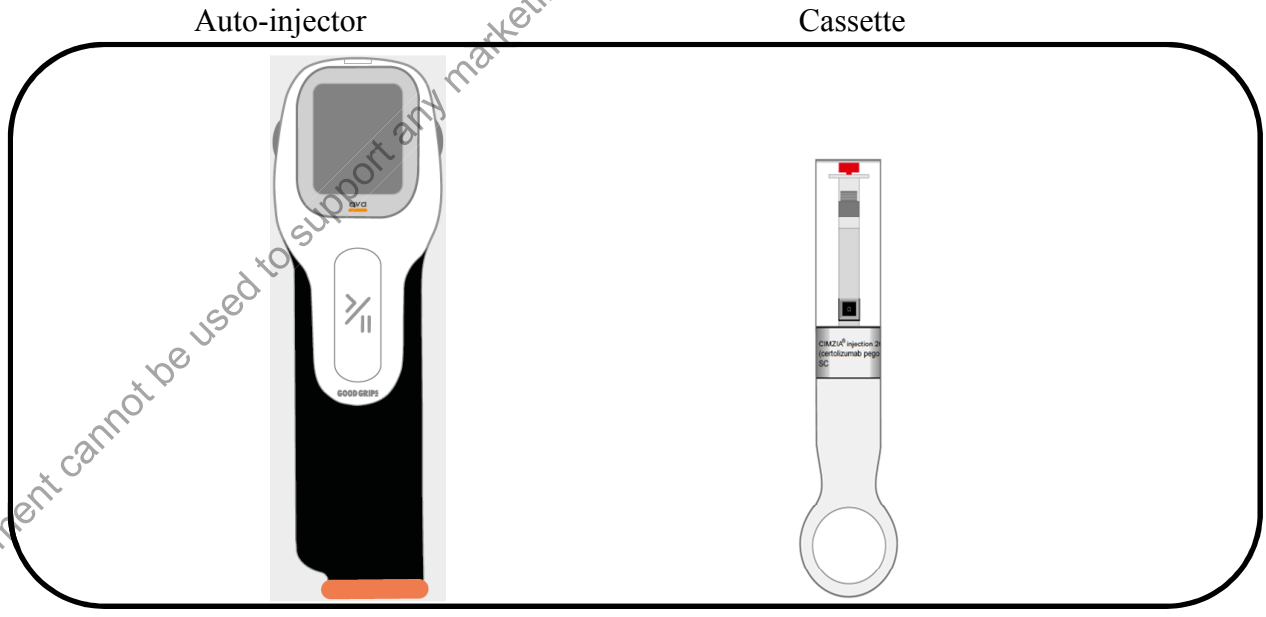
In this study, the term investigational medicinal product (IMP) means the CZP drug substance. The term investigational device means the CZP-cassette and e-Device.

7.1 Description of investigational device

The reusable e-Device (auto-injector and CZP-cassette) is shown in Figure 7–1.

Each single-use cassette contains 1 PFS with needle. The needle is covered by a needle cap until the CZP-cassette has been successfully inserted into the e-Device and the cap removed.

Figure 7–1: CZP e-Device



The e-Device plus e-Device cassettes (containing CZP 200mg) will be supplied by UCB.

7.1.1 Instructions for use of investigational e-Device

At Visit 1, prior to the first self-administration with the e-Device, subjects will be trained on proper self-injection technique and will receive and have the opportunity to review e-Device instruction materials that will be included with the e-Device kit. After the final self-injection and completion of the visual inspection and in vitro functional testing, site staff will print a hardcopy of the e-Device injection log. This log must be retained in the study file prior to disposing of the device. The injection log data may be used in the evaluation of device malfunctions or deficiencies. Details on how the injection log can be downloaded and printed can be found in the IFU.

There is no recommended injection speed for self-injection using the e-Device. The e-Device offers the subject 4 injection speeds: "fastest" (8 seconds), "fast" (11 seconds), "slow" (14 seconds), or "slowest" (17 seconds). The e-Device will come set at the default "fast" (11 seconds) injection speed. As subjects enrolled in this study will be experienced in CZP self-injection using the PFS, they may have a preference for a fast or slow injection based on their experience with PFS self-injection. Subjects will be asked to select 1 of the 4 injection speeds; if they express no preference, then the default injection speed should be used. In either case, the injection speed used should be recorded for each self-injection with the e-Device.

7.2 Treatment to be administered

The treatments are summarized in Table 7–1.

Table 7–1: Treatments to be administered

Delivery system	Reusable e-Device with single-use cassette
Manufacturer	UCB
Content	Loaded with a single-use cassette that houses a PFS containing 200mg/mL, 1mL of CZP liquid formulation in 10mM sodium acetate, 125mM sodium chloride pH 4.7

CZP=certolizumab pegol; PFS=pre-filled syringe

Each dose will be administered as sc injections in either the right or left lateral abdominal wall or the right or left thigh. Treatment of the injection site with an anesthetic cream prior to dosing is not permitted.

Each injection should be administered at a separate injection site, and rotation between the injection sites should be observed.

At Visit 1 and Visit 2, Q2W group subjects will self-inject CZP 200mg (1×200mg injection) using the e-Device. At Visit 1 and Visit 2, Q4W group subjects will self-inject CZP 400mg (2×200mg injections) using the e-Device.

Before injection, the CZP-cassette should be brought to room temperature by removing from the refrigerator and placing on a table at room temperature for 30 to 45 minutes. Subjects will be observed onsite for 30 minutes after self-injection with CZP using the e-Device for any AEs. Subjects will be asked to contact the designated site personnel in case any AEs occur outside of the site visits.

7.3 Packaging

The site will receive uniquely numbered e-Devices and CZP-cassettes for use in this study. The CZP-cassettes will be provided in the intended final packaging.

7.4 Labeling

Clinical drug and investigational device supplies will be labeled in accordance with the current International Council for Harmonisation (ICH) guidelines on Good Clinical Practice (GCP) and Good Manufacturing Practice and will include any locally required statements. If necessary, labels will be translated into the local language.

7.5 Handling and storage requirements

Certolizumab pegol (CZP-cassettes) must be securely stored at 2ºC to 8ºC, ie, in a refrigerator that is either in a locked room or in the pharmacy. Appropriate storage conditions must be ensured by controlled fridge temperature either using automated temperature monitoring and recording system or by using a minimum/maximum thermometer and completing a daily temperature log in accordance with local requirements. In case out of range temperature is noted, the Sponsor or designee must be notified so that the Sponsor or designee can determine whether the product should be used or not.

Each investigational e-Device must be individually stored (per subject) in a secured, limited access area at room temperature. The Investigator or hospital Pharmacist is responsible for the appropriate storage and accountability of the investigational device/CZP (CZP-cassettes) at the site, and documentation of appropriate storage and accountability.

7.6 Drug and device accountability

The Investigator will receive numbered treatments that will be assigned to eligible subjects by an interactive response technology (IXRS) at Visit 1. All drug administrations will be observed by the Investigator or his/her appropriately trained designee.

UCB, or its representatives, will supply a Drug Accountability form, to be kept up to date with record of all IMP administrations, ie, injections by means of the e-Device. This form will serve as source documentation during the course of the study. In addition, a Device Accountability form will be used to record investigational device used on a by-subject basis and will serve as source documentation during the course of the study. Details of any loss (e-Device auto-injectors or e-Device cassettes) due to breakage or wastage, not used, destructed at the study site, or returned to the Sponsor or designee must also be recorded on the appropriate forms. All supplies and pharmacy documentation must be made available throughout the study for UCB (or designee) to review.

The Investigator (or designee) is responsible for retaining all used, unused, and partially used IMP until returned or destroyed. The Investigator may assign some of the Investigator's duties for drug accountability at the study site to an appropriate pharmacist/designee.

The IMP and investigational device (including e-Device auto-injectors and e-Device cassettes) intended for the study cannot be used for any other purpose than that described in this protocol.

7.7 Procedures for monitoring subject compliance

As all CZP self-administrations will be scheduled, performed at the site, and observed by the Investigator or his/her designee, monitoring subject compliance is not applicable.

7.8 Concomitant medications/treatments

7.8.1 Permitted concomitant treatments (medications and therapies)

Subjects are permitted to continue on their prescribed medical therapy for the disease in accordance with the instructions of their treating physician. Concomitant medications/treatments, including over-the-counter products and supplements, must be recorded in the subject's notes (source documentation) and provided on the eCRF. This record should include the name of the drug, the dose, the route, and date(s) of administration, and the indication for use.

7.8.2 Prohibited concomitant treatments (medications and therapies)

Use of topical analgesics at the injection site are prohibited concomitant medications in this study.

7.9 Blinding

This is an open-label study.

7.10 Randomization and numbering of subjects

There will be no randomization in this study. A subject number assigned by an IXRS at Visit 1 will serve as the subject identifier throughout the study.

8 STUDY PROCEDURES BY VISIT

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), the schedule of assessments for the 2 subject populations differs.

8.1 Visit 1/ Screening and Study Treatment Period

Prior to any study activities, all subjects will be asked to read and sign an Informed Consent form that has been approved by an IRB/IEC and which complies with regulatory requirements. Subjects will be given adequate time to consider any information concerning the study, described to them by the Investigator or designee. As part of the informed consent procedure, subjects will be given the opportunity to ask the Investigator any questions regarding potential risks and benefits of participation in the study.

The following procedures will be performed:

- Recording of demographic data
- Verification of eligibility criteria
- General medical and procedures history
- Physical examination, including height and weight
- Measurement of vital signs (BP, pulse, body temperature, respiratory rate [RR])

- Urine pregnancy test (female subjects of childbearing potential)
- Contact IXRS
- Subject completes Cochin Impaired Hand Function questionnaire
- Recording of concomitant medication
- Recording of AEs and ADEs

Once all entry criteria have been verified, the following procedures will be performed:

- Preinjection ASI
- Training on use of e-Device
- Self-administration of CZP using e-Device
- HCP evaluates self-injection

  During self-injection, if the skin sensor at the injection port loses contact with the skin, the e-Device will withdraw the needle and stop administration of CZP. If less than five minutes have elapsed since loss of contact with skin, the subject can reposition the e-Device on a new clean injection site and resume and complete the self-injection. If the subject is unable to complete the self-injection and deliver the entire dose of medication (ie, the device indicates incomplete administration and the CZP-cassette is not seen to be empty), the HCP evaluating the self-injection will document the incomplete self-injection, note the reason why the complete dose was not administered, and using his/her best medical judgment, advise the subject regarding any further dosing.
- Assessment of structural integrity of CZP-cassette
- Pain VAS (immediately postinjection [within 15 minutes])
- Postinjection ASI (within 30 minutes postinjection)
- Recording of AEs and ADEs

8.2 Study procedures by visit for the Q2W group

8.2.1 Visit 2 (Week 2)

The following procedures will be performed:

- Review withdrawal criteria
- Measurement of vital signs (BP, pulse, body temperature, RR)
- Urine pregnancy test (female subjects of childbearing potential)
- Contact IXRS
- Recording of concomitant medication
- Self-administration of CZP using e-Device
- HCP evaluates self-injection

During self-injection, if the skin sensor at the injection port loses contact with the skin, the e-Device will withdraw the needle and stop administration of CZP. If less than five minutes have elapsed since loss of contact with skin, the subject can reposition the e-Device on a new clean injection site and resume and complete the self-injection. If the subject is unable to complete the self-injection and deliver the entire dose of medication (ie, the device indicates incomplete administration and the CZP-cassette is not seen to be empty), the HCP evaluating the self-injection will document the incomplete self-injection, note the reason why the complete dose was not administered, and using his/her best medical judgment, advise the subject regarding any further dosing.

