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

PROTOCOL UP0085

PHASE 1B

SHORT TITLE:

A postmarketing, multicenter, pharmacokinetic study in pregnant women with chronic inflammatory diseases treated with certolizumab pegol

Sponsor:

UCB Biopharma SRL

Allée de la Recherche 60

1070 Brussels

BELGIUM

Regulatory agency identifying number(s):

EudraCT Number:	2019-003410-13
IND Number:	11,197
NCT Number:	Not yet assigned

Confidential Material

PROTOCOL AMENDMENT SUMMARY OF CHANGES TABLE

Document History		
Document	**Date**	**Type of amendment**
Protocol Amendment 2	30 Aug 2022	Substantial
Protocol Amendment 1.1 (France)	01 Mar 2021	Substantial
Protocol Amendment 1	29 Aug 2019	Substantial
Original Protocol	31 Jul 2019	Not applicable

Amendment 2 (30 Aug 2022)

Overall Rationale for the Amendment

The Sponsor wishes to clarify the adequate amount of data per participant which would classify the participant as providing longitudinal data over the pregnancy and postpartum periods.

Section # and Name	Description of Change	Brief Rationale
Title Page	Previous text: UCB SPRL New text: **UCB SRL**	Updated with sponsor's name change.
Section 1.1, Synopsis	Previous text: Enrollment is anticipated until approximately 10 to 12 study participants have complete longitudinal data sets (defined as a data set including all predose samples collected Q4W and postdose samples collected Q8W over the pregnancy period and at least 1 postpartum sample). **New text: Enrollment will occur until a minimum of 10 study participants have longitudinal data (defined as at least 4 quantifiable predose and 2 quantifiable postdose PK samples during pregnancy and at least 1 quantifiable postpartum sample) over the study period.**	To update the planned enrollment needed to provide a sufficient number of participants with adequate data.
Section 1.2, Schema	The post-partum period was changed to from 8-13 weeks to 13 weeks.	Updated to align with the rest of the protocol.

Section 4.1, Overall design	Previous text: The study will continue to enroll participants until approximately of 10 to 12 complete individual longitudinal datasets are obtained. This is inclusive of PK samples (predose and postdose as defined in Section 1.1) obtained during the pregnancy along with postpartum samples. Study enrollment may be stopped after the minimum number of participants is reached, or the study may continue to enroll beyond the minimum number of participants if cumulated PK data are not deemed sufficient to meet the primary objective. **New text: The study will enroll participants based on a minimum of 10 study participants providing longitudinal data (defined as at least 4 quantifiable predose and 2 quantifiable postdose PK samples during pregnancy and at least 1 quantifiable postpartum sample) over the study period. Study enrollment may be stopped after the minimum number of participants is reached, or the study may continue to enroll beyond the minimum number of participants if cumulated study PK data are not deemed sufficient to meet the primary objective.**	To update the planned enrollment needed to provide a sufficient number of participants with adequate data.

Section 9.1, Definition of analysis sets	**New text added: There will be 4 analysis sets for the study; the All Study Participants Screened Set, the Enrolled Set (ES), the Safety Set (SS) and the Pharmacokinetic Per Protocol Set (PK-PPS).** **The All Study Participants Screened Set will consist of all study participants who have signed the ICF and will include all participants who pass screening as well as screen failures. This will be the largest analysis set.**	Updated to align with the most recent SAP amendment.
Section 9.8, Sample size	Previous text: From these 15 evaluable participants, it is expected approximately 10 to 12 complete individual longitudinal datasets will be collected. **New text: These 15 evaluable participants are expected to provide the minimum of 10 study participants providing longitudinal data as defined in Section 4.1.**	To update the planned enrollment needed to provide a sufficient number of participants with adequate data.
Section 9.3.3.1 , Adverse events	Previous text: All AEs will be coded using the Medical Dictionary for Regulatory Activities (MedDRA v19.1) and characterized as treatment-emergent according to the intake of CZP. **New text: All AEs will be coded using the Medical Dictionary for Regulatory Activities (MedDRA v24.1 or higher) and characterized as treatment-emergent according to the intake of CZP.**	Updated to align with the most recent SAP amendment.

Throughout the protocol	Minor typographical edits have been incorporated in the protocol.	

SERIOUS ADVERSE EVENT REPORTING

Serious adverse event reporting (24h)	
Fax	**Europe and Rest of the World:** +32 2 386 24 21 **US and Canada:** +1 800 880 6949 or +1 866 890 3175
Email	**Global:** DS_ICT@ucb.com (for interventional clinical studies)

TABLE OF CONTENTS

LIST OF TABLES

LIST OF FIGURES

1 PROTOCOL SUMMARY

1.1 Synopsis

Protocol title: A postmarketing, multicenter, longitudinal, prospective, pharmacokinetic, Phase 1B study in pregnant women with chronic inflammatory diseases treated with Cimzia® (certolizumab pegol).

Short title: A postmarketing, multicenter, pharmacokinetic study in pregnant women with chronic inflammatory diseases treated with certolizumab pegol.

Rationale:

Certolizumab pegol (CZP) is approved in adults for the treatment of chronic inflammatory diseases (such as rheumatoid arthritis, psoriatic arthritis, plaque psoriasis, Crohn's disease, and axial spondyloarthritis [including ankylosing spondylitis and non-radiographic axial spondyloarthritis]) in multiple countries worldwide.

Depending on the severity and condition, active disease can impact the outcome for the mother and infant and may necessitate therapy, even during pregnancy. For women who continue CZP therapy during pregnancy, there is no robust evidence available regarding the impact of pregnancy on pharmacokinetics (PK) during treatment with CZP. In order to ensure that women who require CZP treatment during pregnancy are able to achieve therapeutic steady state levels of CZP, it is valuable to conduct studies evaluating whether the physiologic changes underlying pregnancy impact the PK profile of CZP during pregnancy.

The objective of this longitudinal, prospective, open-label PK study is to assess any changes in CZP (the study medication in this protocol) plasma concentrations over the course of pregnancy, relative to the postpartum period.

Objectives and endpoints:

Objectives	Endpoints
Primary	
• To assess systemic CZP exposure across the course of pregnancy in study participants with chronic inflammatory diseases	• Predose and postdose plasma CZP concentrations in women during pregnancy, relative to postpartum
Secondary	
• To assess the formation of anti-CZP antibodies across the course of pregnancy	• Plasma levels of anti-CZP antibodies throughout the study period
• To assess the safety of CZP in study participants with chronic inflammatory diseases across the course of pregnancy	• Adverse events from time of informed consent through SFU • Pregnancy outcome
Other	
• To assess changes in BMI, CRP and albumin across the course of pregnancy	• BMI • CRP levels • Albumin levels

BMI=body mass index; CRP=C-reactive protein; CZP=certolizumab pegol; SFU=Safety Follow-Up

Overall design:

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

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

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

The full Schedule of Activities is provided in Table 1–1.

- Screening Period: Women of childbearing potential already on commercial CZP can register to indicate interest in the current study. After confirmation of pregnancy, the women will consent to participate in the study and will be eligible to enroll once CZP levels have reached

steady state. Confirmation of steady state is based on participant records and/or reports from the prescribing physician indicating that the participant has taken CZP for at least 12 weeks at the same dosing regimen prior to the Enrollment Visit, which must take place at ≤10 weeks gestational age.

