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

PROTOCOL RA0138 AMENDMENT 2

PHASE 1B

SHORT TITLE:

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

Sponsor:
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1070 Brussels
BELGIUM

Regulatory agency identifying number(s):

IND Number:	009869

Confidential Material

PROTOCOL AMENDMENT SUMMARY OF CHANGES TABLE

Document history		
Document	**Date**	**Type of amendment**
Amendment 2	18 Mar 2021	Nonsubstantial
Amendment 1	09 Dec 2020	Nonsubstantial
Original Protocol	27 Mar 2020	Not applicable

Amendment 2 (18 Mar 2021)

Overall rationale for the amendment

The primary reasons for this nonsubstantial protocol amendment were to update the Screening Period duration from "7 days" to "up to 28 days," to standardize the use of "inhibitor" vs "antagonist," to update text describing rescreening procedures, to change Visit 3 from a "Home Visit" to a "Clinic Visit," to clarify rescreening procedures, and to clarify the prohibited concomitant medications and permitted rescue medications.

This amendment is considered to be nonsubstantial based on the criteria set forth in Article 10(a) of Directive 2001/20/EC of the European Parliament and the Council of the European Union.

Section # and Name	Description of Change	Brief Rationale
1.1 Synopsis 1.2 Schema 4.1 Overall design	Changed the duration for the Screening Period from "7 days" to "up to 28 days."	The Screening Period was lengthened to 28 days to allow for sufficient time for laboratory samples to be processed ahead of a study participant's first CZP dose.
1.3 Schedule of Activities	Visit 3 was changed from a "Home" visit to a "Clinic" visit.	Due to logistical considerations with in-home nurse availability, this visit was changed from a home visit to a clinic visit.
5.2 Exclusion criteria	Modified the wording of Exclusion Criterion #10 to exclude the term "antagonist." This change resulted in a global use of the term "inhibitor" to describe TNFα inhibitors.	This change was made to avoid confusion in the understanding of TNFα inhibitors vs TNFα antagonists.
5.2 Exclusion criteria	Rescreening text for laboratory assessments was removed from Exclusion Criterion #13	Updated to provide clarity and to be consistent with remainder of protocol and program.

Section # and Name	Description of Change	Brief Rationale
5.4 Screen failures	Clarifying text was added to describe the window in which tests that result in ALT, AST, or ALP up to 25% above the exclusion limit may be repeated for confirmation.	Updated to provide clarity and to be consistent with remainder of protocol and program.
6.5.2 Prohibited concomitant treatments (medications and therapies)	The specific types of prohibited concomitant DMARDs were clarified.	Updated to provide clarity and avoid confusion regarding which DMARDs are prohibited.
6.5.3 Rescue medication	The specific types of permitted rescue medications were clarified.	Updated to provide clarity and avoid confusion regarding which rescue medications are permitted.

SERIOUS ADVERSE EVENT REPORTING

Serious adverse event reporting (24h)	
Fax	**US and Canada:** +1 800 880 6949 or +1 866 890 3175
Email	**Global:** DS_ICT@ucb.com (for interventional clinical studies)

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1 PROTOCOL SUMMARY

1.1 Synopsis

Protocol title: A multi-center, open-label study to evaluate the pharmacokinetics of certolizumab pegol in adults with active rheumatoid arthritis using an electrochemiluminescent immuno-assay

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

Rationale:

Certolizumab pegol (CZP) was approved in the United States (US) for adults with rheumatoid arthritis (RA) in May 2009. Certolizumab pegol pharmacokinetic (PK) and antidrug antibody (ADA) data in the adult RA population has thus far been generated with legacy bioanalytical methods which have more recently been superseded by new methods to comply with updated regulatory standards. As the safety and efficacy of CZP in adults with RA have been extensively studied and established, this Phase 1B study is focused on acquiring PK data in CZP-naive participants who receive CZP at the marketed dose within the study, and are prescribed CZP at the licensed dose (per US Prescribing Information) as part of the therapeutic management of their RA disease, using a PK or ADA electrochemiluminescent immuno-assay (ECLIA). This study is being undertaken in support of the polyarticular juvenile idiopathic arthritis (pJIA) Pediatric Research Equity Act (PREA) requirement for Cimzia.

Objectives and Endpoints

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

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

Overall Design

This is a multi-center, open-label Phase 1B study to assess the PK, safety, and tolerability of CZP in adults with active RA. In this 24-week study, study participants (ie, male or female participants 18 to 69 years of age inclusive) who are naïve to CZP and are eligible to receive a biologic for RA will receive CZP in subcutaneous (sc) loading doses at Weeks 0, 2, and 4, followed by a treatment of 200mg every 2 weeks (Q2W), with the final dose taking place at Week 24.

Number of Participants

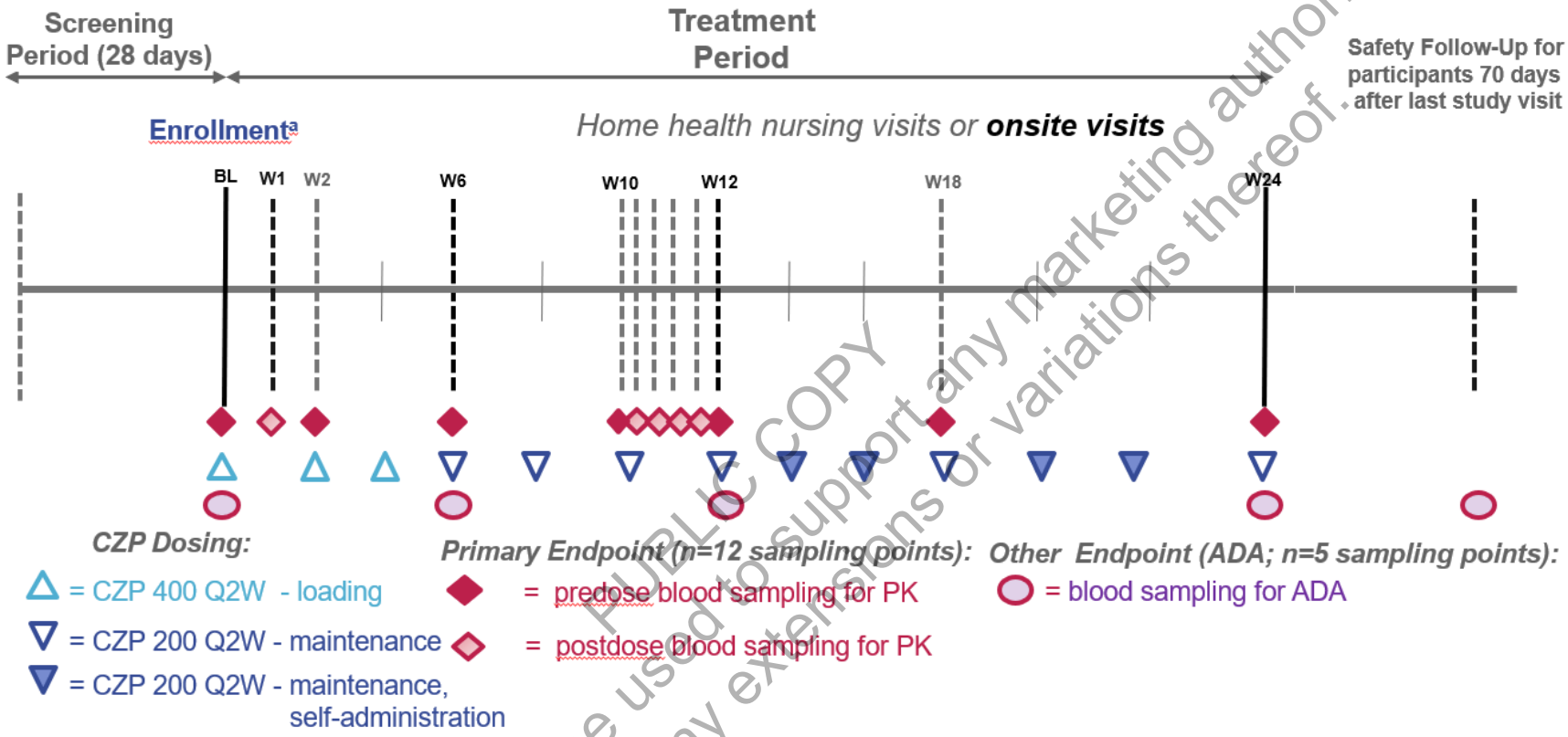
A total of 30 participants will be enrolled to receive CZP, such that a minimum of 25 evaluable participants are expected to complete Visit 13 (Week 12).

Treatment Groups and Duration

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

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

1.2 Schema



ADA=antidrug antibody; BL=Baseline; CZP=certolizumab pegol; PK=pharmacokinetic; Q2W=every 2 weeks; W=week

[a] CZP naïve at enrollment.

1.3 Schedule of Activities

	Screening	Baseline	Treatment Period													SFU/ EDV
									PK profile							
	V1	V2	V3	V4	V5	V6	V7	V8	V9	V10	V11	V12	V13	V14	V15	V16
Procedure	D-28/ W-4	D0	D7/ W1	D14/ W2	D28/ W4	D42/ W6	D56/ W8	D70/ W10	D72 W10	D75 W10	D77/ W11	D80/ W11	D84/ W12	D126/ W18	D168/ W24	70 days after last IMP
Visit window [a]			±1 day	±1 day	±2 days	±2 days	±2 day	±1 day	±6 hrs	±6 hrs	±6 hrs	±6 hrs	±6 hrs	±2 days	±2 days	±7 day
Location [b]	Clinic	Clinic	Clinic	Home	Home	Clinic	Home	Home	Home	Home	Home	Home	Clinic	Home	Clinic	Clinic
Informed consent	X															
Study participant card	X															
Verification of inclusion/exclusion criteria	X															
Demography	X															
General medical/procedure history	X															
Physical examination	X															X
Body weight/height	X															
Vital signs	X															X
Pregnancy test [c]	X												X			X
Laboratory assessments	X												X			X
12-lead ECG [d]	X															
TB questionnaire	X												X		X	

	Screening	Baseline	Treatment Period													SFU/ EDV
									PK profile							
	V1	V2	V3	V4	V5	V6	V7	V8	V9	V10	V11	V12	V13	V14	V15	V16
Procedure	**D-28/ W-4**	**D0**	**D7/ W1**	**D14/ W2**	**D28/ W4**	**D42/ W6**	**D56/ W8**	**D70/ W10**	**D72 W10**	**D75 W10**	**D77/ W11**	**D80/ W11**	**D84/ W12**	**D126/ W18**	**D168/ W24**	**70 days after last IMP**
Visit window [a]			**±1 day**	**±1 day**	**±2 days**	**±2 days**	**±2 day**	**±1 day**	**±6 hrs**	**±6 hrs**	**±6 hrs**	**±6 hrs**	**±6 hrs**	**±2 days**	**±2 days**	**±7 day**
Location [b]	Clinic	Clinic	Clinic	Home	Home	Clinic	Home	Home	Home	Home	Home	Home	Clinic	Home	Clinic	Clinic
TB screening (IGRA)	X															
Adverse event review	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Prior and Concomitant medication review	X	X	X	X	X	X	X	X					X		X	X
IMP administration [e]		X (site)		X (nurse)	X (nurse)	X (site)	X (nurse)	X (nurse)					X (site)	X (nurse or self)	X (site)	
IMP dispensing/ IXRS		X				X							X			
IMP return						X							X		X	
CZP plasma concentration [f, g]		X	X	X		X		X	X	X	X	X	X	X	X	
Anti-CZP antibody sampling [f]		X				X							X		X	X
RAPID3 testing [f]		X											X			

CZP=certolizumab pegol; D=day; ECG=electrocardiogram; EDV=Early Discontinuation Visit; hrs=hours; IGRA=Interferon-gamma release assay; IMP=investigational medicinal product; Q2W=every 2 weeks; PK=pharmacokinetic(s); RAPID3=Routine Assessment of Patient Index Data; SFU=Safety Follow-up; TB=tuberculosis; V=Visit; W=week

[a] Visit days may take place within a window relative to the Visit Day.