- Assessment of structural integrity of CZP-cassette
- In vitro functional evaluation of e-Device
- Pain VAS (immediately postinjection [within 15 minutes])
- Postinjection ASI (within 30 minutes postinjection)
- Self-Injection Preference Questionnaire
- Recording of AEs and ADEs

8.3 Study procedures by visit for the Q4W group

8.3.1 Visit 2 (Week 4)

The following procedures will be performed:

- Review withdrawal criteria
- Measurement of vital signs (BP, pulse, body temperature, RR)
- Urine pregnancy test (female subjects of childbearing potential)
- Contact IXRS
- Recording of concomitant medication
- Self-administration of CZP using e-Device
- HCP evaluates self-injection

  During self-injection, if the skin sensor at the injection port loses contact with the skin, the e-Device will withdraw the needle and stop administration of CZP. If less than five minutes have elapsed since loss of contact with skin, the subject can reposition the e-Device on a new clean injection site and resume and complete the self-injection. If the subject is unable to complete the self-injection and deliver the entire dose of medication (ie, the device indicates incomplete administration and the CZP-cassette is not seen to be empty), the HCP evaluating the self-injection will document the incomplete self-injection, note the reason why the complete dose was not administered, and using his/her best medical judgment, advise the subject regarding any further dosing.

- Assessment of structural integrity of CZP-cassette
- In vitro functional evaluation of e-Device

- Pain VAS (immediately postinjection [within 15 minutes])
- Postinjection ASI (within 30 minutes postinjection)
- Self-Injection Preference Questionnaire
- Recording of AEs and ADEs

8.4 Safety Follow-Up

A Safety Follow-Up by telephone will be conducted 1 week after the subject's final site visit using the e-Device. Any AEs or ADEs will be recorded.

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 telephone call 70 days following their final CZP administration in addition to the 1-week Safety Follow-Up.

9 ASSESSMENT OF SELF-INJECTION

9.1 Injection Site Pain (VAS)

A VAS will be used to assess overall injection pain due to self-injection postinjection 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 postinjection (within 15 minutes). The subject will complete the VAS prior to completion of the postinjection ASI.

Subjects on the Q4W dosing regimen who will self-inject twice (2×200mg 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.

9.2 Assessment of Self Injection (ASI)

The preinjection ASI is composed of 6 items grouped into 2 domains. The postinjection 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.

The preinjection ASI will be completed preinjection at Visit 1, and the postinjection will be completed within 30 minutes postinjection at each visit during the Study Treatment Period. The ASI has been developed from the Self-Injection Assessment Questionnaire and modified to reflect the improved features of the e-Device and is being piloted in this study. It will be validated using a separate psychometric analysis plan.

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

9.3 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 and postinjection ASI have been completed.

9.4 Evaluation of post-use structural integrity of CZP-cassettes

The used CZP-cassettes will be inspected to determine if the entire dose was delivered based on whether the PFS housed in the CZP-cassette is empty or not (as per primary endpoint). During self-injection, if the skin sensor at the injection port loses contact with the skin, the e-Device will withdraw the needle and stop administration of CZP. If less than five minutes have elapsed since loss of contact with skin, the subject can reposition the e-Device on a new clean injection site and resume and complete the self-injection. If the subject is unable to complete the self-injection and deliver the entire dose of medication (ie, the device indicates incomplete administration and the CZP-cassette is not seen to be empty), the HCP evaluating the self-injection will document the incomplete self-injection, note the reason why the complete dose was not administered, and using his/her best medical judgment, advise the subject regarding any further dosing. The visual inspection of the used CZP-cassette will also check for structural integrity and damage (ie, clear evidence of damage/compromised structural integrity—not superficial, cosmetic imperfections). All evaluations will be performed by appropriately trained site staff.

9.5 Evaluation of post-use structural and functional integrity of the e-Device

Following the subject's final self-administration using the e-Device, the e-Device will be visually inspected for structural integrity and damage (ie, clear evidence of damage/compromised structural integrity—not superficial, cosmetic imperfections). The e-Device will also be evaluated for functional integrity (ie, proper functioning) using a training cassette as specified in the in vitro e-Device functional testing directions. All evaluations will be performed by appropriately trained site staff.

9.6 Evaluation of safe and effective self-injection

Safe and effective self-injection will be evaluated by the HCP. Subject self-injection of the complete dose of CZP will be confirmed by a visual inspection of the CZP-cassette(s) which shows the PFS container to be empty. During self-injection, if the skin sensor at the injection port loses contact with the skin, the e-Device will withdraw the needle and stop administration of CZP. If less than five minutes have elapsed since loss of contact with skin, the subject can reposition the e-Device on a new clean injection site and resume and complete the self-injection. If the subject is unable to complete the self-injection and deliver the entire dose of medication (ie, the device indicates incomplete administration and the CZP-cassette is not seen to be empty), the HCP evaluating the self-injection will document the incomplete self-injection, note the reason why the complete dose was not administered, and using his/her best medical judgment, advise the subject regarding any further dosing. The self-injection will be considered safe if there are 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 (2×200mg 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.

10 ASSESSMENT OF SAFETY

In this study, safety reporting requirements apply to the IMP and to all constituents of the investigational device (including the e-Device auto-injector, and the CZP-cassette) per 21 CFR 312.32, 21 CFR 812.150, and 21 CFR 812.3. Subjects in the study are experienced at self-injection and will be aware of their usual injection experience and events typically seen during the normal course of an injection. Effects that are considered usual by the subject and the HCP (eg, minor pain, bruising, or bleeding) during the course of self-injection are not to be classified as AEs.

10.1 Adverse events (IMP)

10.1.1 Definitions (IMP)

10.1.1.1 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 order to ensure complete safety data collection, all AEs occurring during the study (ie, after the signing of the Informed Consent form), including any pretreatment and posttreatment periods required by the protocol, must be reported in the eCRF even if no IMP was taken but specific study procedures were conducted. This includes all AEs not present prior to the initial visit and all AEs that recurred or worsened after the initial visit.

Signs or symptoms of the condition/disease for which the IMP is being studied should be recorded as AEs only if their nature changes considerably or their frequency or intensity increases in a clinically significant manner as compared to the clinical profile known to the Investigator from the subject's history or the Baseline Period.

10.1.1.2 Serious adverse event (IMP)

Once it is determined that a subject experienced an AE, the seriousness of the AE must be determined. An SAE must meet 1 or more of the following criteria:

- Death
- Life-threatening

  (Life-threatening does not include a reaction that might have caused death had it occurred in a more severe form.)
- Significant or persistent disability/incapacity

- Congenital anomaly/birth defect (including that occurring in a fetus)
- Important medical event that, based upon appropriate medical judgment, may jeopardize the patient or subject and may require medical or surgical intervention to prevent 1 of the other outcomes listed in the definition of serious

  (Important medical events may include, but are not limited to potential Hy's Law [see Section 10.1.1.3], allergic bronchospasm requiring intensive treatment in an emergency room or at home, blood dyscrasias that do not result in inpatient hospitalization, or the development of drug dependency or drug abuse.)
- Initial inpatient hospitalization or prolongation of hospitalization

  (A patient admitted to a hospital, even if he/she is released on the same day, meets the criteria for the initial inpatient hospitalization. An emergency room visit that results in admission to the hospital would also qualify for the initial inpatient hospitalization criteria. However, emergency room visits that do not result in admission to the hospital would not qualify for this criteria and, instead, should be evaluated for 1 of the other criteria in the definition of serious [eg, life-threatening adverse experience, important medical event].

  Hospitalizations for reasons not associated with the occurrence of an AE [eg, preplanned surgery or elective surgery for a pre-existing condition that has not worsened or manifested in an unusual or uncharacteristic manner] do not qualify for reporting. For example, if a subject has a condition recorded on his/her medical history and later has a preplanned surgery for this condition, it is not appropriate to record the surgery or hospitalization as an SAE, since there is no AE upon which to assess the serious criteria. Please note that, if the pre-existing condition has worsened or manifested in an unusual or uncharacteristic manner, this would then qualify as an AE and, if necessary, the seriousness of the event would need to be determined.)

10.1.1.2.1 Anticipated serious adverse events (IMP)

The following Anticipated SAEs are anticipated to occur in the population studied in this protocol at some frequency that is independent of drug exposure.

This list does not change the Investigator's obligation to report all SAEs (including Anticipated SAEs) as detailed in Section 10.1.1.2.

Table 10–1: Anticipated serious adverse events for study population

Population	Anticipated SAE
Rheumatoid arthritis	Rheumatoid arthritis
Crohn's disease	Crohn's disease Perianal abscess Abdominal pain
Psoriatic arthritis	Psoriatic arthritis
Ankylosing spondylitis	Ankylosing spondylitis

SAE=serious adverse event

10.1.1.3 Adverse events of special interest (IMP)

An AE of special interest is any AE that a regulatory authority has mandated be reported on an expedited basis, regardless of the seriousness, expectedness, or relatedness of the AE to the administration of a UCB product/compound. For the present study, the AEs of special interest are as follows:

- Serious infections, including opportunistic infections
- Malignancies, including lymphoma
- Congestive heart failure
- Demyelinating-like disorders
- Aplastic anemia, pancytopenia, thrombocytopenia, neutropenia, and leucopenia
- Serious bleeding events
- Lupus and lupus-like syndrome
- Serious skin reactions (ie, Stevens Johnson Syndrome, toxic epidermal necrosis, and erythema multiforme)

Potential Hy's Law, defined as ≥3x upper limit of normal (ULN) alanine aminotransferase (ALT) or aspartate aminotransferase (AST) with coexisting ≥2xULN total bilirubin in the absence of ≥2xULN alkaline phosphatase (ALP), with no alternative explanation for the biochemical abnormality, must ALWAYS be reported to UCB as an AE of special interest (ie, without waiting for any additional etiologic investigations to have been concluded). Follow-up information should then be reported if an alternative etiology is identified during investigation and monitoring of the subject.