- Sampling Period:
  - Pregnancy Period: PK samples will be collected prior to the subsequent dose (predose) every 4 weeks (Q4W) starting with the first dose after enrollment. Further, postdose (7 ± 1 day after dose administration) PK samples will be collected every 8 weeks (Q8W) throughout the pregnancy. It is expected that there will be approximately 6 predose and 3 postdose PK samples collected per study participant (if there are no discontinuations) over the pregnancy.
  - Postpartum Period: A predose sample 12 weeks (±1 week) postpartum will be collected during the Postpartum Period. If possible, 1 additional postdose sample 1 week (±1 day) after the 12 weeks postpartum dose will also be collected.
- Safety Follow-up contact: All study participants will be contacted via telephone for a SFU 5 weeks (±5 days) after final study visit.

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

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

Number of participants:

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

Treatment groups and duration:

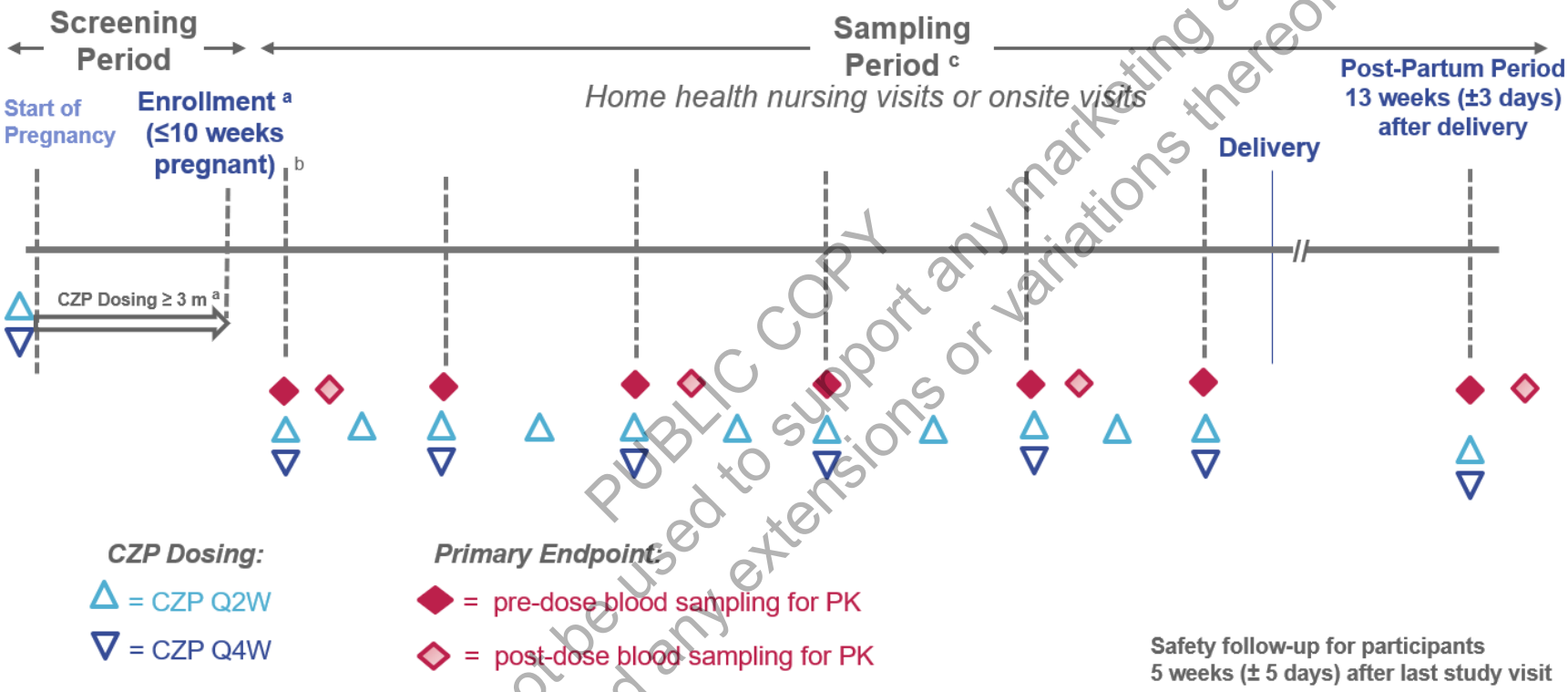
This study will include pregnant women who have decided to continue treatment with commercial CZP in accordance with their treating physician prior to participating in the study. Study participants will be responsible for obtaining and administering commercially available CZP under the care of their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

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

1.2 Schema

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

Figure 1–1: Study Diagram



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

1.3 Schedule of Activities

The Schedule of Activities is provided in Table 1–1.

Table 1–1: Schedule of Activities

Procedure[a]	Screening	Sampling Period					SFU/EWD (via telephone)[c]
		Pregnancy Period			Postpartum Period[b]		
	V1[d]	V2 (Enrollment)	Predose[e] (Q4W)	Postdose[f] (Q8W)	V5 Predose[e]	V6 Postdose[f] (optional)	V7[g]
Informed consent	X						
Demographics and baseline characteristics[h]	X						
Verification of inclusion/exclusion criteria	X	X					
Significant medical/procedures history and concomitant diseases	X						
Concomitant medication and procedures review	X	X	X	X	X	X	X
Adverse event review[i]	X	X	X	X	X	X	X
Recording of commercial CZP treatment[j]	X	X	X	X	X	X	X
Physical examination[k]	X						
Vital signs[l]	X						
Tobacco and alcohol consumption, and drug abuse	X						
TB questionnaire[m]	X						

Table 1–1: Schedule of Activities

Procedure[a]	Screening	Sampling Period					SFU/EWD (via telephone)[c]
		Pregnancy Period			Postpartum Period[b]		
	V1[d]	V2 (Enrollment)	Predose[e] (Q4W)	Postdose[f] (Q8W)	V5 Predose[e]	V6 Postdose[f] (optional)	V7[g]
TB test (if not within 6 months)[n,o]	X						
Blood sampling for plasma CZP PK levels		X	X	X	X	X	
Blood sampling for plasma anti-CZP antibodies		X	X		X		
Study participant diary completion/review	X	X	X	X	X	X	
Blood sampling for CRP and albumin		X	X		X		
Weight (for BMI calculation)		X	X		X		
Pregnancy outcome					X		
SFU contact							X

BCG=Bacillus Calmette–Guérin; BMI=body mass index; CRP=c-reactive protein; CZP=certolizumab pegol; EWD=Early Withdrawal/Discontinuation; ICF=informed consent form; PK=pharmacokinetic; Q4W=every 4 weeks; Q8W=every 8 weeks; SFU=Safety Follow-up; TB=tuberculosis; V=Visit

[a] It is expected that PK samples may not be obtainable in every case. Therefore, missing samples should not be considered major protocol deviations.

[b] Postpartum samples will be collected up to 13 weeks (±3 days) postpartum.

[c] The SFU telephone contact will take place 5 weeks (±5 days) after the last study visit for all study participants.

[d] Visit 1 may take place at an on-site or off-site location, conducted by the investigator or appropriate designee (eg, study participant's local healthcare provider).

[e] Predose samples will be collected within 4 hours prior to dosing.