[b] Home Visits may occur at the clinic/site rather than at home per study participant preference. Assessments at Home Visits will be conducted by the Home Visit nurse.

[c] In WOCBP, at Screening, a serum pregnancy test will be performed; for subsequent visits, urine pregnancy tests will be performed according the to Schedule of Activities.

[d] All ECG recordings should be taken with the study participant resting in the supine position for at least 5 minutes before the recording.

[e] Loading doses of 400mg CZP will be administered at Weeks 0, 2, and 4, followed by treatment with 200mg Q2W. Study participants will have the option to self-inject IMP at home on Weeks 14, 16, 20, and 22.
[f] At Visits in which dosing will take place, all activities should take place prior to IMP administration (including PK collection).
[g] PK profile samples to be collected at 2 (Visit 9), 5 (Visit 10), 7 (Visit 11) and 10 (Visit 12) days post-Week 10 IMP administration.

2 INTRODUCTION

2.1 Study rationale

Certolizumab pegol (CZP) was approved for adults with rheumatoid arthritis (RA) in the United States (US) in May 2009. Certolizumab pegol pharmacokinetic (PK) and antidrug antibody (ADA) data in the adult RA population has thus far been generated with legacy bioanalytical methods which have more recently been superseded by new methods to comply with updated regulatory standards. Since the change in bioanalytical methods, no PK and ADA data have been generated for CZP in adults with RA. Further, there is no mathematical concordance between the previous and current (ECLIA) bioanalytical assays for CZP to enable bridging of PK data from one method to the other.

The polyarticular juvenile idiopathic arthritis (pJIA) development program for CZP, to be based on ECLIA-generated PK data, is reliant on comparative CZP PK data from adults with RA. This study is being undertaken in order to generate this latter ECLIA-based adult PK data. As the safety and efficacy of CZP in adults with RA have been extensively established, this Phase 1B study is focused solely on acquiring ECLIA-based CZP PK data in CZP-naive participants who are eligible to receive a biologic for management of their RA disease.

2.2 Background

2.2.1 Rheumatoid arthritis

Rheumatoid arthritis is a chronic, systemic, autoimmune disease with peripheral synovitis as its primary manifestation. Untreated, RA can lead to destruction, deformation, and dysfunction of affected joints which, in turn, may contribute to significant morbidity and increased mortality (Jacobsson et al, 2007). Moderate-to-severe RA is usually, if not always, treated with disease modifying antirheumatic drug (DMARDs), with methotrexate (MTX) being the agent most commonly used. For patients with an inadequate response to conventional DMARDs, biologic agents which inhibit tumor necrosis factor alpha (TNFα) (known as TNFα blockers), especially in combination with MTX, have been employed (Smolen et al, 2009).

2.2.2 Certolizumab pegol

Certolizumab pegol (CZP) is a recombinant, humanized, monoclonal, antigen-binding prime antibody fragment (Fab'), with specificity for human TNFα, which is conjugated to polyethylene glycol (PEG). Certolizumab pegol has been studied for the treatment of inflammatory diseases, such as Crohn's disease (CD; including pediatric CD), rheumatoid arthritis (RA), psoriatic arthritis, axial spondyloarthritis (including ankylosing spondylitis and nonradiographic axial spondyloarthritis), pJIA, and psoriasis.

Certolizumab pegol was first approved for adults with Crohn's disease in the US in 2008 and for RA in 2009; it is available commercially in the US, EU, and approximately 64 other countries worldwide for the treatment of moderately to severely active RA in adults. Its safety and tolerability have been extensively studied and are detailed within the US Prescribing Information for health care professionals.

Additional information on the nonclinical and clinical data for CZP is also available in the current version of the CZP Investigator's Brochure.

2.3 Benefit/Risk assessment

Adult study participants, naive to CZP, will receive loading doses of 400mg CZP at Weeks 0, 2, and 4, followed by treatment with 200mg every 2 weeks (Q2W), with the final dose taking place at Week 24. This CZP dosing regimen has been approved for use in the US in adults with moderately to severely active RA.

The risks of the present study are essentially those of experiencing an adverse event (AE) following administration of CZP and for progressive disability if the study participant does not respond to CZP. As a therapeutic class, currently available TNFα-inhibitors are known to be associated with serious infections, particularly reactivation of tuberculosis (TB) and opportunistic fungal infections. An association has also been reported with TNFα-inhibitor therapy and the development of malignancies including lymphoma and leukemia, Merkel Cell carcinoma, T-cell lymphoma, and melanoma, although it is not clear whether there is a causal relationship, as confounding factors exist (eg, the increased risk of lymphoma and leukemia associated with autoimmune diseases and immunosuppression). Other serious adverse events (SAEs) that have been reported in participants treated with currently available TNFα-inhibitors, including CZP, include moderate-to-severe congestive heart failure, hypersensitivity reactions including anaphylaxis, new-onset psoriasis, demyelinating disorders, blood dyscrasias including aplastic anemia, immunogenicity including sarcoidosis, lupus, lupus-like illness, and hepatobiliary events. The additional risks to participants due to participation in the study will be nominal (eg, possible complications associated with collection of blood samples and collection of participant data).

For a full list of potential AEs please refer to the Cimzia US Prescribing Information.

3 OBJECTIVES AND ENDPOINTS

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

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

4 STUDY DESIGN

4.1 Overall design

This is a multi-center, open-label Phase 1B study to assess the PK, safety, and tolerability of CZP in adults with active RA. In this 24-week study, study participants who are naïve to CZP and have not previously failed to respond to treatment with ≥1 TNFα inhibitor will receive CZP in subcutaneous loading doses of 400 mg at Weeks 0, 2, and 4, followed by a treatment of 200mg Q2W, with the final dose taking place at Week 24.

A total of 30 study participants will be enrolled and will receive CZP. Study participants may be taking concomitant MTX; however, a minimum of 8 study participants must be enrolled who are not on concurrent administration of MTX.

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

A schematic of the study design is presented in Section 1.2 and the Schedule of Activities for the study is presented in Section 1.3.

4.2 Scientific rationale for study design

This study is being undertaken in support of the pJIA Pediatric Research Equity Act (PREA) requirement for Cimzia in pJIA.

Through extensive interactions between the Food and Drug Administration and external experts, culminating in a collaborative workshop in October 2019 entitled “Accelerating Drug Development for polyarticular Juvenile Idiopathic Arthritis (pJIA)”, a therapeutic bridging approach from RA to pJIA has been derived for TNF-α inhibitors based on the relationship between RA and pJIA and the extensive knowledge of TNF-α inhibitors as therapeutic agents. This approach (based on "Pharmacokinetic (PK) matching") directs that the therapeutic effect of TNF-α inhibitors (such as CZP) in pJIA patients can be expected if the pediatric systemic exposure for the drug is within the therapeutic range for adult RA patients.

Central to application of this approach is the existence of a reference systemic exposure (PK) range which is associated with therapeutic benefit of the drug in adult RA population. Although CZP has been approved in the US for RA in adults since May 2009, CZP PK and ADA data in the adult RA population have thus far been generated with legacy bioanalytical methods, which have more recently been superseded by new methods (namely, ECLIA) to comply with updated regulatory standards. Since the change in bioanalytical methods, no PK and ADA data have been generated for CZP in adults with RA. Further, there is no mathematical concordance between the previous and current (ECLIA) bioanalytical assays for CZP to enable bridging of PK data from one method to the other.

The pJIA development program for CZP, to be based on ECLIA-generated PK data, is reliant on comparative CZP PK data from adults with RA. Thus, a supporting adult reference PK dataset for "PK matching" in the pJIA program will also need to be based on data generated with the ECLIA method. At present, such ECLIA-based PK data for CZP in the adult RA population are not available. Accordingly, this study is being undertaken in order to generate ECLIA-based CZP PK data for CZP in adults with RA. As the safety and efficacy of CZP in adults with RA have been extensively established, this Phase 1B study is focused solely on acquiring ECLIA-based CZP PK data in CZP-naive participants who are eligible to receive a biologic for management of their RA disease.

4.3 Justification for dose

The commercially approved dosing regimen for adult patients with RA (loading doses of 400mg at Weeks 0, 2, and 4 then 200 mg Q2W) will be used for the duration of the study. This CZP dosing regimen has been approved for use in the US in adults with moderately to severely active RA.

4.4 End of study definition

A participant is considered to have completed the study if he/she has completed all portions (Screening, Baseline Visit, Treatment Period [through Week 24], and SFU) of the study.

Following investigational medicinal product (IMP) administration at Week 24, participants may transition to treatment with commercial CZP in consultation with their health care professional. The SFU Visit will be conducted 70 days post last administration of IMP.

The end of the study is defined as the date of the last visit of the last participant in the study.

5 STUDY POPULATION

Prospective approval of protocol deviations to recruitment and enrollment criteria, also known as protocol waivers or exemptions, are not permitted.

5.1 Inclusion criteria

Participants are eligible to be included in the study only if all of the following criteria apply:

Age

1. Participant must be 18 to 69 years of age inclusive, at the time of signing the informed consent.

Type of participant and disease characteristics

2. Participant must have a diagnosis of moderately-to-severely active RA.
3. Participant must have had an inadequate response to, or intolerance to, at least 1 DMARD (nonbiologic or biologic). For example, the study participant had prior inadequate response to MTX (based on the Investigator's clinical judgment).
4. Participant has a negative interferon-gamma release assay (IGRA) at Screening.