10.1.2 Procedures for reporting and recording adverse events (IMP)

The subject will be given the opportunity to report AEs spontaneously. A general prompt will also be given at each study visit to detect AEs. For example:

"Did you notice anything unusual about your health (since your last visit)?"

In addition, the Investigator should review any self-assessment procedures employed in the study.

10.1.2.1 Description of adverse events (IMP)

When recording an AE, the Investigator should use the overall diagnosis or syndrome using standard medical terminology, rather than recording individual symptoms or signs. The eCRF and source documents should be consistent. Any discrepancies between the subject's own words on his/her own records (eg, diary card) and the corresponding medical terminology should be clarified in the source documentation.

Details for completion of the Adverse Event eCRF (including judgment of relationship to IMP) are described in the eCRF Completion Guidelines.

10.1.2.2 Rule for repetition of an adverse event (IMP)

An increase in the intensity of an AE should lead to the repetition of the AE being reported with:

- The outcome date of the first AE that is not related to the natural course of the disease being the same as the start date of the repeated AE, and the outcome of "worsening"
- The AE verbatim term being the same for the first and repeated AE, so that the repeated AE can be easily identified as the worsening of the first one

10.1.2.3 Additional procedures for reporting serious adverse events (IMP)

If an SAE is reported, UCB must be informed within 24 hours of receipt of this information by the site (see contact information for SAE reporting listed in the Serious Adverse Event Reporting section at the front of the protocol). The Investigator must forward to UCB (or its representative) a duly completed "Investigator SAE Report Form for Development Drug" (SAE report form) provided by UCB, even if the data are incomplete, or if it is obvious that more data will be needed in order to draw any conclusions. Information recorded on this form will be entered into the global safety database.

An Investigator SAE report form will be provided to the Investigator. The Investigator SAE Report form must be completed in English.

It is important for the Investigator, when completing the SAE report form, to include the assessment as to a causal relationship between the SAE and the IMP administration. This insight from the Investigator is very important for UCB to consider in assessing the safety of the IMP and in determining whether the SAE requires reporting to the regulatory authorities in an expedited manner.

Additional information (eg, autopsy or laboratory reports) received by the Investigator must be provided within 24 hours. All documents in the local language must be accompanied by a translation in English, or the relevant information included in the same document must be summarized in the Investigator SAE report form.

The Investigator is specifically requested to collect and report to UCB (or its representative) any SAEs (even if the Investigator is certain that they are in no way associated with the IMP), up to completion of the follow-up visit for each subject, and to also inform participating subjects of the need to inform the Investigator of any SAE within this period. Serious AEs that the Investigator

thinks may be associated with the IMP must be reported to UCB regardless of the time between the event and the end of the study.

Upon receipt of the SAE report form, UCB will perform an assessment of expectedness of the reported SAE. The assessment of the expectedness of the SAE is based on the Investigator's Brochure**.**

10.1.3 Follow up of adverse events (IMP)

An AE should be followed until it has resolved, has a stable sequelae, the Investigator determines that it is no longer clinically significant, or the subject is lost to follow up. This follow-up requirement applies to AEs, SAEs, and AEs of special interest.

If an AE is ongoing at the end of the study for a subject, follow up should be provided until resolution/stable level of sequelae is achieved, or until the Investigator no longer deems that it is clinically significant, or until the subject is lost to follow up. If no follow up is provided, the Investigator must provide a justification.

Information on SAEs obtained after clinical database lock will be captured through the Patient Safety (PS) database without limitation of time.

10.2 Adverse events (investigational device)

10.2.1 Definitions (investigational device)

10.2.1.1 Adverse Events (investigational device)

An AE for an investigational device is any untoward medical occurrence, unintended disease or injury, or untoward clinical sign (including abnormal laboratory findings) in subjects enrolled in the study, including any pre- and posttreatment periods (as required by the protocol). This includes the following:

- Events considered unrelated or related to the investigational medical device
- Events related to the procedures involved (even if no investigational device was used).

For users or other persons (eg, caregivers), AEs for a device are restricted to only events related to the investigational medical device.

In order to ensure complete safety data collection, all AEs occurring during the study (ie, after the signing of the Informed Consent form), including any pretreatment and posttreatment periods required by the protocol, must be reported in the eCRF even if no investigational device was used but specific study procedures were conducted. This includes all AEs not present prior to the initial visit and all AEs that recurred or worsened after the initial visit.

Signs or symptoms of the condition/disease for which the Investigational Device is being studied should be recorded as AEs only if their nature changes considerably or their frequency or intensity increases in a clinically significant manner as compared to the clinical profile known to the Investigator from the subject's history or the Baseline Period.

10.2.1.2 Serious adverse event (investigational device)

Once it is determined that a subject experienced an AE for an investigational device, the seriousness of the AE must be determined. An SAE must meet 1 or more of the following criteria:

- Death
- Serious deterioration in the health of the subject that results in at least 1 of the following:
  - Life-threatening illness or injury
  - Permanent impairment of a body structure or body function
  - Inpatient or prolonged hospitalization
  - Medical or surgical intervention to prevent life-threatening illness or injury or permanent impairment to a body structure or body function
  - Fetal distress, fetal death, or a congenital abnormality or birth defect

Planned hospitalization for a pre-existing condition, or a procedure required by the protocol, without serious deterioration in health, is not considered a serious adverse event.

10.2.1.3 Device- or procedure-related

10.2.1.3.1 Adverse device effect (investigational device)

An adverse device effect (ADE) is an AE related to the use of an investigational device. An ADE must meet 1 or more of the following criteria:

- Adverse event resulting from insufficiencies or inadequacies in the instructions for use, the deployment, the implantation, the installation, the operation, or any malfunction of the investigational medical device.
- Adverse event that is a result of a use error or intentional misuse.

10.2.1.3.1.1 Unanticipated adverse device effect (investigational device)

An unanticipated adverse device effect (UADE) is any ADE that meets 1 or more of the following criteria:

- Serious adverse effect on health or safety or any life-threatening problem or death caused by, or associated with a device, if that effect, problem, or death was not previously identified in nature, severity, or degree of incidence in the application
- Any other unanticipated serious problem associated with a device that relates to the rights, safety, or welfare of subjects.

10.2.1.3.2 Serious adverse device effect (investigational device)

A serious adverse device effect (SADE) is an ADE that has resulted in any of the consequences characteristic of a SAE, as described in Section 10.2.1.2. Serious adverse device effects are classified as anticipated (anticipated serious adverse device effect; ASADE) and unanticipated (USADE) (definitions provided below).

An ASADE is a SADE which by its nature, incidence, severity, or outcome has been identified.

An USADE is a SADE which by its nature, incidence, severity, or outcome has not been identified.

10.2.1.3.3 Device deficiency (investigational device)

A device deficiency is an inadequacy of a medical device with respect to its identity, quality, durability, reliability, safety, or performance. Device deficiencies include malfunctions, use errors, and inadequate labeling.

10.2.2 Procedures for reporting and recording adverse events (investigational device), adverse device effects, and device deficiencies

The subject will be given the opportunity to report AEs, ADEs, and device deficiencies spontaneously. A general prompt will also be given at each study visit to detect AEs, ADEs, and device deficiencies. Below is an example prompt:

"Did you notice anything unusual about the device?"

10.2.2.1 Adverse events

Details for completion of the Adverse Event eCRF (including judgment of relationship to Investigational Device or Study procedure) are described in the eCRF Completion Guidelines.

10.2.2.1.1 Serious adverse events

See Section 10.1.1.2 for details.

10.2.3 Follow up of adverse events (investigational device)

See Section 10.1.3.

10.2.3.1 Device-related

10.2.3.1.1 Reporting of adverse device effects

An Investigator Adverse Device Effect and Device Deficiency Form will be provided to the Investigator. The Investigator Adverse Device Effect and Device Deficiency Form must be completed in English.

An Investigator shall submit to UCB a report of any adverse device effect and device deficiency occurring during the study within 24 hours after the Investigator first learns of the event using the Adverse Device Effect and Device Deficiency Form.

10.2.3.1.1.1 Reporting of unanticipated adverse device effects by the Investigator

An Investigator shall submit a report of any unanticipated adverse device effect occurring during an investigation to:

- UCB within 24h, UCB will conduct an evaluation of the reported unanticipated adverse device effect and report the results of such evaluation to FDA and to all reviewing IRB's and participating Investigators within 10 working days after UCB first receives notice of the effect.
- The site IRB and reviewing IRB as soon as possible, but in no event later than 10 working days after the Investigator first learns of the effect.

10.2.3.1.2 Reporting of serious adverse device effects

10.2.3.1.2.1 Reporting of serious adverse device effect including device deficiencies with risk of SAE

If an SADE or a device deficiency that could have led to a serious adverse event, if:

- Either suitable action had not been taken or
- Intervention had not been made or
- Circumstances had been less fortunate

is reported, UCB must be informed within 24 hours of receipt of this information by the site (see contact information for SAE reporting listed in the Serious Adverse Event Reporting section at the front of the protocol). The Investigator must forward to UCB (or its representative) a duly completed "SAE Report Form for Investigational Medical Device" (SAE report form) provided by UCB, even if the data are incomplete, or if it is obvious that more data will be needed in order to draw any conclusions.

A SAE report form will be provided to the Investigator. The Investigator SAE Report form must be completed in English.

It is important for the Investigator, when completing the SAE report form, to include the assessment as to a causal relationship between the SAE and the investigational device and/or study procedure.

Additional information (eg, autopsy or laboratory reports) received by the Investigator must be provided within 24 hours. All documents in the local language must be accompanied by a translation in English, or the relevant information included in the same document must be summarized in the Investigator SAE report form.

The Investigator is specifically requested to collect and report to UCB (or its representative) any SADEs or device deficiency with risk of SAE (even if the Investigator is certain that they are in no way associated with the Investigational device), up to completion of the follow-up visit for each subject, and to also inform participating subjects of the need to inform the Investigator of any SAE within this period. Serious AEs that the Investigator thinks may be associated with the investigational device must be reported to UCB regardless of the time between the event and the end of the study.

10.2.3.1.3 Reporting of device deficiencies

If a device deficiency related to the identity, quality, durability, reliability, safety, or performance of the investigational device is reported (even if the investigational device was not used), UCB must be informed within 1 business day of receipt of this information by the site. The Investigator must forward to UCB (or its representative) a duly completed Investigator Adverse Device Effect and Device Deficiency Form provided by UCB, even if the data are incomplete or if it is obvious that more data will be needed in order to draw any conclusions.

An Investigator Adverse Device Effect and Device Deficiency Form will be provided to the Investigator. The Investigator Adverse Device Effect and Device Deficiency Form must be completed in English.

It is important for the Investigator, when completing the Investigator Adverse Device Effect and Device Deficiency Form, to include an assessment and documentation of whether the device deficiency could have led to a serious adverse event if any of the following occurred:

- Suitable action had not been taken or
- Intervention had not been made or
- Circumstances had been less fortunate

All defective devices must be returned to UCB.