Table 1–1: Schedule of Activities

Procedure[a]	Screening	Sampling Period					SFU/EWD (via telephone)[c]
		Pregnancy Period			Postpartum Period[b]		
	V1[d]	V2 (Enrollment)	Predose[e] (Q4W)	Postdose[f] (Q8W)	V5 Predose[e]	V6 Postdose[f] (optional)	V7[g]

[f] Postdose samples will be collected 7 (±1) days after the dose has been administered.
[g] The SFU will take place 5 weeks (±5 days) after the last study visit.
[h] Demographic and baseline characteristics will include lifestyle, confirmation of pregnancy, height, weight and BMI.
[i] Adverse events will be collected from the time of the signature on the ICF until the SFU contact.
[j] The decision to treat with CZP will be made by the study participant in accordance with her treating physician prior to being recruited for the study. Study participants are responsible for obtaining their own supply of commercial CZP. Final dosing of CZP during the study will be recorded during the SFU.
[k] Physical examinations may be performed by the study participant's local healthcare provider, and a record of that examination is to be provided to the investigator as documentation.
[l] Vital signs include pulse rate, respiratory rate, systolic and diastolic blood pressure, and peripheral body temperature. Study participants should maintain a sitting position for ≥5 minutes before and during vital signs assessments.
[m] Includes signs and symptoms of active TB and risk factors for exposure to TB and requires an assessment every 12 weeks. No chest x-rays or follow-up testing will be performed, as this study will comprise study participants who have a low risk for TB.
[n] Tuberculosis test results that have been obtained within the previous 6 months prior to Screening with negative results are acceptable. Study participants with documented BCG vaccination and low risk of TB do not need to have TB test performed at Screening.
[o] A TB test will only be offered within the study or at study exit if it has been 52 weeks since the last negative test and a test is clinically indicated.

2 INTRODUCTION

Certolizumab pegol has been approved for use in patients with rheumatoid arthritis, psoriatic arthritis, plaque psoriasis, Crohn's disease, and axial spondyloarthritis (including ankylosing spondylitis and non-radiographic axial spondyloarthritis) in multiple countries worldwide. Limited data exist on the use of CZP in pregnant women, and are not sufficient to indicate how the physiologic changes of pregnancy can alter the PK of CZP in pregnant women.

2.1 Study rationale

Certolizumab pegol is an engineered, humanized, antigen-binding antibody fragment (Fab), with specificity for human tumor necrosis factor α, that is conjugated to polyethylene glycol and is approved in adults for the treatment of the aforementioned chronic inflammatory diseases in multiple countries worldwide.

Depending on the severity and condition, active disease can impact the outcome for the mother and infant and may necessitate therapy, even during pregnancy. For women who continue CZP therapy during pregnancy, there is no robust evidence available regarding the impact of pregnancy on PK during treatment with CZP. In order to ensure that women who require CZP treatment during pregnancy are able to achieve therapeutic steady state levels of CZP, it is valuable to conduct studies evaluating whether the physiologic changes underlying pregnancy impact exposure to CZP during pregnancy. As such, this study will evaluate the PK of CZP during pregnancy.

For further information regarding the study rationale see Section 4.2.

2.2 Background

Autoimmune diseases such as rheumatoid arthritis, psoriatic arthritis, plaque psoriasis, Crohn's disease, and axial spondyloarthritis (including ankylosing spondylitis and non-radiographic axial spondyloarthritis) affect women of childbearing age. While disease activity may spontaneously improve during pregnancy, approximately 50% of women with rheumatic chronic inflammatory diseases need effective therapeutic intervention and are faced with difficult questions regarding the impact of active disease on the fetus and the safety of different therapies during pregnancy. Depending on the severity and condition, active disease can impact the outcome for the mother and infant and may necessitate therapy, even during pregnancy. Published data suggest that the risk of adverse pregnancy outcomes in women with rheumatoid arthritis or Crohn's disease is correlated with maternal disease activity and that active disease increases the risk of adverse pregnancy outcomes, including fetal loss, preterm delivery (before 37 weeks of gestation), low birth weight (<2500g) and small for gestational age birth. Consequently, physicians and their patients may decide to continue to treat disease during pregnancy.

As described by Mariette (2018), physiologic changes during pregnancy may substantially alter drug PK; however, there are very limited data available on the impact of pregnancy on CZP PK.

It is valuable to provide data about CZP levels throughout pregnancy to help women and their physicians make informed decisions about the dose of CZP to use during pregnancy, if a decision to continue treatment with CZP has been made.

2.3 Benefit/risk assessment

A clinical postmarketing prospective study (UP0017) evaluating placental transfer of CZP by measuring the plasma concentration of CZP from blood samples taken from infant, mother, and umbilical cord at delivery/birth indicated that there was minimal placental transfer of CZP from mother to infant. The mothers had similar CZP plasma concentrations at delivery to those of nonpregnant women receiving a maintenance dose regimen, and there were no detectable measurements of anti-CZP antibodies using the assay available at the time of the study in either the mothers or the infants, nor were there new safety signals.

UP0085 will only include pregnant women who decided to continue treatment with CZP in accordance with their treating physician prior to participating in the study. Therefore, 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). Study participants will not directly benefit from participation in the study; however, the data obtained will enable physicians, pregnant women, and women of childbearing age to be better informed regarding PK of CZP when used during pregnancy.

For more detailed information (eg, PK and safety), as well as information about the known and expected benefits and risks and expected adverse events (AEs) of CZP, see the current Investigator's Brochure (IB).

As per routine UCB pharmacovigilance activity, all women who are administered CZP prior to the estimated date of conception or at any time during their pregnancy will be asked to complete the UCB Pregnancy Report and Outcome Form together with their treating physician (see Section 10.4). This process will apply also to participants of this study and enable UCB to collect information on the pregnancy and its outcome.

3 OBJECTIVES AND ENDPOINTS

Objectives	Endpoints
Primary	
• To assess systemic CZP exposure across the course of pregnancy in study participants with chronic inflammatory diseases	• Predose and postdose plasma CZP concentrations in women during pregnancy, relative to postpartum
Secondary	
• To assess the formation of anti-CZP antibodies across the course of pregnancy	• Plasma levels of anti-CZP antibodies throughout the study period
• To assess the safety of CZP in study participants with chronic inflammatory diseases across the course of pregnancy	• Adverse events from time of informed consent through SFU • Pregnancy outcome
Other	
• To assess changes in BMI, CRP and albumin across the course of pregnancy	• BMI • CRP levels • Albumin levels

BMI=body mass index; CRP=C-reactive protein; CZP=certolizumab pegol; SFU=Safety Follow-Up

4 STUDY DESIGN

4.1 Overall design

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

The study is interventional due to the additional collection of blood samples from women. However, all other study assessments are part of routine clinical practice (with the exception of the diary), and the decision to continue/discontinue CZP therapy during pregnancy will be made between the participant and her treating physician, taking into account the potential risks to the mother and the benefits of CZP therapy, and according to the applicable local label.