Weight

5. Participant has a body mass index within the range 18.0kg/m^2 to 35.0kg/m^2 (inclusive).

Sex

6. Male or female
   - A female participant is eligible to participate if:
     - she is not pregnant (see Appendix 4 [Section 10.4]),
     - not breastfeeding,
     - at least one of the following conditions applies:
       (1) Not a woman of childbearing potential (WOCBP) as defined in Appendix 4 OR
       (2) A WOCBP who agrees to follow the contraceptive guidance in Appendix 4 during the Treatment Period and until the SFU Visit.

Informed consent

7. The participant is capable of giving signed informed consent as described in Appendix 1 (Section 10.1) which includes compliance with the requirements and restrictions listed in the Informed Consent Form (ICF) and in this protocol.

5.2 Exclusion criteria

Participants are excluded from the study if any of the following criteria apply:

Medical conditions

1. Participant has any medical or psychiatric condition (including clinically significant laboratory abnormalities) that, in the opinion of the Investigator, could jeopardize or would compromise the study participant's ability to participate in this study.
2. Participant has a known hypersensitivity to any components of the study medication (including PEG) or comparative drugs (and/or an investigational device) as stated in this protocol.
3. Participant with known concurrent viral hepatitis or known positivity for hepatitis B surface antigen or hepatitis C virus (HCV) antibody or known human immunodeficiency virus (HIV) infection. At Screening, a hepatitis panel result that indicates immunity due to hepatitis B vaccination is not considered an exclusion criterion. At Screening, a participant may not have any of the following:
   - Hepatitis B surface antigen, hepatitis B core antibody, hepatitis B virus deoxyribonucleic acid (DNA) assay: Positive to any of these.
   - HCV antibody: Positive.
   - HIV antigen or antibody: Positive to either test.
4. Participant with a history of chronic or recurrent infections, or recent serious or life-threatening infection within the 6 months prior to the Baseline Visit (including hospitalization for any infection in the last 6 months or any current sign or symptom that may indicate an infection).
5. Participant has known TB infection, is at high risk of acquiring TB infection, has latent TB infection, or has current or history of nontuberculous mycobacterial (NTMB) infection.
   - Known active TB disease
   - History of active TB involving any organ system unless adequately treated according to World Health Organization/Centers for Disease Control therapeutic guidance and proven to be fully recovered upon consult with a TB specialist
   - Latent tuberculosis infection (unless appropriate prophylaxis is initiated at least 4 weeks prior to IMP dosing and will be continued to completion of prophylaxis). Prophylaxis should be in accordance with applicable clinical guidelines and TB specialist judgment based on the origin of the infection.
   - High risk of acquiring TB infection.
   - Current NTMB infection or history of NTMB infection unless proven to be fully recovered

   Nontuberculous mycobacterial infection is defined as a group of lung infections caused by mycobacteria different from mycobacterium TB infections.

For further information relating to definitions of known active TB, past history of TB, latent TB infection, high risk of acquiring TB infection, and NTMB infection, refer to Section 8.2.5.

6. Participant has active neoplastic disease or a history of neoplastic disease within 5 years of enrollment (except for basal or squamous cell carcinoma of the skin or carcinoma in situ which has been definitively treated with standard of care approaches).
7. Participant has concomitant diagnosis of any other inflammatory condition (eg, psoriatic arthritis, sarcoidosis, or systemic lupus erythematosus).
8. Participant has clinically significant electrocardiogram (ECG) abnormalities at Screening.

Prior/Concomitant therapy

9. Participant has previously been exposed to CZP.
10. Participant is a primary failure to at least 1 TNFα inhibitor (a primary failure is defined as no clinical disease improvement within the first 12 weeks of treatment). Study participants who demonstrated clinical response within 12 weeks of treatment and subsequently lost response after 12 weeks of treatment are eligible.
11. Participant has received a live vaccination within 6 weeks prior to Screening or intends to have a live vaccination during the course of the study or within 3 months following CZP treatment in the study.

Prior/Concurrent clinical study experience

12. Participant has received any investigational drug or experimental procedure within 90 days prior to the first dose of IMP.

Diagnostic assessments

13. Participant has a laboratory abnormality at Screening, including any of the following:
    - >3.0x upper limit of normal (ULN) of any of the following: alanine aminotransferase (ALT), aspartate aminotransferase (AST), alkaline phosphatase (ALP); or >ULN total bilirubin (>1.5xULN total bilirubin if the participant has a documented pre-study diagnosis of Gilbert's syndrome).
    - white blood cell count $<3.00x10^3/\mu L$.
    - absolute neutrophil count (ANC) $<1.5x10^3/\mu L$.
    - lymphocyte count <500 cells/µL.
    - hemoglobin <8.5g/dL.
    - Any other laboratory abnormality, which, in the opinion of the Investigator, will prevent the study participant from completing the study or will interfere with the interpretation of the study results.

5.3 Lifestyle restrictions

5.3.1 Meals and dietary restrictions

No meal or dietary restrictions are required during this study.

5.3.2 Caffeine, alcohol, and tobacco

No caffeine, alcohol, and tobacco restrictions are required during this study; any restrictions (for the purposes of routine clinical management) are left to the judgment of the Investigator.

5.3.3 Activity

No activity restrictions are required during this study.

5.4 Screen failures

Screen failures are defined as participants who consent to participate in the clinical study but are not subsequently entered in the study. A minimal set of screen failure information is required to ensure transparent reporting of screen failure participants to meet the Consolidated Standards of Reporting Trials (CONSORT) publishing requirements and to respond to queries from regulatory authorities. Minimal information includes demography, screen failure details, eligibility criteria, and any SAE.

Individuals who do not meet the criteria for participation in this study (screen failure) may be rescreened.

Tests that result in ALT, AST, or ALP up to 25% above the exclusion limit may be repeated only once for confirmation. This one-time repeat testing may be within the initial screening window or as part of a rescreening following a screen failure. Upon retesting, study participants whose results remain outside the exclusion limit are not to be enrolled.

6 STUDY TREATMENTS

Study treatment is defined as any investigational treatment(s), marketed product(s), placebo, or medical device(s) intended to be administered to a study participant according to the study protocol.

6.1 Treatments administered

Certolizumab pegol is an engineered, humanized, monoclonal antibody Fab' fragment with specificity for human TNFα, produced in an *Escherichia coli* expression system. The antibody fragment is subsequently purified and conjugated with high molecular weight PEG (40kDa).

Intervention name	CZP
Type	Biologic
Dose formulation	Pre-filled syringe (1mL)
Unit dose strength(s)	200mg/mL
Dosage levels	400mg loading dose for first 3 doses (at Weeks 0, 2, and 4), followed by 200mg Q2W maintenance dose thereafter
Route of administration	sc injection
Use	Experimental
Sourcing	Provided by UCB Clinical Trial Supply or designee
Packaging and labeling	The study medication is packaged according to GMP guidelines and applicable laws or regulations; study medication is labeled in accordance with current ICH, GCP, and GMP and includes any locally required statements.
Current/Former names	CDP870, Cimzia, CZP

CZP=certolizumab pegol; GCP=Good Clinical Practice; GMP=Good Manufacturing Practice; ICH=International Council for Harmonisation; Q2W=every 2 weeks; sc=subcutaneous

6.2 Preparation, handling, storage, and accountability requirements

The Investigator or designee must confirm appropriate temperature conditions have been maintained during transit for all study treatment received and any discrepancies reported and resolved before use of the study treatment.

Only participants enrolled in the study may receive study treatment and only authorized site staff and home health nurses may supply and administer study treatment prior to Week 12. After Week 12, study participants will have the choice to self-administer CZP or receive treatment at the clinic/study site. All study treatments must be stored in a secure, environmentally-controlled, and monitored (manual or automated) area in accordance with the labeled storage conditions with access limited to the Investigator and authorized site staff.

The Investigator, institution, or the head of the medical institution (where applicable) is responsible for study treatment accountability, reconciliation, and record maintenance (ie, receipt, reconciliation, and final disposition records).

In case an out-of-range temperature is noted, it must be immediately reported as per instructions contained in the IMP Handling Manual.

The Investigator (or designee) will instruct the participant to store the study medication following the instructions on the label.

Further guidance and information for the final disposition of unused study treatment are provided in the Study Reference Manual.

6.2.1 Drug accountability

The Case Report Form (CRF) will be used to record study medication dispensing and return information on a by-participant basis and will serve as source documentation during the course of the study. Details of any study medication lost, damaged (due to breakage or wastage), not used, partially used, disposed of 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 containers of study medication 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 Investigator must ensure that the study medication is used only in accordance with this protocol.

Periodically, and/or after completion of the clinical phase of the study, all used (including empty containers)/partially used, unused, damaged, and/or expired study medication must be reconciled and either destroyed at the site according to local laws, regulations, and UCB Standard Operating Procedures or returned to UCB (or designee). Investigational medicinal product intended for the study cannot be used for any other purpose than that described in this protocol.

6.3 Measures to minimize bias: randomization and blinding

This is an open-label study.

6.4 Treatment compliance

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

6.5 Concomitant medication(s)/treatment(s)

6.5.1 Permitted concomitant treatments (medications and therapies)

The following concomitant medications are permitted during the study:

- Methotrexate, under the following conditions:
  - Participant must have been stable for at least 1 month before Screening.
  - The participant's route of MTX administration and dose of MTX should not change until after Week 12 of the study.
  - The (minimum of) 8 participants who are not taking MTX upon study entry cannot begin MTX until after Week 12 of the Treatment Period.
  - Dose reductions are permitted at any point during the study for safety reasons.

Other medications not explicitly prohibited per Section 6.5.2 are also included as permitted concomitant treatments.

6.5.2 Prohibited concomitant treatments (medications and therapies)

The following concomitant medications are prohibited during the study:

- Conventional synthetic DMARDs (csDMARDs) other than MTX (see Section 6.5.1 for MTX parameters).
- Targeted synthetic DMARDs (tsDMARDs), eg, the Janus kinase inhibitor, tofacitinib.
- Biologic DMARDs (CZP study medication excepted).
- Any experimental (biological or nonbiological) therapy (within or outside a clinical study).
- Live and live attenuated vaccinations including, but not limited to, oral polio, chicken pox (varicella), measles-mumps-rubella, nasal influenza, and rotavirus. No data are available on the response to live vaccinations or the secondary transmission of infection by live vaccines in study participants receiving CZP.