10.2.3.2 Rule for repetition of an adverse device effect and/or device deficiency

See Section 10.1.2.2 for details.

10.3 Pregnancy

If an Investigator is notified that a subject has become pregnant before or after the first dose IMP via e-Device, the Investigator must immediately notify UCB's Patient Safety (PS) department by providing the completed Pregnancy Report and Outcome form (for contact details see Serious Adverse Event reporting information at the beginning of this protocol). The subject should be withdrawn from the study as soon as pregnancy is known (by positive pregnancy test), and the following should be completed:

- The subject should immediately stop the intake of the IMP.
- A safety follow-up call should be scheduled for 70 days after the last administration of CZP study dose (via e-Device).

The Investigator must inform the subject of information currently known about potential risks and about available treatment alternatives.

The pregnancy will be documented on the Pregnancy Report and Outcome form provided to the Investigator. The progression of the pregnancy and the eventual birth (if applicable) must be followed up using the Pregnancy Report and Outcome form in which the Investigator has to report on the health of the mother and of the child. Every reasonable attempt should be made to follow the health of the child for 30 days after birth for any significant medical issues. In certain circumstances, UCB may request that follow up is continued for a period longer than 30 days. If the subject is lost to follow up and/or refuses to give information, written documentation of attempts to contact the subject needs to be provided by the Investigator and filed at the site. UCB's PS department is the primary contact for any questions related to the data collection for the pregnancy, eventual birth, and follow up.

In cases where the partner of a male subject enrolled in a clinical study becomes pregnant, the Investigator or designee is asked to contact the subject to request consent of the partner via the Partner Pregnancy Consent form that has been approved by the responsible IRB/IEC and should be available in the Investigator site file. In case of questions about the consent process, the Investigator may contact the UCB/contract research organization (CRO) contract monitor for the study. The Investigator will complete the Pregnancy Report and Outcome form and send it to UCB's PS department (for contact details see Serious Adverse Event reporting information at the

beginning of this protocol) only after the partner has agreed that additional information can be captured and has provided the signed Partner Pregnancy Consent form. UCB's PS department is also the primary contact for any questions related to the data collection for the partner pregnancy, eventual birth, and follow up.

A pregnancy becomes a serious adverse event (SAE) in the following circumstances: miscarriage, abortion (elective or spontaneous), unintended pregnancy after hormonal contraceptive failure (if the hormonal contraceptive was correctly used), ectopic pregnancy, fetal demise, or any congenital anomaly/birth defect of the baby. Those SAEs must be additionally reported using the Investigator SAE Report form.

10.4 Suspected transmission of an infectious agent

For the purposes of reporting, any suspected transmission of an infectious agent via a medicinal product should be considered as an SAE; such cases must be reported immediately, recorded in the AE module of the eCRF, and followed as any other SAE. Any organism, virus, or infectious particle (eg, prion protein transmitting transmissible spongiform encephalopathy), pathogenic or nonpathogenic, is considered an infectious agent.

There is no evidence that there is a risk of transmission of an infectious agent with the investigational device.

10.5 Overdose of investigational medicinal product

Excessive dosing (beyond that prescribed in the protocol and including overdose) should be recorded in the eCRF. Any SAE or nonserious AE associated with excessive dosing must be followed as any other SAE or nonserious AE. These events are only considered AEs or SAEs if there are associated clinical signs and symptoms or if the act of taking the excess medicine itself is an AE or SAE (eg, suicide attempt).

There is no evidence that there is a risk of overdose with the IMP with the investigational device.

10.6 Safety signal detection

Selected data from this study will be reviewed periodically to detect as early as possible any safety concern(s) related to the IMP or investigational device so that Investigators, clinical study subjects, regulatory authorities, and IRBs/IECs will be informed appropriately and as early as possible.

The Study Physician or medically qualified designee/equivalent will conduct an ongoing review of SAEs and perform ongoing SAE reconciliations in collaboration with the PS representative.

As appropriate for the stage of development and accumulated experience with the IMP and investigational device, medically qualified personnel at UCB may identify additional safety measures (eg, AEs, vital signs, laboratory or electrocardiogram [ECG] results) for which data will be periodically reviewed during the course of the study.

10.7 Laboratory measurements

For women of childbearing potential, a urine pregnancy test will be performed at Visit 1 and Visit 2. A serum pregnancy test will be performed in the event of a positive urine result.

10.8 Other safety measurements

10.8.1 Vital signs

Vital signs will include systolic and diastolic BP, pulse, RR, and body temperature. Subjects should be supine for 5 minutes before and during the collection of BP and pulse measurements. Vital signs will be measured at Visit 1 and Visit 2.

10.8.2 Physical examination

The physical examination will include general appearance; ear, nose, and throat; eyes, hair, and skin; respiratory; cardiovascular; gastrointestinal; musculoskeletal; hepatic; neurological (including limb reflexes); and mental status. Height and weight will also be measured. The physical examination will be performed at Visit 1. Any clinically significant changes since the physical examination at Visit 1 will be recorded as AEs.

11 STUDY MANAGEMENT AND ADMINISTRATION

11.1 Adherence to protocol

The Investigator should not deviate from the protocol. However, the Investigator should take any measure necessary in deviation from or not defined by the protocol in order to protect clinical study subjects from any immediate hazard to their health and safety. In this case, this action should be taken immediately, without prior notification of the regulatory authority, IRB/IEC, or Sponsor.

After implementation of such measure, the Investigator must notify the Clinical Project Manager of the Sponsor within 24 hours and follow any local regulatory requirements.

11.2 Monitoring

UCB (or designee) will monitor the study to meet the Sponsor's monitoring Standard Operating Procedures (SOPs), ICH-GCP guideline, and applicable regulatory requirements, and to ensure that study initiation, conduct, and closure are adequate. Monitoring of the study may be delegated by UCB to a CRO or a contract monitor.

The Investigator and his/her staff are expected to cooperate with UCB (or designee) and to be available during the monitoring visits to answer questions sufficiently and to provide any missing information. The Investigator(s)/institution(s) will permit direct access to source data/documents for study-related monitoring, audits, IRB/IEC review, and regulatory inspection(s).

The Investigator will allow UCB (or designee) to periodically review all eCRFs and corresponding source documents (eg, hospital and laboratory records for each study participant). Monitoring visits will provide UCB (or designee) with the opportunity to evaluate the progress of the study, verify the accuracy and completeness of eCRFs, ensure that all protocol requirements, applicable authorities regulations, and Investigator's obligations are being fulfilled, and resolve any inconsistencies in the study records.

11.2.1 Definition of source data

All source documents must be accurate, clear, unambiguous, permanent, and capable of being audited. They should be made using some permanent form of recording (ink, typing, printing,

optical disc). They should not be obscured by correction fluid or have temporary attachments (such as removable self-stick notes). Photocopies and/or printouts of eCRFs are not considered acceptable source documents.

Source documents are original records in which raw data are first recorded. These may include hospital/clinic/general practitioner records, charts, diaries, x-rays, laboratory results, printouts, pharmacy records, care records, ECG or other printouts, completed scales, or quality of life questionnaires, for example. Source documents should be kept in a secure, limited access area.

Source documents that are computer generated and stored electronically must be printed for review by the monitor (eg, ECG reports). Once printed, these copies should be signed and dated by the Investigator and become a permanent part of the subject's source documents. The Investigator will facilitate the process for enabling the monitor to compare the content of the printout and the data stored in the computer to ensure all data are consistent.

Electronic data records, such as Holter monitor records or electroencephalogram records, must be saved and stored as instructed by UCB (or designee).

11.2.2 Source data verification

Source data verification ensures accuracy and credibility of the data obtained. During monitoring visits, reported data are reviewed with regard to being accurate, complete, and verifiable from source documents (eg, subject files, recordings from automated instruments, tracings [ECG], x-ray films, laboratory notes). All data reported on the eCRF should be supported by source documents, unless otherwise specified in Section 11.2.1.

11.3 Data handling

11.3.1 Case Report form completion

The Investigator is responsible for prompt reporting of accurate, complete, and legible data in the eCRFs and in all required reports.

Any change or correction to the eCRF after saving must be accompanied by a reason for the change.

Corrections made after the Investigator's review and approval (by means of a password/electronic signature) will be reapproved by the Investigator.

The Investigator should maintain a list of personnel authorized to enter data into the eCRF.

Detailed instructions will be provided in the CRF Completion Guidelines.

11.3.2 Database entry and reconciliation

Case Report forms/external electronic data will be entered/loaded into a validated electronic database using a clinical data management system (CDMS). Computerized data cleaning checks will be used in addition to manual review to check for discrepancies and to ensure consistency of the data. The data are entered into the eCRFs once and are subsequently verified.

An electronic audit trail system will be maintained within the CDMS to track all data changes in the database once the data have been saved initially into the system or electronically loaded. Regular backups of the electronic data will be performed.

11.3.3 Subject Screening and Enrollment log/Subject Identification Code list

The subject's screening and enrollment will be recorded in the Subject Screening and Enrollment log.

The Investigator will keep a Subject Identification Code list. This list remains with the Investigator and is used for unambiguous identification of each subject.

The subject's consent and enrollment in the study must be recorded in the subject's medical record. These data should identify the study and document the dates of the subject's participation.

11.4 Termination of the study

UCB reserves the right to temporarily suspend or prematurely discontinue this study either at a single site, multiple sites, or at all sites at any time for reasons including, but not limited to, safety or ethical issues, inaccurate or incomplete data recording, noncompliance, or unsatisfactory enrollment with respect to quality or quantity.

If the study is prematurely terminated or suspended, UCB (or its representative) will inform the Investigators/institutions and the regulatory authority(ies) of the termination or suspension and the reason(s) for the termination or suspension, in accordance with applicable regulatory requirement(s). The IRB/IEC should also be informed and provided with reason(s) for the termination or suspension by the Sponsor or by the Investigator/institution, as specified by the applicable regulatory requirement(s). In addition, arrangements will be made for the return of all unused IMP and investigational devices, and other material in accordance with UCB procedures for the study.

11.5 Archiving and data retention

The Investigator will maintain adequate records for the study, including CRFs, medical records, laboratory results, Informed Consent documents, drug dispensing and disposition records, safety reports, information regarding participants who discontinued, and other pertinent data.

All essential documents are to be retained by the Investigator until at least 2 years after the last approval of a marketing application in an ICH region and until there are no pending or contemplated marketing applications in an ICH region, or at least 2 years have elapsed since the formal discontinuation of clinical development of the IMP. These documents should be retained for a longer period, however, if required by the applicable regulatory requirement(s) or by an agreement with UCB (CPMP/ICH/135/95, 2002 [Section 4.9.5]). The Investigator will contact UCB for authorization prior to the destruction of any study records or in the event of accidental loss or destruction of any study records. The Investigator will also notify UCB should he/she relocate or move the study-related files to a location other than that specified in the Sponsor's trial master file.

