NONINTERVENTIONAL STUDY PROTOCOL PS0026
AMENDMENT 1

A MULTICENTER, NONINTERVENTIONAL, PROSPECTIVE STUDY TO ASSESS THE EFFECTIVENESS OF CERTOLIZUMAB PEGOL IN PATIENTS WITH MODERATE TO SEVERE PLAQUE PSORIASIS IN DAILY PRACTICE (CIMREAL)

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Final Noninterventional Study Protocol 07 Feb 2019
Noninterventional Study Protocol Amendment 1 20 Aug 2019

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### STUDY CONTACT INFORMATION

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Clinical Monitoring Contract Research Organization

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<th>Name:</th>
<th>PAREXEL International GmbH</th>
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<tr>
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<td>Peri/Post-Approval Services</td>
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<td></td>
<td>Klinikum Westend-Haus 18</td>
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Contact Details for the Transmission of (Serious) Adverse Event/(Serious) Adverse Drug Reaction, (Serious) Adverse Device Effect, and Other Relevant Safety Information to UCB

<table>
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<th>Country</th>
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<td>Canada</td>
<td>+1 (866) 876 7</td>
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<td>Czech Republic</td>
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<td>United Kingdom</td>
<td>+44 (0) 1753 45</td>
<td>+44 1753 447858</td>
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</table>

Product Quality Complaints Contacts

In case of a product quality complaint regarding the dose-dispenser cartridge and ava electronic device, please contact UCB Cares within 1 working day. The contact details can be found at https://www.ucb.com/UCBCares.
DECLARATION AND SIGNATURE OF TREATING PHYSICIAN

I confirm that I have carefully read and understood this noninterventional study protocol and agree to conduct this study as outlined in this noninterventional study protocol, as well as local laws and requirements.

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

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

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

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

TREATING PHYSICIAN

Printed name ___________________________ Date/Signature ___________________________
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LIST OF ABBREVIATIONS

ADE  adverse device effect
ADR  adverse drug reaction
AE   adverse event
AI   auto-injector
CDMS clinical data management system
CI   confidence interval
CRO  contract research organization
CZP  certolizumab pegol
DD   device deficiency
DDC  dose-dispenser cartridge
DLQI Dermatology Life Quality Index
eCRF electronic Case Report form
EES  Effectiveness Evaluable Set
EU   European Union
Fc   fragment crystallizable
HRQoL health-related quality of life
IEC  Independent Ethics Committee
MedDRA Medical Dictionary for Regulatory Activities
NIS  noninterventional study
OP   observational point
PASI Psoriasis Area and Severity Index
PASI50, PASI75, PASI90, PASI100 Psoriasis Area and Severity Index 50%, 75%, 90%, 100% response
PFS prefilled syringe
PSO  psoriasis
Q2W  once every 2 weeks
SADE serious adverse device effect
SAE  serious adverse event
SAP  Statistical Analysis Plan
SIAQ Self-injection Assessment Questionnaire
SmPC Summary of Product Characteristics
<table>
<thead>
<tr>
<th>Abbreviation</th>
<th>Description</th>
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<tbody>
<tr>
<td>TNFα</td>
<td>tumor necrosis factor alpha</td>
</tr>
<tr>
<td>US</td>
<td>United States</td>
</tr>
<tr>
<td>USADE</td>
<td>unanticipated serious adverse device effect</td>
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1 BACKGROUND AND RATIONALE FOR THE STUDY

Psoriasis (PSO) is a common, chronic inflammatory skin disease characterized by a series of linked cellular changes in the skin such as hyperplasia of epidermal keratinocytes, vascular hyperplasia and ectasia, and infiltration of T lymphocytes, neutrophils, and other types of leucocytes in affected skin. Though the pathophysiology of PSO is not fully understood, the importance of T-cells and inflammatory cytokines has been demonstrated by the clinical benefit provided by therapies directed at these targets (Krueger and Ellis, 2005).

In addition to the impact on skin, PSO has a multitude of psychosocial and emotional effects on patients, including increased self-consciousness, frustration, fatigue, depression, and suicidal ideation. As a result, patients frequently report sleeping problems, difficulties at work, problems interacting with family members, disrupted leisure activities, and sexual difficulties (Dowlatshahi et al, 2014; Gottlieb, 2005; Mukhtar et al, 2004; Ortonne, 2004; Krueger et al, 2001).

Psoriasis has a variety of forms including plaque, guttate, pustular, erythrodermic, and psoriatic arthritis. Plaque PSO is the most common, comprising approximately 80% to 90% of all cases. Therapy for patients with PSO varies according to the severity of disease. Limited or mild disease is often treated with topical therapies such as corticosteroids and vitamin D analogs, and phototherapy. Approximately 17% of patients with PSO have moderate to severe disease that requires systemic therapies (Kurd et al, 2008), including chemophototherapy, methotrexate, or biologic agents.

Biologics, including tumor necrosis factor alpha (TNFα) inhibitors (etanercept, infliximab, and adalimumab) and anti-interleukin-17 antibodies (secukinumab and ixekizumab), are the treatment options of choice for patients with moderate to severe chronic plaque PSO who are candidates for systemic therapy or chemophototherapy. The effectiveness of multiple TNFα inhibitors in the treatment of PSO has been demonstrated in many Phase 3 clinical studies and has led to approvals for use in patients with moderate to severe chronic plaque PSO.