6.5.3 Rescue medication

The Sponsor will not supply rescue medications. Such medicines should be sourced/prescribed locally by the treating physician. The following rescue medications may be used:

- Any RA rescue medications available, excluding biologic DMARDs (CZP study medication excepted), csDMARDs other than MTX (see Section 6.5.1), and tsDMARDs. Any participants who use a biologic DMARD (other than study medication), csDMARD other than MTX (as per Section 6.5.1), or tsDMARD should be immediately withdrawn from the study.

The date and time of rescue medication administration as well as the name and dosage regimen of the rescue medication must be recorded.

If the study participant requires administration of a biologic DMARD, csDMARD other than MTX (as per Section 6.5.1), or tsDMARD, they must be removed from the study (Section 7.2).

6.6 Dose modification

No dose modifications of the IMP will be allowed in this study, outside the transition from the loading doses to the maintenance dose (Section 6.1).

6.6.1 Dose interruptions

Dose interruptions may only take place due to safety concerns. Participants who have a dose interruption will be followed according to the Schedule of Activities (Section 1.3).

6.7 Criteria for study hold or dosing stoppage

As this is a study of an approved therapeutic for an approved indication, there are no anticipated study hold or dosing stoppage criteria planned.

6.8 Treatment after the end of the study

Study participants may transition to treatment with commercially-available CZP in consultation with their health care professional following completion of the last administration of IMP.

7 DISCONTINUATION OF STUDY MEDICATION AND PARTICIPANT DISCONTINUATION/WITHDRAWAL

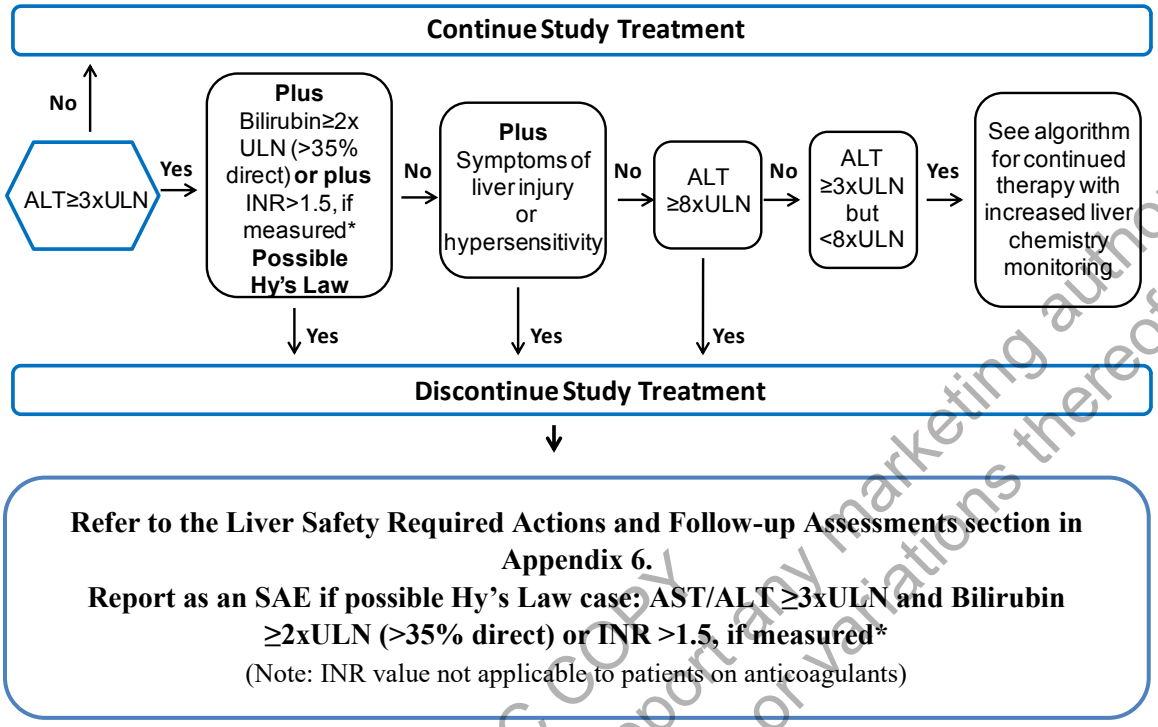
7.1 Discontinuation of study medication

7.1.1 Liver chemistry stopping criteria

Discontinuation of study treatment for abnormal liver function should be considered by the Investigator when a participant meets one of the conditions outlined in Figure 7-1 or if the Investigator believes that it is in best interest of the participant.

Study medication will be discontinued immediately and permanently for a participant if liver chemistry stopping criteria are met.

Figure 7-1: Liver Chemistry Stopping Criteria and Increased Monitoring Algorithm



Abbreviations: ALT=alanine transaminase; AST=aspartate aminotransferase; INR=international normalized ratio; SAE=serious adverse event; ULN=upper limit of normal

Liver Safety: Suggested Actions and Follow-up Assessments can be found in Appendix 6 (Section 10.6).

7.2 Participant Discontinuation/Withdrawal from the study

Participants are free to withdraw from the study at any time, without prejudice to their continued care.

A participant may withdraw from the study at any time at his/her own request, or may be withdrawn at any time at the discretion of the Investigator for safety, behavioral, compliance, or administrative reasons.

If the participant withdraws consent for disclosure of future information, the Sponsor may retain and continue to use any data collected before such a withdrawal of consent.

If a participant withdraws from the study, he/she may request destruction of any samples taken and not tested, and the Investigator must document this in the site study records.

See the Schedule of Activities (Section 1.3) for data to be collected at the time of study discontinuation and follow-up and for any further evaluations that need to be completed.

Participants should be withdrawn from the study if any of the following events occur:

1. Participant develops an illness that would interfere with his/her continued participation.
2. Participant is noncompliant with the study procedures or medications in the opinion of the Investigator.
3. Participant takes prohibited concomitant medications as defined in this protocol.
4. Participant may withdrawal at any time due to lack of efficacy. At study discontinuation, the participant may be offered other treatment options, at the Investigator's discretion.
5. Participant withdraws his/her consent.
6. Participant has confirmation of a pregnancy during the study, as evidenced by a positive pregnancy test.
7. The Sponsor or a regulatory agency requests withdrawal of the participant.

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

7.3 Lost to follow-up

A participant will be considered lost to follow-up if he or she repeatedly fails to return for scheduled visits and is unable to be contacted by the study site.

The following actions must be taken if a participant fails to return to the clinic for a required study visit:

- The site must attempt to contact the participant and reschedule the missed visit as soon as possible and counsel the participant on the importance of maintaining the assigned visit schedule and ascertain whether or not the participant wishes to and/or should continue in the study.
- Before a participant is deemed lost to follow-up, the Investigator or designee must make every effort to regain contact with the participant (at least 1 phone call and 1 written message to the participant), 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 participant, must be recorded in the source documents. The CRF must document the primary reason for withdrawal.

Should the participant continue to be unreachable, he/she will be considered to have withdrawn from the study with a primary reason of lost to follow-up documented in the CRF.

8 STUDY ASSESSMENTS AND PROCEDURES

Study procedures and their timing are summarized in the Schedule of Activities (Section 1.3).

Protocol waivers or exemptions are not allowed. Immediate safety concerns should be discussed with the Sponsor immediately upon occurrence or awareness to determine if the participant should continue or discontinue study treatment.

Adherence to the study design requirements, including those specified in the Schedule of Activities (Section 1.3), is essential and required for study conduct. All Screening evaluations

must be completed and reviewed to confirm that potential participants meet all eligibility criteria. The Investigator will maintain a screening log to record details of all participants screened and to confirm eligibility or record reasons for screening failure, as applicable.

Procedures conducted as part of the participant's routine clinical management (eg, blood count) and obtained before signing of the ICF may be utilized for Screening or Baseline purposes provided the procedures met the protocol-specified criteria and were performed within the time frame defined in the Schedule of Activities (Section 1.3).

The maximum amount of blood collected from each participant over the duration of the study, including any extra assessments that may be required, will not exceed 100mL. Repeat or unscheduled samples may be taken for safety reasons or for technical issues with the samples.

8.1 Efficacy assessments

8.1.1 Multi-dimensional Health Assessment Questionnaire (MDHAQ) and RAPID3 scoring

The MDHAQ items that make up the Routine Assessment of Patient Index Data 3 RAPID3 (Appendix 12 [Section 10.12]) will be assessed at Baseline and Week 12 as indicated in the Schedule of Activities (Section 1.3). The MDHAQ is derived from the HAQ, and the sections that will be utilized are the following:

- MDHAQ-FN : Physical function listed in 10 activities; converted to a scale from 0 to 10 for the RAPID3 score
- MDHAQ-PN : Pain assessed as 0.5 increments from 0 to 10
- MDHAQ-PTGL : Patient's global status assessed as 0.5 increments from 0 to 10

RAPID3 is calculated as the sum (0 to 30) of FN, PN, and PTGL.

8.2 Safety assessments

Planned time points for all safety assessments are provided in the Schedule of Activities (Section 1.3).

8.2.1 Physical examination

A complete physical examination will include, at a minimum, vital signs; general appearance; ear, nose, and throat; eyes, hair, and skin; and assessments of the Cardiovascular, Respiratory, Gastrointestinal Neurological, Musculoskeletal, and Hepatic systems. Height and weight will also be measured and recorded.

Investigators should pay special attention to clinical signs related to previous serious illnesses.

Clinically relevant findings or worsening of previous findings will be recorded as AEs.

8.2.2 Vital signs

Oral temperature, pulse rate, respiratory rate, and blood pressure will be measured as described in the Schedule of Activities (Section 1.3).

8.2.3 Electrocardiograms

Single 12-lead ECG will be obtained as outlined in the Schedule of Activities (see Section 1.3) using an ECG machine that automatically calculates heart rate and measures PR, QRS, QT, and QTc intervals.

All ECG recordings should be taken with the study participant resting in the supine position for at least 5 minutes before the recording.

8.2.4 Clinical safety laboratory assessments

See Appendix 2 (Section 10.2) for the list of clinical laboratory tests to be performed and to the Schedule of Activities (Section 1.3) for the timing and frequency.

The Investigator must review the laboratory report, document this review, and record any clinically relevant changes occurring during the study in the AE section of the CRF. The laboratory reports must be filed with the source documents. Clinically significant abnormal laboratory findings are those which are not associated with the underlying disease, unless judged by the Investigator to be more severe than expected for the participant's condition.

All laboratory tests with values considered to be clinically significantly abnormal during participation in the study should be repeated until the values return to normal or Baseline or are no longer considered clinically significant by the Investigator or Medical Monitor.

If such values do not return to normal/baseline within a period of time judged reasonable by the Investigator, the etiology should be identified and the Sponsor notified.