11.6 Audit and inspection

The Investigator will permit study-related audits mandated by UCB, after reasonable notice, and inspections by domestic or foreign regulatory authorities.

The main purposes of an audit or inspection are to confirm that the rights and well-being of the subjects enrolled have been protected, that enrolled subjects (ie, signing consent and undergoing

study procedures) are appropriate for the study, and that all data relevant for the evaluation of the IMP have been processed and reported in compliance with the planned arrangements, the protocol, investigational site, and IRB/IEC SOPs, ICH GCP, and applicable regulatory requirements.

The Investigator will provide direct access to all study documents, source records, and source data. If an inspection by a regulatory authority is announced, the Investigator will immediately inform UCB (or designee).

11.7 Good Clinical Practice

Noncompliance with the protocol, ICH-GCP, or local regulatory requirements by the Investigator, institution, institution staff, or designees of the Sponsor will lead to prompt action by UCB to secure compliance. Continued noncompliance may result in the termination of the site's involvement in the study.

12 STATISTICS

A description of statistical methods follows and will be described in more detail in the Statistical Analysis Plan.

12.1 Definition of analysis sets

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).

Safety variables will be analyzed using the Safety Set (SS).

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. All outcome variables will be analyzed using the FAS.

12.2 General statistical considerations

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

The Baseline value is defined as the last nonmissing measurement prior to self-injection at Visit 1. Results from the Cochin Impaired Hand Function questionnaire at Visit 1 will be summarized.

No imputation of missing data will be performed.

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

12.3 Planned analyses

All statistical analyses will be descriptive in nature. No inferential statistical analyses are planned.

12.3.1 Analysis of the primary outcome variable

The primary outcome variable is the proportion (%) of all 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 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 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 (2×200mg 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 for the FAS overall, by dosing group, and by indication. A subgroup analysis will be performed for subjects in the FAS with impaired hand function. The 90% CIs for the proportion based on the Exact Binomial method will be reported as well.

12.3.2 Analyses of secondary outcome variables

The secondary outcome variables include:

- 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 (2×200mg 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.

- 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)

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

12.3.3 Analyses of other outcome variables

Other outcome variables are:

- Injection site pain due to self-injection (using a Visual Analog Scale [VAS]; 100mm) by visit at all visits after self-injection using the e-Device
- Responses to the preinjection ASI at Visit 1
- Responses to the postinjection ASI by visit at all visits after self-injection using the e-Device
- In vitro functional evaluation of the e-Device following the final use per subject:
  - The percentage of e-Devices found to be functionally compromised

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

12.4 Planned safety analyses

12.4.1 Safety analyses

Safety endpoints include AEs and changes from baseline in vital signs. Analyses of the safety data will be done on the SS.

All summaries of continuous safety variables will be presented at scheduled time points. No statistical testing will be conducted on the safety parameters. All AE data will be listed. Only treatment-emergent adverse events (TEAEs) will be included in the summary tables. Treatment-emergent AEs are defined as AEs starting after the time of first injection in the study up to 70 days after the last self-administration of study medication. All AEs will be coded and classified by system organ class, high level term, and preferred term according to the latest version of the Medical Dictionary for Regulatory Activities (MedDRA®).

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.

Physical examination findings 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.

12.5 Handling of 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 project 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.

12.6 Handling of dropouts or missing data

There will be no special procedures for handling missing data. All imputation of missing or partial dates for safety assessments will be detailed in the Statistical Analysis Plan.

12.7 Planned interim analysis and data monitoring

No interim analysis is planned.

There will be no Data Monitoring Committee established for this study.

12.8 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 (Poiraudeau 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.

13 ETHICS AND REGULATORY REQUIREMENTS

13.1 Informed consent

Subject's informed consent must be obtained and documented in accordance with local regulations, ICH-GCP requirements, and the ethical principles that have their origin in the principles of the Declaration of Helsinki.

Prior to obtaining informed consent, information should be given in a language and at a level of complexity understandable to the subject in both oral and written form by the Investigator (or designee). Each subject will have the opportunity to discuss the study and its alternatives with the Investigator.

Prior to participation in the study, the Informed Consent form should be signed and personally dated by the subject and by the person who conducted the informed consent discussion (Investigator or designee). The subject must receive a copy of the signed and dated Informed

Consent form. As part of the consent process, each subject must consent to direct access to his/her medical records for study-related monitoring, auditing, IRB/IEC review, and regulatory inspection.

If the Informed Consent form is amended during the study, the Investigator (or the Sponsor, if applicable) must follow all applicable regulatory requirements pertaining to the approval of the amended Informed Consent form by the IRB/IEC and use of the amended form.

All studies conducted at centers in the United States must include the use of a Health Insurance Portability and Accountability Act Authorization form.

The subject may withdraw his/her consent to participate in the study at any time. A subject is considered as enrolled in the study when he/she has signed the Informed Consent form. An eCRF must not be started, nor may any study-specific procedure be performed for a given subject, without having obtained his/her written consent to participate in the study.

13.2 Subject identification cards

Upon signing the Informed Consent form, the subject will be provided with a subject identification card in the language of the subject. The Investigator will fill in the subject identifying information and medical emergency contact information. The Investigator will instruct the subject to keep the card with him/her at all times.

13.3 Institutional Review Boards and Independent Ethics Committees

The study will be conducted under the auspices of an IRB/IEC, as defined in local regulations, ICH-GCP, and in accordance with the ethical principles that have their origin in the Declaration of Helsinki.

The Investigator/UCB will ensure that an appropriately constituted IRB/IEC that complies with the requirements of the current ICH-GCP version or applicable country-specific regulations will be responsible for the initial and continuing review and approval of the clinical study. Prior to initiation of the study, the Investigator/UCB will forward copies of the protocol, Informed Consent form, Investigator's Brochure, Investigator's curriculum vitae (if applicable), advertisement (if applicable), and all other subject-related documents to be used for the study to the IRB/IEC for its review and approval.

Before initiating a study, the Investigator will have written and dated full approval from the responsible IRB/IEC for the protocol.

The Investigator will also promptly report to the IRB/IEC all changes in the study, all unanticipated problems involving risks to human subjects or others, and any protocol deviations, to eliminate immediate hazards to subjects.

The Investigator will not make any changes in the study or study conduct without IRB/IEC approval, except where necessary to eliminate apparent immediate hazards to the subjects. For minor changes to a previously approved protocol during the period covered by the original approval, it may be possible for the Investigator to obtain an expedited review by the IRB/IEC as allowed.

As part of the IRB/IEC requirements for continuing review of approved studies, the Investigator will be responsible for submitting periodic progress reports to the IRB/IEC (based on IRB/IEC requirements), at intervals appropriate to the degree of subject risk involved, but no less than once per year. The Investigator should provide a final report to the IRB/IEC following study completion.

UCB (or its representative) will communicate safety information to the appropriate regulatory authorities and all active Investigators in accordance with applicable regulatory requirements. The appropriate IRB/IEC will also be informed by the Investigator or the Sponsor, as specified by the applicable regulatory requirements in each concerned country. Where applicable, Investigators are to provide the Sponsor (or its representative) with evidence of such IRB/IEC notification.

13.4 Subject privacy

UCB staff (or designee) will affirm and uphold the subject's confidentiality. Throughout this study, all data forwarded to UCB (or designee) will be identified only by the subject number assigned at Screening.

The Investigator agrees that representatives of UCB, its designee, representatives of the relevant IRB/IEC, or representatives of regulatory authorities will be allowed to review that portion of the subject's primary medical records that directly concerns this study (including, but not limited to, laboratory test result reports, ECG reports, admission/discharge summaries for hospital admissions occurring during a subject's study participation, and autopsy reports for deaths occurring during the study).

13.5 Protocol amendments

Protocol changes may affect the legal and ethical status of the study and may also affect the statistical evaluations of sample size and the likelihood of the study fulfilling its primary objective.

Significant changes to the protocol will only be made as an amendment to the protocol and must be approved by UCB, the IRB/IEC, and the regulatory authorities (if required), prior to being implemented.

14 FINANCE, INSURANCE, AND PUBLICATION

Insurance coverage will be handled according to local requirements.

Finance, insurance, and publication rights are addressed in the Investigator and/or CRO agreements, as applicable.

15 REFERENCES

CPMP/ICH/135/95 Note for guidance on Good Clinical Practice (EMEA) Jul 2002.

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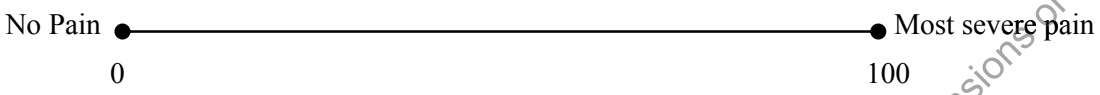
16 APPENDICES

16.1 Injection Site Pain (VAS)

This scale should be completed immediately postinjection (within 15 minutes).

Injection site pain due to self-injection immediately (within 15 minutes) after injection

Please mark a vertical line on the scale below to show how much pain you experience at the injection site right now



16.2 Assessment of Self Injection

The ASI comprises 2 modules, the PRE-self-injection and the POST-self-injection modules. The PRE-self-injection module should be administered before subjects start their first self-injection in this study. The POST-self-injection module should be administered within 30 minutes after each self-injection in this study. Subjects should complete the ASI alone and in a quiet place. The questionnaire should be reviewed only for completeness by healthcare professionals; the content of the subjects' answers should not be queried.

Assessment of Self-Injection (ASI)

[and draft new items]

PRE-Self-Injection

Introduction

The following questions ask about injections in general and your feelings about giving yourself an injection. Thank you for completing this questionnaire by yourself, preferably in a quiet environment. Take as much time as you need to complete it. There are no right or wrong answers. Your answers will remain strictly confidential and anonymous.

Please answer each question below by circling the number that best represents your opinion (circle only one number per question).

FEELINGS ABOUT INJECTIONS

The following questions concern your **feelings about injections**.

Please answer each question below by circling the number that best represents your opinion (circle only one number per question).

1. In general, how afraid are you of needles?

Not at all 1	A little 2	Moderately 3	Very 4	Extremely 5

2. In general, how afraid are you of having an injection?

Not at all 1	A little 2	Moderately 3	Very 4	Extremely 5

3. How anxious do you feel about giving **yourself** an injection?

Not at all 1	A little 2	Moderately 3	Very 4	Extremely 5

SELF-CONFIDENCE

The following questions concern your **confidence** about giving yourself an injection.

Please answer each question below by circling the number that best represents your opinion (circle only one number per question).