Study participants should have taken CZP for at least 12 weeks at their dosing regimen prior to enrollment and before the end of 10 weeks gestational age (see Inclusion Criterion [IC] 3). The study will enroll participants based on a minimum of 10 study participants providing longitudinal data (defined as at least 4 quantifiable predose and 2 quantifiable postdose PK samples during

pregnancy and at least 1 quantifiable postpartum sample) over the study period. Study enrollment may be stopped after the minimum number of participants is reached, or the study may continue to enroll beyond the minimum number of participants if the cumulative study PK data are not deemed sufficient to meet the primary objective. Study participants will be provided with a diary to record all CZP dosing dates and times over the study period. Pharmacokinetic samples (for the determination of CZP concentration and anti-CZP antibody titers) will be collected as detailed above, and samples will be collected for assessment of C-reactive protein (CRP) and albumin (covariates of the PK parameters). Overall safety and welfare of the mother and fetus are of paramount importance while performing any study-related activity.

If a study participant has at least 1 PK sample obtained during pregnancy and then CZP dosing is interrupted and restarted, or dosing is modified during pregnancy, the study participant will continue to be followed and all samples will be obtained per protocol guidelines (including postpartum samples).

If a study participant has multiple PK samples obtained during pregnancy and discontinues CZP during pregnancy (with the intention to restart CZP after delivery), a PK predose sample will be obtained at 12 weeks (±1 week) postpartum with a potential postdose sample 1 week (±1 day) after the predose postpartum sample. If the study participant does not take CZP for at least 12 weeks and provides a PK sample within this window, the study participant will be discontinued from the study.

The informed consent form (ICF) for this study may be available electronically and used by prospective study participants at a study center or a remote location. If a study participant consents to participate, she will enter the Screening Period and all elements of eligibility will be confirmed prior to entering the Sampling Period. It is anticipated that the sampling visits will be completed in the study participant's home setting or at a designated convenient location in the presence of a qualified remote healthcare nurse. To facilitate these visits, the study participant should have access to a telephone. In most cases, remote healthcare nurses performing a visit to a study participant may complete study data forms that can be entered into the database by the contract research organization (CRO) or site staff. In other cases, study participants may visit a clinic, study site, or other health care provider's office for assessments or to provide blood samples.

Laboratory kits will be provided to the health care providers, remote healthcare nurses, and the study participants (as back up) for collection of CZP plasma levels, anti-CZP antibody assessments, CRP and albumin during collection of the final PK sample, in addition to a safety evaluation. Albumin was previously found to be a significant covariate in CZP population PK analyses, and CRP is a PK covariate and marker of inflammatory state. All samples will be initially delivered to a central laboratory. Pharmacokinetic samples will then be periodically shipped to a bioanalytical laboratory for PK and immunogenicity assessments. Samples will be collected for analysis of PK, immunogenicity, CRP, and albumin. At the Screening Visit, which may be at an on-site or off-site location and may be conducted by the investigator or appropriate designee (eg, study participant's local healthcare provider), a physical examination will be performed, and vital signs will be measured. Additionally, tuberculosis (TB) testing will be performed if the study participant has not been tested within 6 months prior to Screening and has no associated clinical evidence of an active TB infection. Procedures and documentation will

comply with local Institutional Review Board (IRB)/ Independent Ethics Committee (IEC) requirements.

4.2 Scientific rationale for study design

Clinical studies typically exclude pregnant women and withdraw study participants once they become pregnant. This has created a lack of data regarding drug exposure that leaves both pregnant women and treating physicians without objective scientific evidence regarding dosing of CZP during pregnancy. Additionally, depending on the severity and condition, active disease can impact the outcome for the mother and infant and may necessitate therapy, even during pregnancy. For women who continue CZP therapy during pregnancy, there is no robust evidence available regarding the impact of pregnancy on PK during treatment with CZP. In order to ensure that women who require CZP treatment during pregnancy are able to achieve therapeutic steady state levels of CZP, it is valuable to conduct studies evaluating whether the physiologic changes underlying pregnancy impact exposure to CZP during pregnancy. This study (UP0085) will generate further data regarding steady state dosing of CZP during pregnancy, which can help to provide guidance on PK variability and the impact of pregnancy on CZP plasma levels.

The objective of this longitudinal, prospective, open label PK study is to assess any changes in CZP plasma concentrations that may result from physiological changes that occur during pregnancy. Women who take CZP for approved indications and maintenance dosing regimens (200mg every 2 weeks [Q2W] or 2 x 200mg Q4W or 400mg Q2W) and who continue with CZP treatment after they have become pregnant will be eligible to be considered for enrollment into this study, which will generate important information on CZP exposure during pregnancy. To measure CZP plasma concentration at steady state during pregnancy and after delivery, blood samples will be collected predose Q4W, postdose Q8W during the pregnancy, and 1 predose sample 12 weeks (±1 week) postpartum (with potential postdose sample 1 week [±1 day] after the postpartum sample). Each study participant will serve as her own control.

4.3 Justification for dose

The study will recruit pregnant women who are prescribed commercial CZP for an approved indication in the country where the study will be conducted. No dose adjustments or any other changes to treatment will be mandated by the study protocol (see Section 6.6). The commercially approved dosing regimens (200mg Q2W or 400mg Q4W or 400mg Q2W) will be permitted following the guidance of each study participant's physician. After entry into the study, the study participant's physician may modify the dosing regimen as necessary. In such cases, non-approved CZP dosing regimens will also be allowed, at the discretion of the study participant's physician and in a manner independent of this study, as long as the regimen does not exceed 400mg Q2W and the dose is recorded in the diary.

4.4 End of study definition

A participant is considered to have completed the study if she has completed all phases of the study per protocol including the final study contact (SFU).

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

5 STUDY POPULATION

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

5.1 Inclusion criteria

To be eligible to participate/enroll in this study, all of the following criteria must be met at the Screening Visit (Visit 1). Eligibility must also be confirmed at Enrollment Visit (Visit 2), ie, just prior to blood sampling for PK. If a participant does not initially meet the enrollment criteria, she may be rescreened; however, a study participant may not be enrolled for consecutive pregnancies.

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

Age

1. Participant must be ≥18 years of age at the time of signing the ICF.

Type of participant and disease characteristics

2. Participant must be considered reliable and capable of adhering to the protocol and visit schedule according to the judgment of the investigator.
3. Participant is pregnant and ≤10 weeks gestation at the time of enrollment.
4. Participant must have been on stable, maintenance dose CZP treatment for at least 12 weeks independent of and prior to being enrolled in this study, for an approved indication in accordance with her treating physician.
5. Participant expects to continue CZP therapy throughout pregnancy and for at least 12 weeks postpartum.
6. Participant has a negative interferon gamma release assay (IGRA) or tuberculin skin test (TST) within the prior 6 months, and there has been no change in the study participant's clinical status, or social, family, or travel history. Participants with documented Bacillus Calmette–Guérin (BCG) vaccine and at low risk for TB may enroll without having a TB test performed.

Sex

7. Participants who are female.

Informed consent

8. Participant is capable of giving signed informed consent as described in Section 10.1 (Appendix 1) which includes compliance with the requirements and restrictions listed in the ICF and in this protocol.