All protocol-required laboratory assessments, as defined in Appendix 2 (Section 10.2), must be conducted in accordance with the laboratory manual and the Schedule of Activities (Section 1.3).

If laboratory values from non-protocol specified laboratory assessments performed at the institution’s local laboratory require a change in participant management or are considered clinically significant by the Investigator (eg, SAE or AE or dose modification), then the results must be recorded in the CRF.

8.2.5 Tuberculosis assessment

The Investigator should consider all potential sites of infection when assessing for TB during the physical examination and other evaluations, and based on the study participant’s medical or social history.

8.3 Adverse events and serious adverse events

The definitions of AEs and SAEs are provided in Appendix 3 (Section 10.3).

AE will be reported by the participant (or, when appropriate, by a caregiver, surrogate, or the participant's legally authorized representative).

The Investigator and any designees are responsible for detecting, documenting, and recording events that meet the definition of an AE or SAE and remain responsible for following up AEs that are serious, considered related to the study treatment or study procedures, or that caused the participant to discontinue the CZP (Section 7).

8.3.1 Time period and frequency for collecting AE and SAE information

All AEs and SAEs will be collected from the signing of the ICF until the SFU visit as specified in the Schedule of Activities (Section 1.3).

In order to ensure complete safety data collection, all AEs occurring during the study (ie, after the signing of the ICF), including any pretreatment and posttreatment periods required by the protocol, must be reported in the CRF even if no study medication 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.

All SAEs will be recorded and reported to the Sponsor or designee within 24 hours, as indicated in Appendix 3 (Section 10.3). The Investigator will submit any updated SAE data to the Sponsor within 24 hours of it being available.

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 study medication), up to 70 days from the end of the study for each participant, and to also inform participants of the need to inform the Investigator of any SAE within this period. Serious AEs that the Investigator thinks may be associated with the study medication must be reported to UCB regardless of the time between the event and the end of the study.

The method of recording, evaluating, and assessing causality of AE and SAE and the procedures for completing and transmitting SAE reports are provided in Appendix 3 (Section 10.3).

8.3.2 Method of detecting AEs and SAEs

Care will be taken not to introduce bias when detecting AEs and/or SAEs. Open-ended and non-leading verbal questioning of the participant is the preferred method to inquire about AE occurrences.

8.3.3 Follow-up of AEs and SAEs

After the initial AE/SAE report, the Investigator is required to proactively follow each participant at subsequent visits/contacts. All SAEs, and non-serious AEs of special interest (as defined in Section 8.3.6), will be followed until resolution, stabilization, the Investigator determines that it is no longer clinically significant, the event is otherwise explained, or the participant is lost to follow-up (as defined in Section 7.3). Further information on follow-up procedures is given in Appendix 3 (Section 10.3).

8.3.4 Regulatory reporting requirements for SAEs

Prompt notification by the Investigator to the Sponsor of an SAE is essential so that legal obligations and ethical responsibilities towards the safety of participants and the safety of a study treatment under clinical investigation are met.

The Sponsor has a legal responsibility to notify both the local regulatory authority and other regulatory agencies about the safety of a study treatment under clinical investigation. The Sponsor will comply with country-specific regulatory requirements relating to safety reporting to the regulatory authority, Institutional Review Boards (IRB)/Independent Ethics Committees (IEC), and Investigators.

Investigator safety reports must be prepared for suspected unexpected serious adverse reactions according to local regulatory requirements and Sponsor policy and forwarded to Investigators as necessary.

An Investigator who receives an Investigator safety report describing an SAE or other specific safety information (eg, summary or listing of SAEs) from the Sponsor will review and then file it along with the Investigator's Brochure and will notify the IRB/IEC, if appropriate according to local requirements.

8.3.5 Pregnancy

Details of all pregnancies in female participants and, if indicated, female partners of male participants will be collected after the start of study treatment and until SFU Visit.

If a pregnancy is reported, the Investigator must inform the Sponsor within 24 hours of learning of the pregnancy and should follow the procedures outlined in Appendix 4 (Section 10.4).

The participant should be withdrawn from the study as soon as pregnancy is known (by positive pregnancy test), and the following should be completed:

- The participant should immediately stop the intake of the study medication.
- The participant should return for an Early Discontinuation Visit.
- An SFU Visit should be scheduled 70 days after the participant has discontinued her study medication.
- The participant should complete a Pregnancy Outcome Form per UCB Standard Operating Procedures.

Abnormal pregnancy outcomes (eg, spontaneous abortion, fetal death, stillbirth, congenital anomalies, ectopic pregnancy) are considered SAEs.

8.3.6 Adverse events of special interest

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 CZP, the following events require immediate reporting (within 24 hours regardless of seriousness) to UCB:

- Hy's Law
  - Potential Hy's Law, defined as ≥3xULN ALT or AST with coexisting ≥2xULN total bilirubin in the absence of ≥2xULN ALP, with no alternative explanation for the biochemical abnormality (ie, without waiting for any additional etiologic investigations to have been concluded). Follow-up information should be reported if an alternative etiology is identified during investigation and monitoring of the participant.
- Serious infections, including opportunistic infections.
- Malignancies, including lymphoma.
- Congestive heart failure.
- Demyelinating-like disorders.

- Aplastic anemia, pancytopenia, thrombocytopenia, neutropenia, and leukopenia.
- Serious bleeding events.
- Lupus and lupus-like syndrome.
- Serious skin reactions (eg, Stevens-Johnson syndrome, toxic epidermal necrosis, and erythema multiforme).

8.3.7 Anticipated serious adverse events

The anticipated SAE in Table 8-1 is 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 8.3.4 and Appendix 3 (Section 10.3).

Table 8-1: Anticipated serious adverse event for RA population

Preferred term:	Rheumatoid arthritis

8.4 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 study medication so that Investigators, clinical study participants, 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 Patient Safety representative.

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

8.5 Treatment of overdose

Excessive dosing (beyond that prescribed in the protocol and including overdose) should be recorded in the Drug Accountability module of the CRF. 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).

UCB does not recommend specific treatment for an overdose. In the event of an overdose, the Investigator should:

1. Contact the Medical Monitor immediately.
2. Closely monitor the participant for any AE/SAE and laboratory abnormalities until CZP can no longer be detected systemically (at least 70 days).
3. Obtain a plasma sample for PK analysis within 70 days from the date of the last dose of study treatment if requested by the Medical Monitor (determined on a case-by-case basis).

4. Document the quantity of the excess dose as well as the duration of the overdose in the CRF.

Decisions regarding dose interruptions or modifications will be made by the Investigator in consultation with the Medical Monitor based on the clinical evaluation of the participant.

8.6 Pharmacokinetics

Pharmacokinetic samples will be tested using the ECLIA method. All PK assessments will be evaluated as described in the Schedule of Activities (Section 1.3).

Whole blood samples of approximately 5 mL will be collected for measurement of plasma concentrations of CZP as specified in the Schedule of Activities (Section 1.3). A maximum of 3 samples may be collected at additional time points during the study if warranted and agreed upon between the Investigator and the Sponsor. Instructions for the collection and handling of biological samples will be provided by the Sponsor. The actual date and time (24-hour clock time) of each sample will be recorded.

Samples will be used to evaluate the PK of CZP. Samples collected for analyses of CZP (plasma/serum/whole blood) concentration may also be used to evaluate safety or efficacy aspects related to concerns arising during or after the study.

Genetic analyses will not be performed on the plasma or whole blood samples.

8.7 Genetics

Genetics will not be evaluated in this study.

8.8 Pharmacodynamics

Pharmacodynamic parameters will not be evaluated in this study.

8.9 Biomarkers

Biomarkers will not be evaluated in this study.

8.9.1 Immunogenicity assessments

Immunogenicity samples will be tested using the ECLIA method. Antibodies to CZP will be evaluated in plasma samples collected from all participants according to the Schedule of Activities (Section 1.3). These samples will be tested by the Sponsor or Sponsor's designee.

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

8.10 Health economics or medical resource utilization and health economics

Health economics/medical resource utilization and health economics parameters are not evaluated in this study.

9 STATISTICAL CONSIDERATIONS

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

9.1 Definition of analysis sets

The following analysis sets will be used in the study:

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

9.2 General statistical considerations

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

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

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

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

9.3 Planned safety and other analyses

Safety will be assessed using the SS. Pharmacokinetics and immunogenicity will be assessed using the PKS.

All safety endpoints will be analyzed using descriptive statistics. Safety summaries will include presentations of AEs, laboratory values, and vital signs.

Adverse events will be coded according to the Medical Dictionary for Regulatory Activities. Treatment-emergent AEs will be defined as events that have a start date on or following the first administration of study treatment in RA0138 through the final administration of study treatment +70 days.

9.3.1 Other analyses

9.3.1.1 Pharmacokinetic analyses

Pharmacokinetic analysis will be performed on the PKS population.

Concentration-time profiles will be summarized by visit, and descriptive statistics performed, including: n, geometric mean, CV%, maximum, minimum, arithmetic mean, and standard deviation.

A PK analysis will be performed to derive noncompartmental CZP PK parameters (C_{min} and AUC) after their Week 10 dose. If needed, additional PK parameters may be derived based on the data. Further details of the analysis will be specified in the Statistical Analysis Plan.

9.3.1.2 Immunogenicity analyses

The incidence of immunogenicity will be summarized by body weight group and visit, as specified. Individual plots of the CZP concentrations, clinical response, and safety will be expressed by ADA titer category.

9.3.1.3 RAPID3 analysis

As this is a PK study, the RAPID3 assessment (utilizing the MDHAQ) is included to assist in clinical decision-making, and RAPID3 data will be listed (including change from Baseline) based on the SS population (Appendix 12 [Section 10.12]).

9.4 Handling of protocol deviations

Important protocol deviations are deviations from the protocol which potentially could have a meaningful impact on study conduct or on the primary efficacy, key safety, or PK outcomes for an individual study participant. The criteria for identifying important protocol deviations and the classification of important protocol deviations will be defined within the Important Protocol Deviations Template. To the extent feasible, 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 study participants.

All important protocol deviations will be listed by study participant.

9.5 Handling of dropouts or missing data

Missing or partial dates for safety evaluations will be imputed and full details of these algorithms will be presented in the Statistical Analysis Plan.

As discussed in Section 9.2, Baseline is defined as the last nonmissing pretreatment measurement. Therefore, data from the Screening Visit (if available) will be used as Baseline values, if data are missing at Week 0.

No further imputations of any other missing data are planned.

9.6 Planned interim analysis and data monitoring

No interim analysis or data monitoring is planned.

9.7 Determination of sample size

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

deviation of <16%). Participants who withdraw from the study may be replaced at the discretion of the Investigator and Sponsor, depending on the circumstances.