4. How confident are you about …	Not at all	A little	Moderately	Very	Extremely
a. Giving yourself an injection in **the right way**?	1	2	3	4	5
b. Giving yourself an injection in a **clean and sterile way**?	1	2	3	4	5
c. Giving yourself an injection **safely**?	1	2	3	4	5

THANK YOU FOR COMPLETING THIS QUESTIONNAIRE

Assessment of Self-Injection (ASI)

[and draft new items]

POST-Self-Injection

Introduction

The following questions concern the self-injection of your medication and must be answered after giving yourself an injection **using the [prefilled syringe / AutoClicks prefilled pen / ava®].**

Thank you for completing this questionnaire by yourself, preferably in a quiet environment. Take as much time as you need to complete it. There are no right or wrong answers. Your answers will remain strictly confidential and anonymous.

FEELINGS ABOUT INJECTIONS

The following questions concern your **feelings about injections.**

Please answer each question below by circling the number that best represents your opinion (circle only one number per question).

1. In general, how afraid are you of needles?

Not at all 1	A little 2	Moderately 3	Very 3	Extremely 4

2. In general, how afraid are you of having an injection?

Not at all 1	A little 2	Moderately 3	Very 4	Extremely 5

3. How anxious do you feel about giving yourself an injection?

Not at all 1	A little 2	Moderately 3	Very 4	Extremely 5

SELF-IMAGE

The following questions concerns **your self-image when using the [prefilled syringe / AutoClicks prefilled pen / ava®].**

Please answer the questions below by circling the number that best represents your opinion (circle only one number per question).

4. How **self-conscious** would you feel about **using the prefilled syringe / AutoClicks prefilled pen / ava®**…	**Not at all**	**A little**	**Moderately**	**Very**	**Extremely**
a. … around your **family**?	1	2	3	4	5
b. … around your **friends**?	1	2	3	4	5
c. … around **people you don't know**?	1	2	3	4	5

SELF-CONFIDENCE

The following questions concern your **confidence** about giving yourself an injection **using the [prefilled syringe / AutoClicks prefilled pen / ava®].**

Please answer each question below by circling the number that best represents your opinion (circle only one number per question).

5. How confident are you about …	**Not at all**	**A little**	**Moderately**	**Very**	**Extremely**
a. Giving yourself an injection in **the right way**?	1	2	3	4	5
b. Giving yourself an injection in a **clean and sterile way**?	1	2	3	4	5
c. Giving yourself an injection **safely**?	1	2	3	4	5

PAIN AND SKIN REACTIONS DURING OR AFTER THE INJECTION

The following questions ask about **pain and skin reactions** you may have experienced during or after the injection **using the [prefilled syringe / AutoClicks prefilled pen / ava®].**

Please answer each question below by circling the number that best represents your opinion (circle only one number per question).

6. During and/or after the injection, how bothered were you by:	**Not at all**	**A little**	**Moderately**	**Very**	**Extremely**
a. **pain**?	1	2	3	4	5
b. **burning sensation**?	1	2	3	4	5
c. **cold sensation**?	1	2	3	4	5
d. **itching** at the injection site?	1	2	3	4	5
e. **redness** at the injection site?	1	2	3	4	5
f. **swelling** at the injection site?	1	2	3	4	5
g. **bruising** at the injection site?	1	2	3	4	5
h. **hardening** at the injection site?	1	2	3	4	5
i. **bleeding** from the injection site?	1	2	3	4	5
j. **medication leaking from the skin** at the injection site?	1	2	3	4	5

EASE OF USE OF THE SELF-INJECTION DEVICE

The following questions ask about the **ease of use of the [prefilled syringe / AutoClicks prefilled pen / ava®].**

Please answer each question below by circling the number that best represents your opinion (circle only one number per question).

7. How difficult or easy was it to:	**Very difficult**	**Difficult**	**Somewhat difficult**	**Somewhat easy**	**Easy**	**Very easy**
a. read and follow the prefilled syringe / AutoClicks prefilled pen / ava® **instructions**?	1	2	3	4	5	6
b. learn **how to use** the prefilled syringe / AutoClicks prefilled pen / ava®?	1	2	3	4	5	6
c. Remove the **needle cap** of the prefilled syringe / AutoClicks prefilled pen / ava®?	1	2	3	4	5	6
d. **hold** the prefilled syringe / AutoClicks prefilled pen / ava® while preparing it and giving yourself medication?	1	2	3	4	5	6

7. How difficult or easy was it to:	Very difficult	Difficult	Somewhat difficult	Somewhat easy	Easy	Very easy
e. hold the prefilled syringe / AutoClicks prefilled pen / ava® at the **correct angle** for injection?	1	2	3	4	5	6
f. depress the **plunger or button** on the prefilled syringe / AutoClicks prefilled pen / ava®?	1	2	3	4	5	6
g. **administer** the injection without any help?	1	2	3	4	5	6
h. control the injection **speed**?	1	2	3	4	5	6
i. **pause** when giving yourself an injection?	1	2	3	4	5	6
j. **stop** when giving yourself an injection?	1	2	3	4	5	6
k. be sure that the injection gave you the **correct amount** of medication?	1	2	3	4	5	6
l. know when the injection is **complete**?	1	2	3	4	5	6
m. **remember** when to take my **next** injection?	1	2	3	4	5	6

7. How difficult or easy was it to:	Very difficult	Difficult	Somewhat difficult	Somewhat easy	Easy	Very easy
n. **store** the prefilled syringe / AutoClicks prefilled pen / ava®?	1	2	3	4	5	6
o. **travel** with the prefilled syringe / AutoClicks prefilled pen / ava®	1	2	3	4	5	6
p. **use** the prefilled syringe / AutoClicks prefilled pen / ava®?	1	2	3	4	5	6

8. How does the [prefilled syringe / AutoClicks prefilled pen / ava®] **fit in your hand**?

Very uncomfortably	Uncomfortably	Somewhat uncomfortably	Somewhat comfortably	Comfortably	Very comfortably
1	2	3	4	5	6

SATISFACTION WITH SELF-INJECTION

The following questions ask about your **satisfaction with the [prefilled syringe / AutoClicks prefilled pen / ava®].**

Please answer each question below by circling the number that best represents your opinion (circle only one number per question).

9. How satisfied are you with the way the [prefilled syringe / AutoClicks prefilled pen / ava®] **delivers**your **medication** (syringe needle or medication cassette)?

Very dissatisfied	Dissatisfied	Neither dissatisfied nor satisfied	Satisfied	Very satisfied
1	2	3	4	5

10. After this study, how **confident** would you be to give yourself injections at home with the [prefilled syringe / AutoClicks prefilled pen / ava®]?

Not at all	A little	Moderately	Very	Extremely
1	2	3	4	5

11. How **easy** was it to give yourself an injection with the [prefilled syringe / AutoClicks prefilled pen / ava®]?

Not at all	A little	Moderately	Very	Extremely
1	2	3	4	5

12. How satisfied are you with your **ability to control** your injection (e.g., stop, pause, change speed) with the [prefilled syringe / AutoClicks prefilled pen / ava®]?

Very dissatisfied	Dissatisfied	Neither dissatisfied nor satisfied	Satisfied	Very satisfied
1	2	3	4	5

13. How satisfied are you with the **time it takes to inject the medication with the** [prefilled syringe / AutoClicks prefilled pen / ava®]?

Very dissatisfied	Dissatisfied	Neither dissatisfied nor satisfied	Satisfied	Very satisfied
1	2	3	4	5

14. Overall, how **convenien**t is the [prefilled syringe / AutoClicks prefilled pen / ava®]?

Very inconvenient	Inconvenient	Neither inconvenient nor convenient	Convenient	Very convenient
1	2	3	4	5

15. After this study, would you **choose to continue** self-injecting your medication with the [prefilled syringe / AutoClicks prefilled pen / ava®]?

Definitely not	Probably not	I don't know	Yes, probably	Yes, definitely
1	2	3	4	5

16. Overall, how **satisfied** are you with the [Prefilled syringe / AutoClicks prefilled pen / ava®]?

Very dissatisfied	Dissatisfied	Neither dissatisfied nor satisfied	Satisfied	Very satisfied
1	2	3	4	5

THANK YOU FOR COMPLETING THIS QUESTIONNAIRE

16.3 Self-Injection Preference Questionnaire

SELF-INJECTION PREFERENCE QUESTIONNAIRE

The following questions concern your **preferences about injections**.

Please answer each question below by circling the number that best represents your opinion (circle only one number per question).

1. Which self-injection device do you prefer based on how **safe the device is to use?**

ava®	your latest device[1]	no preference
1	2	3

2. Which self-injection device do you prefer based on how **confident you are when using the device**?

ava®	your latest device[1]	no preference
1	2	3

3. Which self-injection device do you prefer based on how **easy the device is to hold**?

ava®	your latest device[1]	no preference
1	2	3

4. Which self-injection device do you prefer based on your **ability to control your injection (for example, stop, pause, change speed)?**

ava®	your latest device	no preference
1	2	3

5. Which self-injection device do you prefer based on how **easy the device is to store**?

ava®	your latest device[1]	no preference
1	2	3

[1] Pre-filled syringe or AutoClick pre-filled pen

6. Which self-injection device do you prefer based on how **easy it is to travel with the device**?

ava®	your latest device[1]	no preference
1	2	3

7. Which self-injection device do you prefer based on the **time needed to perform your injection**?

ava®	your latest device[1]	no preference
1	2	3

8. Which self-injection device do you prefer based on how **convenient the device is to use?**

ava®	your latest device[1]	no preference
1	2	3

9. Overall, **which self-injection device do you prefer**?

ava®	your latest device[1]		no preference
1	2		3

THANK YOU FOR COMPLETING THIS QUESTIONNAIRE

[1] Pre-filled syringe or AutoClick pre-filled pen

16.4 Cochin Scale

<Study>	Visit: _____	Visit Date: DD MMM YY	Subject No.	Page 1 of 3

Cochin Scale

In the kitchen
1. Can you hold a bowl? ☐ 0 = Yes, without difficulty ☐ 1 = Yes, with a little difficulty ☐ 2 = Yes, with some difficulty ☐ 3 = Yes, with much difficulty ☐ 4 = Nearly impossible to do ☐ 5 = Impossible to do
2. Can you grasp a full bottle and raise it? ☐ 0 = Yes, without difficulty ☐ 1 = Yes, with a little difficulty ☐ 2 = Yes, with some difficulty ☐ 3 = Yes, with much difficulty ☐ 4 = Nearly impossible to do ☐ 5 = Impossible to do
3. Can you hold a plate full of food? ☐ 0 = Yes, without difficulty ☐ 1 = Yes, with a little difficulty ☐ 2 = Yes, with some difficulty ☐ 3 = Yes, with much difficulty ☐ 4 = Nearly impossible to do ☐ 5 = Impossible to do
4. Can you pour liquid from a bottle into a glass? ☐ 0 = Yes, without difficulty ☐ 1 = Yes, with a little difficulty ☐ 2 = Yes, with some difficulty ☐ 3 = Yes, with much difficulty ☐ 4 = Nearly impossible to do ☐ 5 = Impossible to do
5. Can you unscrew the lid from a jar that has been opened before? ☐ 0 = Yes, without difficulty ☐ 1 = Yes, with a little difficulty ☐ 2 = Yes, with some difficulty ☐ 3 = Yes, with much difficulty ☐ 4 = Nearly impossible to do ☐ 5 = Impossible to do
6. Can you cut meat with a knife? ☐ 0 = Yes, without difficulty ☐ 1 = Yes, with a little difficulty ☐ 2 = Yes, with some difficulty ☐ 3 = Yes, with much difficulty ☐ 4 = Nearly impossible to do ☐ 5 = Impossible to do