5.2 Exclusion criteria

Study participants are excluded from the study if any of the following criteria are met at the Screening Visit (Visit 1) or Enrollment Visit (Visit 2):

Medical conditions

1. Participant has any medical or psychiatric condition 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 recent history of alcohol or drug abuse in the investigator's medical judgment.
3. Participant has any evidence or medical history of an obstetrical or psychiatric condition, or she or her fetus has any medical condition or history (eg, primary or secondary antiphospholipid syndrome or hypercoagulable state) that, in the opinion of the investigator, could jeopardize or would compromise the study participant's ability to participate in this study or the outcome of the pregnancy.
4. Participant has any evidence of clinically significant anemia in the opinion of the investigator.
5. Participant has had significant documented morbidity during the past 12 weeks.
6. Participant is not permitted to enroll into the study if she meets any of the following TB exclusion criteria:
   - Known active TB disease
   - History of active TB involving any organ system
   - Latent TB infection
   - High risk of acquiring TB infection
   - Current nontuberculous mycobacterial (NTM) infection or history of NTM infection (unless proven to be fully recovered)
7. Significant allergies to humanized monoclonal antibodies.
8. Clinically significant multiple or severe drug allergies, or severe post-treatment hypersensitivity reactions (including, but not limited to, erythema multiforme major, linear immunoglobulin A dermatosis, toxic epidermal necrolysis, and exfoliative dermatitis).
9. Current or chronic history of clinically significant liver disease, or known hepatic or biliary abnormalities (with the exception of Gilbert's syndrome or asymptomatic gallstones).

Prior/concomitant therapy

10. Study participant is taking a prohibited medication or has taken a prohibited medication as defined in Section 6.5.2.
11. Live vaccine(s) within 1 month prior to Screening, or plans to receive such vaccines during the study.

Prior/concurrent clinical study experience

12. Participant has been dosed with an investigational medicinal product (IMP), blinded IMP, or has received an investigational medical device or procedure within the previous 120 days or 5 half-lives (whichever is longer) prior to Screening or is currently participating in another study of an IMP, blinded IMP, or will receive an investigational medical device or procedure (excluding noninterventional or registry studies).

Diagnostic assessments

13. Study participant has any clinically significant pregnancy-related clinical or test abnormality, as judged by the investigator.
14. Study participant had a positive or indeterminate IGRA or TST test at Screening. In case of indeterminate result, a retest is allowed if time permits; 2 results of indeterminate require exclusion of the study participant.
15. Study participant has a history of human immunodeficiency virus, Hepatitis B surface antigen (HBsAg), or Hepatitis C antibody prior to starting the study.

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 publishing requirements and to respond to queries from regulatory authorities. Minimal information includes demography, screen failure details, eligibility criteria, and any serious adverse event (SAE).

Individuals who do not meet the criteria for participation in this study (screen failures) may be rescreened; however, a study participant may not be enrolled for consecutive pregnancies. Rescreened participants should be assigned the same participant number as for the initial Screening.

6 STUDY TREATMENT

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 Treatment administered

This study will only include pregnant women who have decided to continue treatment with CZP in accordance with their treating physician prior to participating in the study. The CZP is not provided by the Sponsor. Study participants will be responsible for obtaining and administering commercially available CZP under the care of their physician.

The commercially approved dosing regimens (200mg Q2W or 400mg Q4W or 400mg Q2W) will be permitted following the guidance of each study participant's physician.

After entry into the study, the study participant's physician may modify the dosing regimen as necessary. In such cases, non-approved CZP dosing regimens will also be allowed, at the discretion of the study participant's physician and in a manner independent of this study, as long as the regimen does not exceed 400mg Q2W and the dose is recorded in the diary. Study participants will receive CZP in accordance with their treating physician until at least 12 weeks (±1 week) after delivery.

6.2 Preparation, handling, storage, and accountability requirements

Study participants will be responsible for obtaining and administering commercially available CZP under the care of their physician.

Commercial CZP can be self-administered by subcutaneous injection using a prefilled syringe or prepared and administered by a health care professional if lyophilized powder is used.

6.3 Measures to minimize bias: Randomization and blinding

All study participants will receive CZP under the care of their physician; thus there is no opportunity for bias. Based on this study design, randomization and blinding are not possible and are therefore not applicable to this study.

6.4 Treatment compliance

Study participants will be provided with a diary to record all CZP dosing dates and times over the study period.

6.5 Concomitant medication(s)/treatment(s)

Unless otherwise prohibited per protocol exclusion criteria, study participants are permitted to continue on their prescribed medical therapy for the disease in accordance with the instructions of their treating physician.

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

For the purposes of this study:

- Past medications are those that are ongoing at the time of first day of the last menstrual period and those that started after the first day of the last menstrual period that stopped prior to entering the Screening Period.

- Prior medications are those that are ongoing at the time of first day of the last menstrual period and those that started after the first day of the last menstrual period prior to entering the Screening Period.
- Concomitant medications are medications with at least 1 day in common with the Screening or Sampling Periods.
- Prior medications may include both past medications and concomitant medications.

6.5.1 Permitted concomitant treatments (medications and therapies)

All concomitant medications are permitted, except for those noted in Section 6.5.2.

6.5.2 Concomitant medications that lead to study withdrawal

The study participant must not participate in any other interventional clinical study or receive any unauthorized medication throughout the study period. Non-Interventional study (NIS) participation is allowed.

There are no specific prohibited concomitant medications in this study, as it is not the intention to interfere with the physician's decision on treatment. However, there are certain exclusion criteria and withdrawal criteria associated with concomitant medication use to ensure robust and interpretable data. These criteria include:

- Any medication taken 12 weeks prior to conception with strong positive evidence of a human fetal risk of teratogenicity during pregnancy.
  - The study participant must be withdrawn from the study if she takes any medication (during the pregnancy) with strong positive evidence of a human fetal risk or other adverse outcomes.
- Any biological therapeutic agent, including anti-TNFs other than CZP.
- Any biological disease modifying drug (other than CZP), whether licensed or unlicensed, for the study participant's disease during the pregnancy.

6.6 Dose modification

The study will recruit pregnant women who are prescribed commercial CZP for an approved indication in the country where study will be conducted. No dose adjustments will be mandated by the study protocol. However, in the best interest of the study participant, the treating physician can modify the dosing regimen in accordance with local medical practice in the management of her disease, or the study participant might modify her dosing regimen herself and any changes in dosing should be recorded in the diary. In these cases, the study participant will still be followed per protocol since the resultant data will be informative with the data analytical methodologies to be employed.

As described in Section 6.1, after entry into the study, the study participant's physician may modify the dosing regimen as necessary. In such cases, non-approved CZP dosing regimens will also be allowed, at the discretion of the study participant's physician and in a manner independent of this study, as long as the regimen does not exceed 400mg Q2W and the dose is recorded in the diary.

6.7 Treatment after the end of the study

Study participants may continue to be treated with commercially-available CZP in accordance with their treating physician following completion of the study.

7 DISCONTINUATION OF STUDY MEDICATION AND PARTICIPANT DISCONTINUATION/WITHDRAWAL

7.1 Discontinuation of study medication

Administration of CZP is not dictated by this protocol; therefore there are no protocol-defined reasons a participant should permanently discontinue CZP treatment.

7.1.1 Temporary discontinuation

If a study participant has at least 1 PK sample obtained during pregnancy and then CZP dosing is interrupted and restarted, or dosing is modified during pregnancy, the study participant will continue to be followed and all samples will be obtained per protocol guidelines (including postpartum samples).

If a study participant has multiple PK samples obtained during pregnancy and discontinues CZP during pregnancy (with the intention to restart CZP after delivery), a PK predose sample will be obtained at 12 weeks (±1 week) postpartum with a potential postdose sample 1 week (±1 day) after the predose postpartum sample. If the study participant does not take CZP for at least 12 weeks and provides a PK sample within this window, the study participant will be discontinued from the study.