10 SUPPORTING DOCUMENTATION AND OPERATIONAL CONSIDERATIONS

10.1 Appendix 1: Regulatory, ethical, and study oversight considerations

10.1.1 Regulatory and ethical considerations

The study will be conducted under the auspices of an IRB/IEC, as defined in local regulations, International Council for Harmonisation (ICH)-Good Clinical Practice (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, ICF, Investigator's Brochure, Investigator's curriculum vitae (if applicable), advertisement (if applicable), and all other participant-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 participants or others, and any protocol deviations, to eliminate immediate hazards to participants.

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 participants. 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 participant 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.

10.1.2 Financial disclosure

Insurance coverage will be handled according to local requirements.

Finance and insurance are addressed in the Investigator and/or contract research organization agreements, as applicable.

10.1.3 Informed consent process

A participant'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 participant, in both oral and written form, by the Investigator (or designee). Each participant will have the opportunity to discuss the study and its alternatives with the Investigator.

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

If the ICF 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 ICF by the IRB/IEC and use of the amended form.

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

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

10.1.4 Data protection

UCB staff (or designee) will affirm and uphold the participant's confidentiality. Throughout this study, all data forwarded to UCB (or designee) will be identified only by the participant 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 participant'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 participant's study participation, and autopsy reports for deaths occurring during the study).

The participant must be informed that his/her personal study-related data will be used by the Sponsor in accordance with local data protection law. The level of disclosure must also be explained to the participant.

The participant must be informed that his/her medical records may be examined by Clinical Quality Assurance auditors or other authorized personnel appointed by the Sponsor, by appropriate IRB/IEC members, and by inspectors from regulatory authorities.

10.1.5 Committees structure

Not applicable.

10.1.6 Data quality assurance

All participant data relating to the study will be recorded on printed or electronic CRF unless transmitted to the Sponsor or designee electronically (eg, laboratory data). The Investigator is responsible for verifying that data entries are accurate and correct by physically or electronically signing the CRF.

The Investigator must maintain accurate documentation (source data) that supports the information entered in the CRF.

The Investigator must permit study-related monitoring, audits, IRB/IEC review, and regulatory agency inspections and provide direct access to source data documents.

The Sponsor or designee is responsible for the data management of this study including quality checking of the data.

Study monitors will perform ongoing source data verification to confirm that data entered into the CRF by authorized site personnel are accurate, legible, contemporaneous, original, and attributable from source documents; that the safety and rights of participants are being protected; and that the study is being conducted in accordance with the currently approved protocol and any other study agreements, ICH GCP, and all applicable regulatory requirements.

All essential documents must be retained by the Investigator for the minimum retention period mandatory under the applicable local laws and regulations. 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.

10.1.6.1 Case Report form completion

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

Any change or correction to the CRF 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 electronic CRF.

Detailed instructions will be provided in the CRF Completion Guidelines.

10.1.7 Source documents

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).

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, quality of life questionnaires, or video, 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 participant'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).

10.1.8 Study and Site Closure

The Sponsor designee reserves the right to close the study site or terminate the study at any time for any reason at the sole discretion of the Sponsor. Study sites will be closed upon study completion. A study site is considered closed when all required documents and study supplies have been collected and a study-site closure visit has been performed.

The Investigator may initiate study-site closure at any time, provided there is reasonable cause and sufficient notice is given in advance of the intended termination.

Reasons for the early closure of a study site by the Sponsor or Investigator may include, but are not limited to:

- Failure of the Investigator to comply with the protocol, requirements of the IRB/IEC or local health authorities, Sponsor's procedures, or GCP guidelines
- Inadequate recruitment of participants by the Investigator
- Discontinuation of further study medication development

10.1.9 Publication Policy

The results of this study may be published or presented at scientific meetings. If this is foreseen, the Investigator agrees to submit all manuscripts or abstracts to the Sponsor before submission. This allows the Sponsor to protect proprietary information and to provide comments.

The Sponsor will comply with the requirements for publication of study results. In accordance with standard editorial and ethical practice, the Sponsor will generally support publication of multicenter studies only in their entirety and not as individual site data. In this case, a coordinating Investigator will be designated by mutual agreement.

Authorship will be determined by mutual agreement and in line with International Committee of Medical Journal Editors authorship requirements.

10.2 Appendix 2: Clinical Laboratory Tests

- The tests detailed in the table below will be performed by the central laboratory (PK and ADA samples) or by the local laboratory (safety samples).
- Local laboratory results are only required in the event that the central laboratory results are not available in time for either study treatment administration and/or response evaluation. If a local sample is required, it is important that the sample for central analysis is obtained at the same time. Additionally, if the local laboratory results are used to make either a study treatment decision or response evaluation, the results must be entered into the CRF.
- Protocol-specific requirements for inclusion or exclusion of participants are detailed in Section 5.1 and Section 5.2 of the protocol.
- Additional tests may be performed at any time during the study as determined necessary by the Investigator or required by local regulations.

Protocol-Required Safety Laboratory Assessments

<table>
<tr><th>Laboratory Assessments</th><th colspan="4">Parameters</th></tr>
<tr><td>Hematology</td><td>Platelet Count
RBC Count
Hemoglobin
Hematocrit</td><td colspan="2">RBC Indices:
MCV
MCH
%Reticulocytes</td><td>WBC Count with Differential:
Neutrophils
Lymphocytes
Monocytes
Eosinophils
Basophils</td></tr>
<tr><td>Clinical Chemistry[a]</td><td>Blood Urea Nitrogen
Creatinine
Glucose (nonfasting)</td><td>Potassium
Sodium
Calcium</td><td>AST/ Serum glutamic-oxaloacetic transaminase
ALT/ Serum glutamic-pyruvic transaminase
ALP</td><td>Total and direct bilirubin
Total protein</td></tr>
<tr><td>Routine Urinalysis</td><td colspan="4">• pH, glucose, protein, blood, ketones, bilirubin, urobilinogen, nitrite, leukocyte esterase by dipstick</td></tr>
<tr><td>Other Screening Tests</td><td colspan="4">• Serum or urine alcohol and drug screen (to include at minimum: amphetamines, barbiturates, cocaine, opiates, cannabinoids and benzodiazepines)
• Serum or urine hCG pregnancy test (as needed for women of childbearing potential)[b]
All study-required laboratory assessments will be performed by a central laboratory, with the exception of the urine pregnancy test.

The results of each test must be entered into the CRF.</td></tr>
</table>

Laboratory Assessments	Parameters

ALP=alkaline phosphatase; ALT=alanine aminotransferase; AST=aspartate aminotransferase; eCRF=electronic Case Report form; hCG=human chorionic gonadotropin; HIV=human immunodeficiency virus; IEC=Independent Ethics Committee; INR=international normalized ratio; IRB=Institutional Review Board; LDH=lactate dehydrogenase; MCH=mean corpuscular hemoglobin; MCHC=mean corpuscular hemoglobin concentration; MCV=mean corpuscular volume; RBC=red blood cell; ULN=upper limit of normal; WBC=white blood cell

[a] Details of liver chemistry stopping criteria and required actions and follow-up assessments after liver stopping or monitoring events are given in Section 7.1.1 and Appendix 6 (Section 10.6). All events of ALT ≥3 ×upper limit of normal (ULN) and bilirubin ≥2 × ULN (>35% direct bilirubin) or ALT ≥3 × ULN and international normalized ratio (INR) >1.5, if INR measured, may indicate severe liver injury (possible Hy's Law) and must be reported as an SAE (excluding studies of hepatic impairment or cirrhosis).

[b] Local urine testing will be standard for the protocol unless serum testing is required by local regulation or IRB/IEC.

Investigators must document their review of each laboratory safety report.

10.3 Appendix 3: Adverse Events – Definitions and Procedures for Recording, Evaluating, Follow-up, and Reporting

Definition of AE

AE Definition
• An AE is any untoward medical occurrence in a patient or clinical study participant, temporally associated with the use of study medication, whether or not considered related to the study medication. • NOTE: An AE can therefore be any unfavorable and unintended sign (including an abnormal laboratory finding), symptom, or disease (new or exacerbated) temporally associated with the use of study medication.

Events Meeting the AE Definition
• Any abnormal laboratory test results (hematology, clinical chemistry, or urinalysis) or other safety assessments (eg, ECG, radiological scans, vital signs measurements), including those that worsen from baseline, considered clinically significant in the medical and scientific judgment of the Investigator (ie, not related to progression of underlying disease). • Exacerbation of a chronic or intermittent pre-existing condition including either an increase in frequency and/or intensity of the condition. • New conditions detected or diagnosed after study medication administration even though it may have been present before the start of the study. • Signs, symptoms, or the clinical sequelae of a suspected drug-drug interaction. • Signs, symptoms, or the clinical sequelae of a suspected overdose of either study medication or a concomitant medication. Overdose per se will not be reported as an AE/SAE unless it is an intentional overdose taken with possible suicidal/self-harming intent. Such overdoses should be reported regardless of sequelae. • The signs, symptoms, and/or clinical sequelae resulting from lack of efficacy will be reported as an AE or SAE if they fulfil the definition of an AE or SAE. Also, "lack of efficacy" or "failure of expected pharmacological action" also constitutes an AE or SAE.

Events NOT Meeting the AE Definition
• Any clinically significant abnormal laboratory findings or other abnormal safety assessments which are associated with the underlying disease, unless judged by the Investigator to be more severe than expected for the participant's condition. • The disease/disorder being studied or expected progression, signs, or symptoms of the disease/disorder being studied, unless more severe than expected for the study participant's condition. • Medical or surgical procedure (eg, endoscopy, appendectomy): the condition that leads to the procedure is the AE. • Situations in which an untoward medical occurrence did not occur (social and/or convenience admission to a hospital). • Anticipated day-to-day fluctuations of pre-existing disease(s) or condition(s) present or detected at the start of the study that do not worsen.

Definition of SAE

If an event is not an AE per definition above, then it cannot be an SAE even if serious conditions are met (eg, hospitalization for signs/symptoms of the disease under study, death due to progression of disease).