<Study>	Visit: _____	Visit Date: DD MMM YY	Subject No.	Page 2 of 3

7. Can you prick things well with a fork?
   - ☐ 0 = Yes, without difficulty
   - ☐ 1 = Yes, with a little difficulty
   - ☐ 2 = Yes, with some difficulty
   - ☐ 3 = Yes, with much difficulty
   - ☐ 4 = Nearly impossible to do
   - ☐ 5 = Impossible to do

8. Can you peel fruit?
   - ☐ 0 = Yes, without difficulty
   - ☐ 1 = Yes, with a little difficulty
   - ☐ 2 = Yes, with some difficulty
   - ☐ 3 = Yes, with much difficulty
   - ☐ 4 = Nearly impossible to do
   - ☐ 5 = Impossible to do

Dressing

9. Can you button your shirt?
   - ☐ 0 = Yes, without difficulty
   - ☐ 1 = Yes, with a little difficulty
   - ☐ 2 = Yes, with some difficulty
   - ☐ 3 = Yes, with much difficulty
   - ☐ 4 = Nearly impossible to do
   - ☐ 5 = Impossible to do

10. Can you open and close a zip?
    - ☐ 0 = Yes, without difficulty
    - ☐ 1 = Yes, with a little difficulty
    - ☐ 2 = Yes, with some difficulty
    - ☐ 3 = Yes, with much difficulty
    - ☐ 4 = Nearly impossible to do
    - ☐ 5 = Impossible to do

Hygiene

11. Can you squeeze a new tube of toothpaste?
    - ☐ 0 = Yes, without difficulty
    - ☐ 1 = Yes, with a little difficulty
    - ☐ 2 = Yes, with some difficulty
    - ☐ 3 = Yes, with much difficulty
    - ☐ 4 = Nearly impossible to do
    - ☐ 5 = Impossible to do

12. Can you hold a toothbrush efficiently?
    - ☐ 0 = Yes, without difficulty
    - ☐ 1 = Yes, with a little difficulty
    - ☐ 2 = Yes, with some difficulty
    - ☐ 3 = Yes, with much difficulty
    - ☐ 4 = Nearly impossible to do
    - ☐ 5 = Impossible to do

<Study>	Visit: _____	Visit Date: DD MMM YY	Subject No.	Page 3 of 3

At the office

13. Can you write a short sentence with an ordinary pen?
- ☐ 0 = Yes, without difficulty
- ☐ 1 = Yes, with a little difficulty
- ☐ 2 = Yes, with some difficulty
- ☐ 3 = Yes, with much difficulty
- ☐ 4 = Nearly impossible to do
- ☐ 5 = Impossible to do

14. Can you write a letter with an ordinary pen?
- ☐ 0 = Yes, without difficulty
- ☐ 1 = Yes, with a little difficulty
- ☐ 2 = Yes, with some difficulty
- ☐ 3 = Yes, with much difficulty
- ☐ 4 = Nearly impossible to do
- ☐ 5 = Impossible to do

Other

15. Can you turn a round door knob?
- ☐ 0 = Yes, without difficulty
- ☐ 1 = Yes, with a little difficulty
- ☐ 2 = Yes, with some difficulty
- ☐ 3 = Yes, with much difficulty
- ☐ 4 = Nearly impossible to do
- ☐ 5 = Impossible to do

16. Can you cut a piece of paper with scissors?
- ☐ 0 = Yes, without difficulty
- ☐ 1 = Yes, with a little difficulty
- ☐ 2 = Yes, with some difficulty
- ☐ 3 = Yes, with much difficulty
- ☐ 4 = Nearly impossible to do
- ☐ 5 = Impossible to do

17. Can you pick up coins from a table top?
- ☐ 0 = Yes, without difficulty
- ☐ 1 = Yes, with a little difficulty
- ☐ 2 = Yes, with some difficulty
- ☐ 3 = Yes, with much difficulty
- ☐ 4 = Nearly impossible to do
- ☐ 5 = Impossible to do

18. Can you turn a key in a lock?
- ☐ 0 = Yes, without difficulty
- ☐ 1 = Yes, with a little difficulty
- ☐ 2 = Yes, with some difficulty
- ☐ 3 = Yes, with much difficulty
- ☐ 4 = Nearly impossible to do
- ☐ 5 = Impossible to do

M.M. Lefevre-Colau et al. 2001 Responsiveness of the Cochin rheumatoid hand disability scale after surgery

Cochin Scale

	Score
In the kitchen	
1. Can you hold a bowl?	<<see codelist below>>
2. Can you grasp a full bottle and raise it?	
3. Can you hold a plate full of food?	
4. Can you pour liquid from a bottle into a glass?	
5. Can you unscrew the lid from a jar that has been opened before?	
6. Can you cut meat with a knife?	
7. Can you prick things well with a fork?	
8. Can you peel fruit?	
Dressing	
9. Can you button your shirt?	
10. Can you open and close a zip?	
Hygiene	
11. Can you squeeze a new tube of toothpaste?	
12. Can you hold a toothbrush efficiently?	
At the office	
13. Can you write a short sentence with an ordinary pen?	
14. Can you write a letter with an ordinary pen?	
Other	
15. Can you turn a round door knob?	
16. Can you cut a piece of paper with scissors?	
17. Can you pick up coins from a table top?	
18. Can you turn a key in a lock?	

Codelist for dropdown menu

0 = Yes, without difficulty
1 = Yes, with a little difficulty
2 = Yes, with some difficulty
3 = Yes, with much difficulty
4 = Nearly impossible to do
5 = Impossible to do

COCHIN SCALE

General	• **Please note that the subject should complete all questionnaires prior to any assessments being performed.** • Complete the header information on the worksheet prior to administering to the subject. • The worksheets are completed by the subject and are considered source documentation. • The subject must tick the box that most appropriately describes his or her abilities. ➢ Only one tick mark must be recorded for each question. • Only the subject may make corrections to the worksheet. ➢ If corrections have been made to the worksheet, ensure they are done according to standards (one line through, date/initial). • The worksheet must be reviewed for completeness prior to subject leaving the office. ➢ If upon review site staff discover more than one answer is checked, the staff should ask the subject to choose one. • The subject-completed worksheet must be monitored and entered into the appropriate eCRF screen.

Notes:

http://rheumatology.oxfordjournals.org/content/40/8/843.full.pdf

This questionnaire does not need a license.

16.5 Protocol Amendment 1

Rationale for the amendment

The purpose of this protocol amendment is to clarify subjects in the Q4W dosing regimen, the process of self-injection, and informed consent.

In additions, minor grammatical and typographical errors were corrected.

Modifications and changes

Global changes

The following global change has been made throughout the protocol:

- Clarification was added that the Q4W dosing regimen may include subjects with RA, PsA, or AS.

Specific changes

Change #1

Section 1 Summary, after fifth paragraph

The following paragraph has been added:

During self-injection, if the skin sensor at the injection port loses contact with the skin, the e-Device will withdraw the needle and stop administration of CZP. If less than five minutes have elapsed since loss of contact with skin, the subject can reposition the e-Device on a new clean injection site and resume and complete the self-injection. If the subject is unable to complete the self-injection and deliver the entire dose of medication (ie, the device indicates incomplete administration and the CZP-cassette is not seen to be empty), the HCP evaluating the self-injection will document the incomplete self-injection, note the reason why the complete dose was not administered, and using his/her best medical judgment, advise the subject regarding any further dosing.

Change #2

Section 4.1.1 Primary outcome and variable, after first bullet

The following paragraph has been added:

During self-injection, if the skin sensor at the injection port loses contact with the skin, the e-Device will withdraw the needle and stop administration of CZP. If less than five minutes have elapsed since loss of contact with skin, the subject can reposition the e-Device on a new clean injection site and resume and complete the self-injection. If the subject is unable to complete the self-injection and deliver the entire dose of medication (ie, the device indicates incomplete administration and the CZP-cassette is not seen to be empty), the HCP evaluating the self-injection will document the incomplete self-injection, note the reason why the complete dose was

not administered, and using his/her best medical judgment, advise the subject regarding any further dosing.

Change #3

Section 4.1.2 Secondary variable, after first bullet

The following paragraph has been added:

During self-injection, if the skin sensor at the injection port loses contact with the skin, the e-Device will withdraw the needle and stop administration of CZP. If less than five minutes have elapsed since loss of contact with skin, the subject can reposition the e-Device on a new clean injection site and resume and complete the self-injection. If the subject is unable to complete the self-injection and deliver the entire dose of medication (ie, the device indicates incomplete administration and the CZP-cassette is not seen to be empty), the HCP evaluating the self-injection will document the incomplete self-injection, note the reason why the complete dose was not administered, and using his/her best medical judgment, advise the subject regarding any further dosing.

Change #4

Section 8.1 Visit 1/Screening and Study Treatment Period, after fourteenth bullet

The following paragraph has been added:

During self-injection, if the skin sensor at the injection port loses contact with the skin, the e-Device will withdraw the needle and stop administration of CZP. If less than five minutes have elapsed since loss of contact with skin, the subject can reposition the e-Device on a new clean injection site and resume and complete the self-injection. If the subject is unable to complete the self-injection and deliver the entire dose of medication (ie, the device indicates incomplete administration and the CZP-cassette is not seen to be empty), the HCP evaluating the self-injection will document the incomplete self-injection, note the reason why the complete dose was not administered, and using his/her best medical judgment, advise the subject regarding any further dosing.

Change #5

Section 8.2.1 Visit 2 (Week 2), after seventh bullet

The following paragraph has been added:

During self-injection, if the skin sensor at the injection port loses contact with the skin, the e-Device will withdraw the needle and stop administration of CZP. If less than five minutes have elapsed since loss of contact with skin, the subject can reposition the e-Device on a new clean injection site and resume and complete the self-injection. If the subject is unable to complete the self-injection and deliver the entire dose of medication (ie, the device indicates incomplete administration and the CZP-cassette is not seen to be empty), the HCP evaluating the self-

injection will document the incomplete self-injection, note the reason why the complete dose was not administered, and using his/her best medical judgment, advise the subject regarding any further dosing.