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 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, 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 her continued participation.
2. Participant is noncompliant with the study procedures or medications in the opinion of the investigator.
3. Participant takes concomitant medications that lead to study withdrawal as defined in this protocol (Section 6.5.2).
4. Participant withdraws her consent.

5. The sponsor or a regulatory agency requests withdrawal of the participant.
6. If the study participant has a spontaneous abortion, the study participant will be discontinued from the study and a postpartum sample will not be obtained.
7. If the study participant ceases CZP during pregnancy, and upon restarting after delivery does not take CZP for at least 12 weeks and provides a PK sample within the window defined in Section 7.1.1, the study participant will be discontinued from the study.
8. If the study participant is given a dose of CZP exceeding 400mg Q2W, the study participant will be discontinued from the study.

Study participants should consult with their treating physician to determine the best method of ceasing administration of CZP based on recommendations located on the manufacturer's label.

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 she repeatedly misses scheduled visits and is unable to be contacted by the investigator.

The following actions must be taken if a participant misses a required study visit:

- The investigator 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 eCRF must document the primary reason for withdrawal.

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

8 STUDY ASSESSMENTS AND PROCEDURES

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

Protocol waivers or exemptions are not allowed.

It will be the responsibility of the treating physician to determine if the participant should continue or discontinue treatment. The sponsor should be informed immediately regarding safety concerns upon occurrence or awareness to determine if the participant should continue or discontinue participation in the study.

Adherence to the study design requirements, including those specified in the Schedule of Activities (see 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 (see Section 1.3).

Repeat or unscheduled samples may be taken for safety reasons or for technical issues with the samples.

Study participants will be provided with a diary to record all CZP dosing dates and times over the study period.

8.1 Efficacy assessments

Not applicable.

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 physical examination will take place at Screening, as specified in Section 1.3, and may be performed by the study participant's local healthcare provider, and a record of that examination provided to the investigator as documentation.

A physical examination will include, at a minimum, assessments of the skin, lungs, cardiovascular system, abdomen (liver and spleen).

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

Peripheral body temperature, pulse rate, respiratory rate, and systolic and diastolic blood pressure will be assessed.

Blood pressure and pulse measurements will be assessed with the study participant in a sitting position with a completely automated device. Manual techniques will be used only if an automated device is not available.

Blood pressure and pulse measurements should be preceded by at least 5 minutes of rest for the participant in a quiet setting without distractions (eg, television and/or cell phones).

Vital signs (to be taken before blood collection for laboratory tests) will consist of 1 pulse and 3 blood pressure measurements (3 consecutive blood pressure readings will be recorded at

intervals of at least 1 minute). The average of the 3 blood pressure readings will be recorded on the eCRF.

8.2.3 Electrocardiograms

Electrocardiograms will not be recorded in this study.

8.2.4 Clinical safety laboratory assessments

No clinical safety laboratory assessments will be performed in this study.

8.2.5 Pregnancy outcome

Information regarding pregnancy outcome and maternal hospitalization/delivery will be collected. The investigator should update the Pregnancy Report and Outcome form, as necessary, and send it to the Sponsor.

Additional information regarding collection of pregnancy-related data is located in Appendix 4 (Section 10.4).

8.3 Adverse events

The definitions of an AE and SAE can be found in Appendix 3 (Section 10.3).

Adverse events 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 CZP or study procedures, or that caused the participant to discontinue the study (see 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 at the time points 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 eCRF. 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 CZP), up to 35 days (±5 days) after the final blood sample is obtained 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 CZP 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 AEs and SAEs 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 nonleading 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 nonserious 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 CZP 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 CZP under clinical investigation. The Sponsor will comply with country-specific regulatory requirements relating to safety reporting to the regulatory authority, IRB/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 a SAE or other specific safety information (eg, summary or listing of SAEs) from the Sponsor will review and then file it along with the IB and will notify the IRB/IEC, if appropriate according to local requirements.

8.3.5 Pregnancy

Details of the pregnancies for all study participants will be collected from enrollment into the study and up to the SFU. UCB standing guidance for collection of data pertaining to pregnancy and pregnancy outcomes will be used during this study for the collection of such data (Section 8.2.5). Information regarding collection of pregnancy-related data is located in Appendix 4 Section 10.4.

Abnormal pregnancy outcomes (eg, spontaneous abortion, fetal death, stillbirth, congenital anomalies, and 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 to 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 ≥3x upper limit of normal (ULN) alanine aminotransferase or aspartate aminotransferase with coexisting ≥2xULN total bilirubin in the absence of ≥2xULN alkaline phosphatase, with no alternative explanation for the biochemical abnormality (ie, without waiting for any additional etiologic investigations to have been concluded). Follow-up information should then be reported if an alternative etiology is identified during investigation and monitoring of the participant.
- Serious infections including opportunistic infections
- Malignancies including lymphoma
- Congestive heart failure
- Demyelinating-like disorders
- Aplastic anemia, pancytopenia, thrombocytopenia, neutropenia, and leucopenia
- Serious bleeding events
- Lupus and lupus-like syndrome
- Serious skin reactions (eg, Stevens Johnson Syndrome, toxic epidermal necrosis, and erythema multiforme).

8.3.7 Disease-related events and/or disease-related outcomes not qualifying as AEs or SAEs

Anticipated SAEs are anticipated to occur in the population studied in this protocol at some frequency that is independent of drug exposure. A summary of anticipated SAEs is presented in Table 8–1 (Appendix 3).

This list does not change the investigator's obligation to report all SAEs (including Anticipated SAEs) as detailed in Section 8.3.1 and Section 10.3 (Appendix 3).

Table 8–1: Anticipated SAEs

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

SAE=serious adverse event

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 CZP 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 CZP, medically qualified personnel at UCB may identify additional safety measures (eg, AEs, vital signs) for which data will be periodically reviewed during the course of the study.

8.5 Treatment of overdose

Excessive dosing (beyond that prescribed per the local label) will be recorded by the study participant in the diary and also recorded in the eCRF. The dosing documentation will be reviewed and verified by the investigator and/or home health nurse. Any SAE or nonserious AE associated with excessive dosing must be followed as any other SAE or nonserious AE. Overdose events are only considered AEs or SAEs if there are associated clinical signs and symptoms or if the act of taking the excess CZP 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 treating physician should:

1. Contact the Medical Monitor immediately.
2. Closely monitor the participant for any AE/SAE and laboratory abnormalities until commercial 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 commercial CZP 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 eCRF.

8.6 Pharmacokinetics

Plasma and whole blood samples of approximately 5mL will be collected for measurement of plasma concentrations of CZP as specified in the Schedule of Activities (Section 1.3). 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. Each plasma sample will be divided for PK and immunogenicity analyses. Samples collected for analyses of CZP plasma concentration may also be used to evaluate safety or efficacy aspects related to concerns arising during or after the study.

8.7 Pharmacodynamics

Pharmacodynamic parameters are not evaluated in this study.

8.8 Genetics

Genetics are not evaluated in this study.

8.9 Biomarkers

Immunogenicity assessments will be the only biomarkers evaluated in this study. Additionally, serum CRP and albumin are being measured as these markers have previously been found to be influential determinants in the description of CZP population PK.

8.9.1 Immunogenicity assessments

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.