A SAE is defined as any untoward medical occurrence that, at any dose:
a. Results in death
b. Is life-threatening The term 'life-threatening' in the definition of 'serious' refers to an event in which the participant was at risk of death at the time of the event. It does not refer to an event, which hypothetically might have caused death, if it were more severe.
c. Requires inpatient hospitalization or prolongation of existing hospitalization In general, hospitalization signifies that the participant has been detained (usually involving at least an overnight stay) at the hospital or emergency ward for observation and/or treatment that would not have been appropriate in the physician's office or outpatient setting. Complications that occur during hospitalization are AEs. If a complication prolongs hospitalization or fulfils any other serious criteria, the event is serious. When in doubt as to whether "hospitalization" occurred or was necessary, the AE should be considered serious. Hospitalization for elective treatment of a pre-existing condition that did not worsen from baseline is not considered an AE.
d. Results in persistent disability/incapacity • The term disability means a substantial disruption of a person's ability to conduct normal life functions. • This definition is not intended to include experiences of relatively minor medical significance such as uncomplicated headache, nausea, vomiting, diarrhea, influenza, and accidental trauma (eg, sprained ankle) which may interfere with or prevent everyday life functions but do not constitute a substantial disruption.
e. Is a congenital anomaly/birth defect

f. Important medical events:

- Medical or scientific judgment should be exercised in deciding whether SAE reporting is appropriate in other situations such as important medical events that may not be immediately life-threatening or result in death or hospitalization but may jeopardize the participant or may require medical or surgical intervention to prevent one of the other outcomes listed in the above definition. These events should usually be considered serious.
- Examples of such events include, but are not limited to, potential Hy's law, invasive or malignant cancers, intensive treatment in an emergency room or at home for allergic bronchospasm, blood dyscrasias or convulsions that do not result in hospitalization, or development of drug dependency or drug abuse.

Recording and Follow-up of AE and/or SAE

AE and SAE Recording

- When an AE/SAE occurs, it is the responsibility of the Investigator to review all documentation (eg, hospital progress notes, laboratory reports, and diagnostics reports) related to the event.
- The Investigator will then record all relevant AE/SAE information in the CRF.
- It is **not** acceptable for the Investigator to send photocopies of the participant's medical records to UCB in lieu of completion of the AE/SAE CRF page.
- There may be instances when copies of medical records for certain cases are requested by UCB. In this case, all participant identifiers, with the exception of the participant number, will be redacted on the copies of the medical records before submission to UCB.
- The Investigator will attempt to establish a diagnosis of the event based on signs, symptoms, and/or other clinical information. Whenever possible, the diagnosis (not the individual signs/symptoms) will be documented as the AE/SAE.

Assessment of Intensity

The Investigator will make an assessment of intensity for each AE and SAE reported during the study and assign it to 1 of the following categories:

- Mild: An event that is easily tolerated by the participant, causing minimal discomfort and not interfering with everyday activities.
- Moderate: An event that causes sufficient discomfort and interferes with normal everyday activities.
- Severe: An event that prevents normal everyday activities. An AE that is assessed as severe should not be confused with a SAE. Severe is a category utilized for rating the intensity of an event; and both AEs and SAEs can be assessed as severe.
- An event is defined as 'serious' when it meets at least 1 of the predefined outcomes as described in the definition of an SAE, NOT when it is rated as severe (eg, a severe AE may be either serious or not serious, depending on whether these criteria are also met).

The National Cancer Institute Common Terminology Criteria for Adverse Events should be used as a supportive standardization instrument to evaluate AEs and SAEs, but the final intensity grading by the Investigator must be mild, moderate, or severe.

Assessment of Causality

- The Investigator is obligated to assess the relationship between study medication and each occurrence of each AE/SAE.
- A "reasonable possibility" of a relationship conveys that there are facts, evidence, and/or arguments to suggest a causal relationship, rather than a relationship cannot be ruled out.
- The Investigator will use clinical judgment to determine the relationship.
- Alternative causes, such as underlying disease(s), concomitant therapy, and other risk factors, as well as the temporal relationship of the event to study medication administration will be considered and investigated.
- The Investigator will also consult the Investigator's Brochure and/or Product Information, for marketed products, in his/her assessment.
- For each AE/SAE, the Investigator **must** document in the medical notes that he/she has reviewed the AE/SAE and has provided an assessment of causality.
- There may be situations in which an SAE has occurred and the Investigator has minimal information to include in the initial report to UCB. However, **it is very important that the Investigator always make an assessment of causality for every event before the initial transmission of the SAE data to UCB.**
- The Investigator may change his/her opinion of causality in light of follow-up information and send an SAE follow-up report with the updated causality assessment.
- The causality assessment is one of the criteria used when determining regulatory reporting requirements.

Follow-up of AEs and SAEs

- The Investigator is obligated to perform or arrange for the conduct of supplemental measurements and/or evaluations as medically indicated or as requested by UCB to elucidate the nature and/or causality of the AE or SAE as fully as possible. This may include additional laboratory tests or investigations, histopathological examinations, or consultation with other health care professionals.
- 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 participant is lost to follow-up. This follow-up requirement applies to AEs, SAEs, and AEs of special interest.
- If a participant dies during participation in the study or during a recognized follow-up period, the Investigator will provide UCB with a copy of any post-mortem findings including histopathology.
- New or updated information will be recorded in the originally completed CRF.
- The Investigator will submit any updated SAE data to UCB within 24 hours of receipt of the information.

Reporting of SAEs

SAE Reporting to UCB via an Electronic Data Collection Tool

- The primary mechanism for reporting an SAE to UCB will be the electronic data collection tool.
- If the electronic system is unavailable for more than 24 hours, then the site will use the paper SAE data collection tool (see next section).
- The site will enter the SAE data into the electronic system as soon as it becomes available.
- After the study is completed at a given site, the electronic data collection tool will be taken off-line to prevent the entry of new data or changes to existing data.
- If a site receives a report of a new SAE from a study participant or receives updated data on a previously reported SAE after the electronic data collection tool has been taken off-line, then the site can report this information on a paper SAE form (see next section) or to the Medical Monitor or SAE coordinator by telephone.
- Contacts for SAE reporting can be found in the section on SERIOUS ADVERSE EVENT REPORTING.

SAE Reporting to UCB via Paper CRF

- Facsimile transmission of the SAE paper CRF is the preferred method to transmit this information to the Medical Monitor or SAE coordinator.
- In rare circumstances and in the absence of facsimile equipment, notification by telephone is acceptable with a copy of the SAE data collection tool sent by overnight mail or courier service.
- Initial notification via telephone does not replace the need for the Investigator to complete and sign the SAE CRF pages within the designated reporting time frames.
- Contacts for SAE reporting can be found in the section on SERIOUS ADVERSE EVENT REPORTING.

10.4 Appendix 4: Contraceptive Guidance and Collection of Pregnancy Information

Definitions

A woman is considered fertile following menarche and until becoming post-menopausal unless permanently sterile (see below).

Women in the following categories **are not considered WOCBP**:

1. Premenarchal
2. Premenopausal female with 1 of the following:
   - Documented hysterectomy
   - Documented bilateral salpingectomy
   - Documented bilateral oophorectomy

   Note: Documentation can come from the site personnel's review of the participant's medical records, medical examination, or medical history interview.
3. Postmenopausal female
   - A postmenopausal state is defined as no menses for 12 months without an alternative medical cause. A high follicle stimulating hormone (FSH) level in the postmenopausal range may be used to confirm a postmenopausal state in women not using hormonal contraception or hormonal replacement therapy (HRT). However, in the absence of 12 months of amenorrhea, a single FSH measurement is insufficient.
   - Females on HRT and whose menopausal status is in doubt will be required to use one of the non-estrogen hormonal effective contraception methods if they wish to continue their HRT during the study. Otherwise, they must discontinue HRT to allow confirmation of postmenopausal status before study enrollment.

Contraception Guidance

Female participants

Sexually active female participants of childbearing potential are eligible to participate if they agree to use an effective method of contraception consistently and correctly as described below:

- hormonal contraceptives (stable at least 2 months prior to Screening [Visit 1] if initiated prior to entering the study)
- a combination of barrier and spermicide

Study participants must agree to use an effective contraception during the study and for at least 10 weeks after their final dose of IMP (or longer based on local approved label).

In addition,

- A vasectomized partner is an effective contraception method provided that the partner is the sole male sexual partner of the WOCBP and the absence of sperm has been confirmed. If not, an additional effective method of contraception should be used.

– Sexual abstinence is considered an effective method only if defined as refraining from heterosexual intercourse during the entire period of risk associated with the study medication. The reliability of sexual abstinence needs to be evaluated in relation to the duration of the study and the preferred and usual lifestyle of the participant.

Pregnancy testing

- WOCBP should only be included after a confirmed menstrual period and a negative highly sensitive serum pregnancy test. For women who become WOCBP during the study, her first pregnancy test should be a serum pregnancy test.
- Additional pregnancy testing should be performed during the Treatment Period and at the SFU (10 weeks after the last dose of study medication) and as required locally.
- Pregnancy testing will be performed as outlined in the Schedule of Activities, to the sensitivity specified by the central laboratory.
- Pregnancy testing will also be performed whenever pregnancy is suspected.

Collection of pregnancy information

Male participants with partners who become pregnant

- The Investigator will attempt to collect pregnancy information on any male participant's female partner who becomes pregnant while the male participant is in this study. This applies only to male participants who receive study medication.
- After obtaining the necessary signed informed consent from the pregnant female partner directly, the Investigator will record pregnancy information on the appropriate form and submit it to the Sponsor within 24 hours of learning of the partner's pregnancy. The female partner will also be followed to determine the outcome of the pregnancy. Information on the status of the mother and child will be forwarded to the Sponsor. Generally, the follow-up will be within 30 days after the delivery date. Any termination of the pregnancy will be reported regardless of fetal status (presence or absence of anomalies) or indication for the procedure.

Female participants who become pregnant

- Any female participant who becomes pregnant while participating in the study will discontinue study medication and be withdrawn from the study.

  The Investigator will collect pregnancy information on any female participant who becomes pregnant while participating in this study. Information will be recorded on the appropriate form and submitted to the Sponsor within 24 hours of learning of a participant's pregnancy. The participant will be followed to determine the outcome of the pregnancy. The Investigator will collect follow-up information on the participant and the neonate and the information will be forwarded to the Sponsor. Generally, the follow-up will be within 30 days after the delivery date. Any terminations of pregnancy will be reported, regardless of fetal status (presence or absence of anomalies) or indication for the procedure.
- While pregnancy itself is not considered to be an AE or SAE, any pregnancy complication or elective termination of a pregnancy will be reported as an AE or SAE. A spontaneous abortion is always considered to be an SAE and will be reported as such. Any post-study

pregnancy related SAE considered reasonably related to the study medication by the Investigator will be reported to the Sponsor as described in Section 8.3.5. While the Investigator is not obligated to actively seek this information in former study participants, he or she may learn of an SAE through spontaneous reporting.

10.5 Appendix 5: Genetics

Not applicable.

10.6 Appendix 6: Liver Safety – Suggested Actions and Follow-up Assessments

Participants with potential drug-induced liver injury must be assessed to determine if study medication must be discontinued (Section 7.1.1). In addition, all concomitant medications and herbal supplements that are not medically necessary should be discontinued.