Change #6

Section 8.3.1 Visit 2 (Week 4), after seventh bullet

The following paragraph has been added:

During self-injection, if the skin sensor at the injection port loses contact with the skin, the e-Device will withdraw the needle and stop administration of CZP. If less than five minutes have elapsed since loss of contact with skin, the subject can reposition the e-Device on a new clean injection site and resume and complete the self-injection. If the subject is unable to complete the self-injection and deliver the entire dose of medication (ie, the device indicates incomplete administration and the CZP-cassette is not seen to be empty), the HCP evaluating the self-injection will document the incomplete self-injection, note the reason why the complete dose was not administered, and using his/her best medical judgment, advise the subject regarding any further dosing.

Change #7

Section 9.4 Evaluation of post-use structural integrity of CZP-cassettes

The used CZP-cassettes will be inspected to determine if the entire dose was delivered based on whether the PFS housed in the CZP-cassette is empty or not (as per primary endpoint). The visual inspection of the used CZP-cassette will also check for structural integrity and damage (ie, clear evidence of damage/compromised structural integrity—not superficial, cosmetic imperfections). All evaluations will be performed by appropriately trained site staff.

Has been changed to:

The used CZP-cassettes will be inspected to determine if the entire dose was delivered based on whether the PFS housed in the CZP-cassette is empty or not (as per primary endpoint). **During self-injection, if the skin sensor at the injection port loses contact with the skin, the e-Device will withdraw the needle and stop administration of CZP. If less than five minutes have elapsed since loss of contact with skin, the subject can reposition the e-Device on a new clean injection site and resume and complete the self-injection. If the subject is unable to complete the self-injection and deliver the entire dose of medication (ie, the device indicates incomplete administration and the CZP-cassette is not seen to be empty), the HCP evaluating the self-injection will document the incomplete self-injection, note the reason why the complete dose was not administered, and using his/her best medical judgment, advise the subject regarding any further dosing.** The visual inspection of the used CZP-cassette will also check for structural integrity and damage (ie, clear evidence of damage/compromised structural integrity—not superficial, cosmetic imperfections). All evaluations will be performed by appropriately trained site staff.

Change #8

Section 9.6 Evaluation of safe and effective self-injection

Safe and effective self-injection will be evaluated by the HCP. Subject self-injection of the complete dose of CZP will be confirmed by a visual inspection of the CZP-cassette(s) which shows the PFS container to be empty. The self-injection will be considered safe if there are no AEs related to use of the e-Device (ADEs) that would preclude continued use of the e-Device for self-injection.

Has been changed to:

Safe and effective self-injection will be evaluated by the HCP. Subject self-injection of the complete dose of CZP will be confirmed by a visual inspection of the CZP-cassette(s) which shows the PFS container to be empty. **During self-injection, if the skin sensor at the injection port loses contact with the skin, the e-Device will withdraw the needle and stop administration of CZP. If less than five minutes have elapsed since loss of contact with skin, the subject can reposition the e-Device on a new clean injection site and resume and complete the self-injection. If the subject is unable to complete the self-injection and deliver the entire dose of medication (ie, the device indicates incomplete administration and the CZP-cassette is not seen to be empty), the HCP evaluating the self-injection will document the incomplete self-injection, note the reason why the complete dose was not administered, and using his/her best medical judgment, advise the subject regarding any further dosing.** The self-injection will be considered safe if there are no AEs related to use of the e-Device (ADEs) that would preclude continued use of the e-Device for self-injection.

Change #9

Section 12.1 Definition of analysis sets, third paragraph

The Full Analysis Sets for subjects in the Q2W group (FASa) and for subjects in the Q4W group (FASb) will consist of all subjects in the SS who received at least 1 dose of CZP using the e-Device in the study. All variables will be analyzed using the FASa and FASb.

Has been changed to:

The Full Analysis Sets **(FAS)** ~~for subjects in the Q2W group (FASa) and for subjects in the Q4W group (FASb)~~ will consist of all subjects in the SS who received at least 1 dose of CZP using the e-Device in the study. All **outcome** variables will be analyzed using the FAS~~a and FASb~~.

Change #10

Section 12.2 General statistical considerations, first paragraph, third sentence

Each endpoint will be summarized by dosing regimen (Q2W or Q4W) and within the Q2W group by indication.

Has been changed to:

Each endpoint will be summarized by dosing regimen (Q2W or Q4W) and ~~within the Q2W group~~ by indication.

Change #11

Section 12.3.1 Analysis of the primary outcome variable, third paragraph

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

Has been changed to:

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

Change #12

Section 12.3.2 Analysis of secondary variables, third paragraph

The secondary variables will be summarized using descriptive statistics. All summary statistics will be presented for the FASa and FASb, and by indication for the FASa. A subgroup analysis will performed for subjects in the FASa or FASb with impaired hand function.

Has been changed to:

Section 12.3.2 Analysis of secondary outcome variables

The secondary **outcome** variables will be summarized using descriptive statistics. All summary statistics will be presented for the FAS~~a and FASb,~~ **overall, by dosing group,** and by indication ~~for the FASa~~. A subgroup analysis will performed for subjects in the FAS~~a or FASb~~ with impaired hand function.

Change #13

Section 12.3.3 Analysis of the other variables, second paragraph

The other variables will be summarized using descriptive statistics. All other exploratory variables will be summarized for the FASa and FASb, and by indication for the FASa.

Has been changed to:

Section 12.3.3 Analysis of the other outcome variables

The other **outcome** variables will be summarized using descriptive statistics. All other exploratory variables will be summarized for the FAS~~a and FASb,~~ **overall, by dosing group,** and by indication ~~for the FASa~~.

Change #14

Section 12.4.1 Safety analyses, third paragraph, second sentence

Adverse events will be summarized separately as AEs associated with the study drug and those AEs related to use of the e-Device (ADEs) (including the CZP-cassette).

Has been changed to:

Adverse events **related to use of the e-Device (ADEs) (including the CZP-cassette)** will be summarized separately ~~as AEs associated with the study drug and those AEs related to use of the e-Device (ADEs) (including the CZP-cassette)~~.

Change #15

Section 12.5 Handling of protocol deviations, first sentence

Only subjects who had no important protocol deviations affecting the primary outcome variable, as confirmed during ongoing data cleaning meetings prior to database lock, will be included in the FASa/FASb.

Has been removed.

Change #16

Section 13.1 Informed consent, third paragraph

Prior to participation in the study, the Informed Consent form should be signed and personally dated by the subject, or his/her legal representative, and by the person who conducted the informed consent discussion (Investigator or designee). The subject or his/her legal representative must receive a copy of the signed and dated Informed Consent form. As part of the consent process, each subject must consent to direct access to his/her medical records for study-related monitoring, auditing, IRB/IEC review, and regulatory inspection.

Has been changed to:

Prior to participation in the study, the Informed Consent form should be signed and personally dated by the subject~~, or his/her legal representative,~~ and by the person who conducted the informed consent discussion (Investigator or designee). The subject ~~or his/her legal representative~~ must receive a copy of the signed and dated Informed Consent form. As part of the consent process, each subject must consent to direct access to his/her medical records for study-related monitoring, auditing, IRB/IEC review, and regulatory inspection

Change #17

Section 13.2 Subject identification cards

Upon signing the Informed Consent form, the subject or legal representative will be provided with a subject identification card in the language of the subject. The Investigator will fill in the

subject identifying information and medical emergency contact information. The Investigator will instruct the subject to keep the card with him/her at all times.

Has been changed to:

Upon signing the Informed Consent form, the subject ~~or legal representative~~ will be provided with a subject identification card in the language of the subject. The Investigator will fill in the subject identifying information and medical emergency contact information. The Investigator will instruct the subject to keep the card with him/her at all times.

16.6 Protocol Amendment 2

Rationale for the amendment

The purpose of this protocol amendment is to clarify the composition of subjects in the sample size.

Modifications and changes

Specific changes

Change #1

Section 1 Summary, last paragraph, last sentence

These 60 subjects will be composed of a minimum of 15 subjects with either RA, PsA, or AS in each of the dosing groups (Q2W and Q4W); a minimum of 15 subjects with CD; and a minimum of 10 subjects with impaired hand function.

Has been changes to:

Th~~ese~~ 60 subjects **using the e-Device at Visit 1** will be composed of a minimum of 15 subjects ~~with either RA, PsA, or AS~~ in each of the dosing groups (Q2W ~~and~~ **vs** Q4W) **with** a minimum of 15 subjects with CD and a minimum of 10 subjects with impaired hand function.

Change #2

Section 5.1.2 Planned number of subjects and sites, second sentence

These 60 subjects will be composed of a minimum of 15 subjects with either RA, PsA, or AS in each of the dosing groups (Q2W and Q4W); a minimum of 15 subjects with CD; and a minimum of 10 subjects with impaired hand function.

Has been changed to:

T~~h~~ese 60 subjects **using the e-Device at Visit 1** will be composed of a minimum of 15 subjects ~~with either RA, PsA, or AS~~ in each of the dosing groups (Q2W ~~and~~ **vs** Q4W) **with** a minimum of 15 subjects with CD and a minimum of 10 subjects with impaired hand function.

Change #3

Section 12.8 Determination of sample size, second sentence

The 60 subjects using the e-Device at Visit 1 will be composed of a minimum of 15 subjects with either RA, PsA, or AS in each of the dosing groups (Q2W vs Q4W); a minimum of 15 subjects with CD; and a minimum of 10 subjects with impaired hand function.

Has been changed to:

The~~se~~ 60 subjects **using the e-Device at Visit 1** will be composed of a minimum of 15 subjects ~~with either RA, PsA, or AS~~ in each of the dosing groups (Q2W ~~and~~ **vs** Q4W) **with** a minimum of 15 subjects with CD and a minimum of 10 subjects with impaired hand function.

17 DECLARATION AND SIGNATURE OF INVESTIGATOR

I confirm that I have carefully read and understood this protocol and agree to conduct this clinical study as outlined in this protocol, according to current Good Clinical Practice and local laws and requirements.

I will ensure that all subinvestigators and other staff members read and understand all aspects of this protocol.

I have received and read all study-related information provided to me.

The objectives and content of this protocol as well as the results deriving from it will be treated confidentially, and will not be made available to third parties without prior authorization by UCB.

All rights of publication of the results reside with UCB, unless other agreements were made in a separate contract.

Investigator:

Printed name	Date/Signature

18 SPONSOR DECLARATION

I confirm that I have carefully read and understand this protocol and agree to conduct this clinical study as outlined in this protocol and according to current Good Clinical Practice.

RA0098 Protocol Amendment 2

ELECTRONIC SIGNATURES

Signed by	Meaning of Signature	Server Approval Date (dd-mon-yyyy (HH:mm))
[redacted]	Clinical Approval	02-Oct-2017 20:45 GMT+02
[redacted]	Clinical Approval	02-Oct-2017 21:29 GMT+02