The detection and characterization of antibodies to CZP will be performed using a validated assay method by or under the supervision of the Sponsor. All samples collected for detection of antibodies to CZP will be used to assess the effect on CZP exposure.

9 STATISTICAL CONSIDERATIONS

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

9.1 Definition of analysis sets

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

The All Study Participants Screened Set will consist of all study participants who have signed the ICF and will include all participants who pass screening as well as screen failures. This will be the largest analysis set.
The Enrolled Set (ES) will include all study participants who are confirmed as having signed the ICF to participate in the study and have provided the first blood sample.

The Safety Set (SS) will include all enrolled study participants who received at least 1 dose of CZP after Screening.

The Pharmacokinetic Per-Protocol Set (PK-PPS) is a subset of the SS, consisting of those study participants who had no important protocol deviations affecting the CZP plasma concentration and for whom a sufficient number of samples are available.

9.2 General statistical considerations

All analyses will be performed using statistical analysis system (SAS®, SAS Institute, Cary, NC, USA) Version 9.4 or higher using validated program code according to relevant UCB standard operating procedures.

In general, summary statistics (n [number of available measurements], arithmetic mean, standard deviation [SD], median, minimum, and maximum) for quantitative variables and frequency

tables for qualitative data will be presented. The arithmetic mean and SD will be replaced by the geometric mean and coefficient of variation (CV), respectively, for quantitative PK data. Any further deviations from this general approach will be outlined in the SAP.

Baseline characteristics will be summarized based on the ES. Adverse event data collected will be summarized based on the SS. For PK measurements, the data will be summarized based on the PK-PPS.

For summaries of plasma concentration data, baseline will be defined as the predose measurement 12 weeks (±1 week) postpartum.

9.3 Planned PK, immunogenicity, and safety analyses

Details regarding study participant disposition and characteristics will be provided in the SAP.

9.3.1 Pharmacokinetic analyses

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

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

The CZP plasma concentrations (primary variable) will be analyzed using a linear mixed effect model (disease phenotype, time point, trimester [trimester 1, 2, 3, or postpartum] and whether the sample was predose or postdose [binary indicator] may be used as fixed effects, and the random effect will be study participant). Mean differences with 95% CI of CZP plasma concentrations between samples taken during pregnancy and baseline (predose measurement at 12 weeks (±1 week) postpartum and potential postdose sample 1 week [±1 day] after the predose postpartum sample) will be estimated within this mixed effect model using contrasts. A forest plot of mean trough CZP plasma concentrations with 95% CI of each sampling time point during pregnancy and postpartum will be displayed. Data analysis may be conducted on log-transformed data (and back-transformed results displayed). Then, the change from baseline in CZP plasma concentrations across trimesters will be adjusted for the clinical covariates of albumin, body mass index (BMI), CRP (or any other relevant covariates) and disease phenotype using a multivariate linear mixed-effects model. The resulting coefficient b-estimate represents the change in CZP plasma concentrations for a unit increase in that predictor.

Pharmacokinetic data from this study will also be analyzed using population PK methodologies, which will enable derivation of (posthoc) PK parameters throughout the study periods, as well as enable accounting for individual variations in dosing regimens and times.

Any additional analyses may be defined in the SAP.

9.3.2 Immunogenicity analyses

Immunogenicity (anti-CZP antibody levels) will be assessed through summary tables, figures and listings of individual results by study participant. All analyses will be performed using the SS, unless otherwise specified. For all tabulations, percentages will be calculated based on the number of study participants with nonmissing data. More details will be provided in the SAP.

9.3.3 Safety analyses

All safety analyses will be performed using the SS. All safety variables will be summarized by study part (each sampling point or postpartum).

9.3.3.1 Adverse events

All AEs will be coded using the Medical Dictionary for Regulatory Activities (MedDRA v24.1 or higher) and characterized as treatment-emergent according to the intake of CZP.

The occurrence and incidence of treatment-emergent adverse events (TEAEs) will be summarized by MedDRA system organ class and preferred term. The occurrence and incidence of TEAEs will also be summarized by intensity and by relationship to CZP. Adverse events leading to discontinuation and SAEs will also be summarized.

9.3.3.2 Vital signs

Measured values of vital signs (blood pressure [systolic and diastolic], respiratory rate, pulse rate, and peripheral body temperature) at Screening will be summarized descriptively.

9.3.3.3 Physical examinations

Physical examination abnormalities will be listed.

9.3.3.4 Pregnancy outcome

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

9.4 Planned efficacy/outcome analyses

Not applicable.

9.5 Handling of protocol deviations

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

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

9.6 Handling of dropouts or missing data

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

9.7 Planned interim analysis and data monitoring

Not applicable.

9.8 Determination of sample size

Because no formal hypothesis testing will be conducted, the sample size of 15 study participants is deemed sufficient for a small exploratory Phase 1B study. It is expected that up to 25 to 30 women will need to be screened to ensure that approximately 20 study participants are enrolled, in order to allow for approximately 15 evaluable study participants. These 15 evaluable participants are expected to provide the minimum of 10 study participants providing longitudinal data as defined in Section 4.1.

10 SUPPORTING DOCUMENTATION AND OPERATIONAL CONSIDERATIONS

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

10.1.1 Regulatory and ethical considerations

This 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, IB, 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 CRO agreements, as applicable.

10.1.3 Informed consent process

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 her legal representative, and by the person who conducted the informed consent discussion (investigator or designee). The participant or 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 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 United States must include the use of a Health Insurance Portability and Accountability Act Authorization form.

The participant may withdraw her consent to participate in the study at any time. A participant is considered as enrolled in the study when she has signed the ICF. An eCRF must not be started, nor may any study specific procedure be performed for a given participant, without having obtained 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 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 her personal study-related data will be used by the Sponsor in accordance with local data protection laws. The level of disclosure must also be explained to the participant.

The participant must be informed that 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 the eCRF 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 eCRF.

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

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

10.1.6.1 Electronic Case Report Form completion

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

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

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

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

Detailed instructions will be provided in the eCRF Completion Guidelines.

10.1.6.2 Apps

Not applicable.

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, or 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, 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. 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, the requirements of the IRB/IEC or local health authorities, the 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

No clinical safety laboratory tests will be performed in this study. CRP and albumin will be assessed as described in Section 8.9.

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, 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 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 fulfills 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 eCRF.
- It is **not** acceptable for the investigator to send photocopies of the participant's medical records to UCB in lieu of completion of the UCB/AE/SAE eCRF 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 IB 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 a 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 eCRF.
- 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 by telephone. • 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

All study participants will be pregnant females (IC 3).

- The investigator will collect pregnancy information on any pregnant female participating in this study. 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 at least 12 weeks after the delivery date. In certain circumstances, UCB may request that follow up is continued for a period longer than 12 weeks. Any termination 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 CZP 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.

Pregnancy and neonatal outcomes will be followed via Pregnancy Report and Outcome Forms which is the standard methodology for follow-up of all reported pregnancies and is a routine process unrelated to study procedure.

10.5 Appendix 5: Genetics

Not applicable.

10.6 Appendix 6: Liver safety – Suggested actions and follow-up assessments

No safety laboratory assessments will be performed in this study; as such, no evaluation of liver safety will be conducted.