Investigators should attempt to obtain information on study participants in the case of study medication discontinuation to complete the final evaluation.

Study participants with potential drug-induced liver injury should not be withdrawn from the study until investigation and monitoring are complete. All results of these evaluations and observations, as well as the reason(s) for study medication discontinuation and/or participant withdrawal (if applicable), must be recorded in the source documents. The CRF must document the primary reason for discontinuation of study medication.

A specific monitoring plan must be agreed between the UCB Study Physician and the Investigator for study participants who have ALT >5xULN. The monitoring plan should include any necessary follow-up assessments (until resolution of the abnormal lab values).

Liver chemistry stopping criteria are designed to assure participant safety and to evaluate liver event etiology.

Liver Chemistry Stopping Criteria and Follow-up assessments

Liver Chemistry Stopping Criteria	
ALT-absolute	ALT ≥8xULN
ALT Increase	ALT ≥5xULN but <8xULN persists for ≥2 weeks ALT ≥3xULN but <5xULN persists for ≥4 weeks
Bilirubin[a,b]	ALT ≥3xULN **and** bilirubin ≥2xULN (>35% direct bilirubin)
INR[b]	ALT ≥3xULN **and** international normalized ratio (INR) >1.5, if INR measured
Cannot Monitor	ALT ≥5xULN but <8xULN and cannot be monitored weekly for ≥2 weeks ALT ≥3xULN but <5xULN and cannot be monitored weekly for ≥4 weeks
Symptomatic[c]	ALT ≥3xULN associated with symptoms (new or worsening) believed to be related to liver injury or hypersensitivity

Suggested Actions and Follow-up Assessments	
Actions	**Follow-up Assessments**
• **Immediately** discontinue study medication. • Report the event to UCB within **24 hours.** • Complete the liver event case report form (CRF), and complete a serious adverse event (SAE) data collection tool if the event also met the criteria for an SAE.[b] • Perform liver chemistry follow-up assessments.	• Viral hepatitis serology.[d] • Obtain INR and recheck with each liver chemistry assessment until the transaminase values show downward trend. • Only in those with underlying chronic hepatitis B at study entry (identified by positive hepatitis B surface antigen),

Liver Chemistry Stopping Criteria	
• Monitor the participant until liver chemistry test abnormalities resolve, stabilize, or return to baseline (see **MONITORING**). • **Do not restart/rechallenge** participant with study medication unless allowed per protocol and UCB approval is granted. • If restart/rechallenge **not allowed per protocol or not granted**, permanently discontinue study medication and continue participant in the study for any protocol-specified follow-up assessments.Consider the need for a toxicology screening. **MONITORING:** **<u>For bilirubin or INR criteria</u>** • Repeat liver chemistry tests (include ALT, aspartate transaminase [AST], alkaline phosphatase, bilirubin) and perform liver event follow-up assessments within **24 hours.** • Monitor participant twice weekly until liver chemistry test abnormalities resolve, stabilize, or return to baseline. • A specialist or hepatology consultation is recommended. **<u>For all other criteria</u>** • Repeat liver chemistry tests (include ALT, AST, alkaline phosphatase, bilirubin) and perform liver chemistry follow-up assessments within **24 to 72 hours.** • Monitor participants weekly until liver chemistry abnormalities resolve, stabilize, or return to baseline.	quantitative hepatitis B deoxyribonucleic acid (DNA), and hepatitis delta antibody.[e] • Obtain blood sample for pharmacokinetic (PK) analysis as soon as possible.[f] • Serum creatine phosphokinase (CPK) and lactate dehydrogenase (LDH). • Fractionate bilirubin, if total bilirubin ≥2xULN. • Obtain complete blood count with differential to assess eosinophilia. • Record the appearance or worsening of clinical symptoms of liver injury (eg, fatigue, nausea, vomiting, right upper quadrant pain), or hypersensitivity, on the adverse event (AE) report form. • Record use of concomitant medications (including acetaminophen, herbal remedies, and other over-the-counter medications) on the concomitant medications CRF. • Record alcohol use on the liver event alcohol intake CRF. • Exclude pregnancy. **<u>For bilirubin or INR criteria:</u>** • Anti-nuclear antibody, anti-smooth muscle antibody, Type 1 anti-liver kidney microsomal antibodies, and quantitative total immunoglobulin G (IgG) or gamma globulins. • Serum acetaminophen adduct high performance liquid chromatography (HPLC) assay (quantifies potential acetaminophen contribution to liver injury in participants with definite or likely acetaminophen use in the preceding week; James, 2009). **NOTE: Not required in China**. • Liver imaging (ultrasound, magnetic resonance, or computerized tomography) and/or liver biopsy to evaluate liver disease; complete Liver Imaging and/or Liver Biopsy CRFs.

[a] Serum bilirubin fractionation should be performed if testing is available. If serum bilirubin fractionation is not immediately available, discontinue study medication if ALT ≥3xULN **and** bilirubin ≥2xULN. Additionally, if serum bilirubin fractionation testing is unavailable, **record the absence/presence of detectable urinary bilirubin on dipstick** which is indicative of direct bilirubin elevations suggesting liver injury.

[b] All events of ALT ≥3xULN and bilirubin ≥2xULN (>35% direct bilirubin) or ALT ≥3xULN and INR >1.5 may indicate severe liver injury **(possible 'Hy's Law') and must be reported as an SAE (excluding studies of**

hepatic impairment or cirrhosis). The INR measurement is not required and the stated threshold value will not apply to participants receiving anticoagulants.

[c] New or worsening symptoms believed to be related to liver injury (such as fatigue, nausea, vomiting, right upper quadrant pain or tenderness, or jaundice) or hypersensitivity (such as fever, rash or eosinophilia).

[d] Includes: Hepatitis A immunoglobulin M (IgM) antibody; HBsAg and HBcAb; hepatitis C RNA; cytomegalovirus IgM antibody; Epstein-Barr viral capsid antigen IgM antibody (or if unavailable, heterophile antibody or monospot testing); and hepatitis E IgM antibody.

[e] If hepatitis delta antibody assay cannot be performed, it can be replaced with a polymerase chain reaction (PCR) of hepatitis D RNA virus (where needed; Le Gal, 2005).

[f] Record the date/time of the PK blood sample draw and the date/time of the last dose of study medication prior to the PK blood sample draw on the CRF. If the date or time of the last dose is unclear, provide the participant's best approximation. If the date/time of the last dose cannot be approximated OR a PK sample cannot be collected in the time period indicated above, do not obtain a PK sample. Instructions for sample handling and shipping are in the Study Reference Manual.

10.7 Appendix 7: Medical Device Adverse Events (AEs), Adverse Device Effects (ADEs), Serious Adverse Events (SAEs) and Device Deficiencies: Definition and Procedures for Recording, Evaluating, Follow-up, and Reporting

Not applicable.

10.8 Appendix 8: Rapid Alert Procedures

Not applicable.

10.9 Appendix 9: Country-specific Requirements

Not applicable.

10.10 Appendix 10: Abbreviations and Trademarks

ADA	antidrug antibody
AE	adverse event
ALP	alkaline phosphatase
ALT	alanine aminotransferase
AST	aspartate aminotransferase
CONSORT	Consolidated Standards of Reporting Trials
CRF	Case Report form
csDMARD	conventional synthetic disease modifying antirheumatic drug
CV	coefficient of variation
CZP	certolizumab pegol
DMARD	disease modifying antirheumatic drug
DNA	deoxyribonucleic acid
ECG	electrocardiogram
ECLIA	electrochemiluminescent immuno-assay
FSH	follicle stimulating hormone
GCP	Good Clinical Practice
HCV	hepatitis C virus
HIV	human immunodeficiency virus
HRT	hormonal replacement therapy
ICF	Informed Consent Form
ICH	International Council for Harmonisation
IEC	Independent Ethics Committee
IGRA	Interferon-gamma release assay
IMP	investigational medicinal product
IRB	Institutional Review Board
MDHAQ	Multi-dimensional Health Assessment Questionnaire
MTX	methotrexate
NTMB	nontuberculous mycobacterial
PDILI	potential drug-induced liver injury
PEG	polyethylene glycol
pJIA	polyarticular juvenile idiopathic arthritis

PK	pharmacokinetic
PKS	Pharmacokinetic Set
PREA	Pediatric Research Equity Act
Q2W	every 2 weeks
RA	rheumatoid arthritis
RAPID3	Routine Assessment of Patient Index Data 3
SAE	serious adverse event
SFU	Safety Follow-up
SS	Safety Set
TB	tuberculosis
TNF	tumor necrosis factor
tsDMARD	targeted synthetic disease modifying antirheumatic drug
ULN	upper limit of normal
US	United States
WOCBP	woman of childbearing potential

10.11 Appendix 11: Protocol Amendment History

The Protocol Amendment Summary of Changes Table for the current amendment is located directly before the Table of Contents.

Amendment 1 (09 Dec 2020)

Overall rationale for the amendment

The primary reason for this nonsubstantial protocol amendment was to update the Schedule of Activities (Section 1.3) to include a safety laboratory assessment at Week 12 (Visit 13) that was omitted in error and to correct the study day associated with Visit 14.

This amendment is considered to be nonsubstantial based on the criteria set forth in Article 10(a) of Directive 2001/20/EC of the European Parliament and the Council of the European Union.

Section # and Name	Description of Change	Brief Rationale
Global	Minor administrative, formatting, and typographical changes have been made.	Updated to provide clarity and to be consistent with remainder of protocol and program.
1.3 Schedule of Activities	Included a safety laboratory assessment at Week 12 (Visit 13).	This was planned but omitted in the original protocol.
1.3 Schedule of Activities	Corrected the study day for Visit 14 from Day 140 to Day 126.	Updated to correct an error.

10.12 Appendix 12: RAPID3 Assessment

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

[redacted]

How to calculate RAPID3 scores

1. Ask the patient to complete questions 1, 2, and 3 while in the waiting room prior to his/her visit.

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

11 REFERENCES

Jacobsson LT, Turesson C, Nilsson JA, et al. Treatment with TNF blockers and mortality risk in patients with rheumatoid arthritis. Ann Rheum Dis. 2007;66(5):670-5.

James LP, Letzig L, Simpson PM, et al. Pharmacokinetics of Acetaminophen-Adduct in Adults with Acetaminophen Overdose and Acute Liver Failure. Drug Metab Dispos. 2009;37:1779-84.

Smolen J, Landewé RB, Mease P, et al. Efficacy and safety of certolizumab pegol plus methotrexate in active rheumatoid arthritis: the RAPID 2 study. A randomised controlled trial. Ann Rheum Dis. 2009;68(6):797-804.

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.

Approval Signatures

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