10.7 Appendix 7: Medical device incidents – 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

AE	adverse event
BCG	Bacillus Calmette–Guérin
BMI	body mass index
CI	confidence interval
CPMP	Committee for Proprietary Medicinal Products
CRO	contract research organization
CRP	C-reactive protein
CV	Coefficient of variation
CZP	certolizumab pegol
eCRF	electronic Case Report Form
ES	Enrolled Set
EWD	Early Withdrawal or Discontinuation
Fab	antibody fragment
GCP	Good Clinical Practice
HBsAg	Hepatitis B surface antigen
IB	Investigator's Brochure
IC	inclusion criterion
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
LLOQ	lower limit of quantification
MedDRA	Medical Dictionary for Regulatory Activities
NTM	nontuberculous mycobacterial
PK	pharmacokinetics
PK-PPS	Pharmacokinetic Per-Protocol Set
Q2W	every 2 weeks
Q4W	every 4 weeks
Q8W	every 8 weeks

RNA	ribonucleic acid
SAE	serious adverse event
SAP	Statistical Analysis Plan
SAS	statistical analysis system
SD	standard deviation
SFU	Safety Follow-up
SS	Safety Set
TB	tuberculosis
TEAE	treatment-emergent adverse event
TST	tuberculin skin test
ULN	upper limit of normal

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 (Aug 29 2019)

Amendment 1 (29 Aug 2019)

Overall Rationale for the Amendment

The purpose of this substantial amendment is to implement pre-review feedback received from the Central IRB US (Advarra) dated 31 Jul 2019.

The first version of the protocol was not formally submitted.

Section # and Name	Description of Change	Brief Rationale
Title page	EudraCT number 2019-003410-13 has been added.	EudraCT number was omitted in original protocol.
Section 4.1	Previous text: This study is considered interventional due to the collection of blood samples from the women, which is not part of routine clinical practice. However, it is noninterventional regarding treatment with CZP and will only include pregnant women who decided with their treating physician to continue treatment with CZP prior to being recruited for and enrolled in the study. Study participants who start CZP treatment after confirmation of pregnancy will not be eligible to participate in the study. Study participants are responsible for procuring their own supply of commercial CZP as it is not provided as part of the study. New text: **The study is interventional due to the additional collection of blood samples from women. However, all other study assessments are part of routine clinical practice (with the exception of the diary), and the decision to continue/discontinue CZP therapy during pregnancy will be made between the participant and her**	To clarify the text and to describe further that there is no intention to interfere with treating physician's decisions on the care of their patient

	treating physician, taking into account the potential risks to the mother and the benefits of CZP therapy, and according to the applicable local label.	
Section 6.5	Added text: Unless otherwise prohibited per protocol exclusion criteria, study participants are permitted to continue on their prescribed medical therapy for the disease in accordance with the instructions of their treating physician	To clarify the intention is for study participants to continue their prescribed therapy for their disease unless prohibited per protocol exclusion criteria.
Section 6.5.2	Section heading changed from: Prohibited concomitant treatments (medications and therapies) To: **Concomitant medications that lead to study withdrawal**	To further clarify that the intention is not to interfere with the physician's decision.
Section 6.5.2	Previous text: The study participant must not participate in any other interventional clinical study or receive any unauthorized medication throughout the Study Period. New text: **The study participant must not participate in any other interventional clinical study or receive any unauthorized medication throughout the study period. Non-Interventional study (NIS) participation is allowed.**	To allow for non-interventional study participation where applicable.
	Previous text: There are certain exclusion criteria and withdrawal criteria associated with	To further clarify that there is no intention to interfere with the treating physician's decision on treatment of their patient and to add

	concomitant medication use; to protect the safety of the study participant and to ensure robust and interpretable data, there is no intention to interfere with the physician's decision on treatment. The following concomitant medications are prohibited during the study: New text: **There are no specific prohibited concomitant medications in this study, as it is not the intention to interfere with the physician's decision on treatment. However, there are certain exclusion criteria and withdrawal criteria associated with concomitant medication use to ensure robust and interpretable data. These criteria include:.**	language to describe that the use of any medications listed in section 6.5.2 would result in withdrawal from the study.
Section 7.2	Previous text: 3. Participant takes prohibited concomitant medications as defined in this protocol (Section 6.5.2). New Text: 3. Participant takes ~~prohibited~~ concomitant medications **that lead to study withdrawal** as defined in this protocol (Section 6.5.2).	To align the withdrawal criteria with updates made in Section 6.5.2
Section 8	Previous text: Immediate safety concerns should be discussed with the sponsor immediately upon occurrence or awareness to determine if the participant should continue or discontinue CZP.	To clarify it is the treating physician's responsibility to determine if the patient continues or is discontinues treatment.

	New text **It will be the responsibility of the treating physician to determine if the participant should continue or discontinue treatment. The sponsor should be informed immediately regarding safety concerns upon occurrence or awareness to determine if the participant should continue or discontinue participation in the study.**	
Section 8.3.5	Previous text: Women who become pregnant while taking CZP, and choose not to participate in the study, will still have their pregnancy followed per normal UCB guidance on pregnancy reporting. New Text: **Information regarding collection of pregnancy-related data is located in Appendix 4 section 10.4**	To align text with Section 10.4
Section 8.5	Previous text: Excessive dosing (beyond that prescribed in the protocol and including overdose) should be recorded in the Drug Accountability module of the eCRF New text: **Excessive dosing (beyond that prescribed per the local label) will be recorded by the study participant in the diary and also recorded in the eCRF. The dosing documentation will be reviewed and**	To clarify that dosing will be captured by the study participant in the diary and verified by the investigator and/or home health nurse in addition to documented in the eCRF.

	verified by the investigator and/or home health nurse	
	Deleted text: 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.	To clarify that dosing decisions are the responsibility of the treating physician
Section 10.4	Previous text: Women who become pregnant while taking CZP, and choose not to participate in the study, will still have their pregnancy followed per normal UCB guidance on pregnancy reporting. New text: **Pregnancy and neonatal outcomes will be followed via Pregnancy Report and Outcome Forms which is the standard methodology for follow-up of all reported pregnancies and is a routine process unrelated to study procedure.**	To clarify how pregnancy and neonatal outcomes will be followed-up.
Throughout	Change of "study treatment" to "CZP")	Deleted reference to ‘study treatment’ and clarified that this refers to CZP.

11 REFERENCES

CIMZIA© Prescribing information accessed at https://www.accessdata.fda.gov/drugsatfda_docs/label/2017/125160s270lbl.pdf on 15 Jul 2019.

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

Mariette X, Förger F, Abraham B, et al. Lack of placental transfer of certolizumab pegol during pregnancy: results from CRIB, a prospective, postmarketing, pharmacokinetic study. Ann Rheum Dis. 2018:77(2):228-233.

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

Name: UP0085-protocol-amend-2

Version: 1.0

Document Number: CLIN-000202273

Title: A postmarketing, multicenter, longitudinal, prospective, pharmacokinetic, Phase 1B study

Approved Date: 31 Aug 2022

Document Approvals	
Approval Verdict: Approved	Name: [redacted] Capacity: Clinical Date of Signature: 30-Aug-2022 21:22:47 GMT+0000
Approval Verdict: Approved	Name: [redacted] Capacity: Medical Date of Signature: 31-Aug-2022 08:07:51 GMT+0000
Approval Verdict: Approved	Name: [redacted] Capacity: Clinical Date of Signature: 31-Aug-2022 15:32:42 GMT+0000