Certolizumab pegol (CDP870, CZP), the drug substance of Cimzia®, is a recombinant, humanized, antibody Fab’ fragment with specificity for human TNFα. Certolizumab pegol is an inhibitor of TNFα, and the unique feature of CZP among TNF antagonists is the lack of a fragment crystallizable (Fc) region, which prevents the molecule from initiating potential Fc-mediated effects such as complement-mediated cytotoxicity or antibody-dependent, cell-mediated cytotoxicity (Mease, 2011). UCB has 3 drug delivery presentations for CZP administration, including a prefilled syringe (PFS), an auto-injector (AI) (known as a prefilled pen in the European Union [EU]), and a dose-dispenser cartridge (DDC), which is to be used with a handheld electronic injection device (ava®). Each drug delivery presentation is designed to administer the entire contents of a naked PFS, which is housed within each of the 3 drug delivery presentations. The DDC and ava electronic device are not available in Canada.

Certolizumab pegol has been studied for the treatment of inflammatory diseases, such as Crohn’s disease, rheumatoid arthritis, psoriatic arthritis, axial spondyloarthritis including ankylosing spondylitis, juvenile idiopathic arthritis, and PSO. Clinical data and CZP approval status in these indications are listed in locally approved prescribing information (ie, Summary of Product Characteristics [SmPC] in Europe or Product Monograph in Canada).
Two Phase 2 clinical studies have been completed assessing CZP in adult subjects with moderate to severe chronic plaque PSO. The first study, C87040, demonstrated that CZP in doses of 200mg once every 2 weeks (Q2W) (with a 400mg dose at Week 0) or 400mg Q2W improved the signs and symptoms of PSO as measured by Psoriasis Area and Severity Index 75% (PASI75) and Physician’s Global Assessment, with up to 82.8% of subjects responding to treatment (PASI75) at the higher dose.

Following successfully completed Phase 2 studies with CZP, three Phase 3 studies with CZP in PSO were carried out (PS0002, PS0003, and PS0005). These Phase 3 studies investigated the efficacy of CZP in subjects with moderate to severe plaque PSO compared with placebo treatment (PS0002 and PS0005) and with an active comparator (etanercept) and placebo treatment (PS0003). All 3 studies demonstrated efficacy and a positive benefit-risk balance of CZP (200mg Q2W and 400mg Q2W) in the treatment of subjects with moderate to severe plaque PSO.

Certolizumab pegol received approval for PSO in the United States (US) on 24 May 2018 and in the EU on 07 Jun 2018. To date, data on the efficacy and safety of CZP in patients with moderate to severe plaque PSO have been collected from clinical study populations, and information on treatment with CZP in routine clinical practice is limited. This noninterventional study (NIS) is the first NIS with CZP in patients with moderate to severe plaque PSO. It is designed to assess the effectiveness of CZP in routine clinical practice when CZP is administered in accordance with locally approved prescribing information for drug delivery presentations of CZP, as applicable. Data pertaining to the patients’ quality of life and experience with self-injection under real world conditions will also be collected. Patients will be followed according to current diagnostic procedures and treatment in their country. The decision for initiating CZP will be independent of study participation, and CZP will be prescribed as per locally approved prescribing information.

2 STUDY TYPE

This is an observational, noninterventional study (NIS) designed to evaluate clinical outcomes in patients with moderate to severe plaque PSO newly prescribed CZP. The overall duration of observation per patient will be approximately 48 weeks under standard clinical practice care.

3 STUDY OBJECTIVES

3.1 Primary objective

The primary objective of this NIS is to assess the effectiveness of CZP in patients with moderate to severe plaque PSO as part of routine clinical practice.

3.2 Secondary objectives

The secondary objectives of this NIS are:

- To assess the impact of CZP on quality of life in patients with moderate to severe plaque PSO as part of routine clinical practice.
- To assess the effectiveness of CZP in patients with moderate to severe plaque PSO who are biologic treatment naïve versus pretreated with 1, or more (≥2) biologics.
3.3 Other objectives

The other objectives of this NIS are:

- To assess the effectiveness of CZP in patients with moderate to severe plaque PSO per the continuous reporting of prescribed maintenance doses at observational point (OP) 2 (approximately Week 12 [Week 11 through Week 18]), OP 3 (approximately Week 24 [Week 19 through Week 37]), and OP 4 (approximately Week 48 [Week 38 through Week 56]).

- To assess the effectiveness of CZP in patients with moderate to severe plaque PSO with prior biologic exposure who indicated a treatment failure (ie, primary failure [nonresponse] or secondary failure [loss of response]) to the last reported biologic.

- To gain information on comorbidities and concomitant medications in patients with moderate to severe plaque PSO treated with CZP.

- To assess the usage of the prescribed maintenance dose CZP 400mg Q2W or CZP 200mg Q2W in daily practice at OP 3.

- To assess patient retention on CZP treatment as the percentage of patients remaining in the study over time up to OP 4.

- To assess patient satisfaction and experience with CZP self-injection using PFS, AI, or the DDC and ava electronic device at OP 2.

- To assess the safety and tolerability of CZP in patients with moderate to severe plaque PSO.

4 STUDY VARIABLES

In this NIS, assessments will be performed per the standard of care, and data will be collected at 4 OPs: OP 1 at Week 0 (Baseline; start of first CZP dose), OP 2 at approximately Week 12 (Week 11 through Week 18), OP 3 at approximately Week 24 (Week 19 through Week 37), and OP 4 at approximately Week 48 (Week 38 through Week 56).

Assessments of CZP effectiveness are described in Section 10. Safety assessments are described in Section 11. Other assessments are described in Section 12.

Primary and secondary variables will be assessed for the subgroups defined in Section 13.2.4.

4.1 Primary variable

The primary variable will be the percentage of patients achieving PASI75 at OP 2.

4.2 Secondary variables

The secondary variables are:

- Change from Baseline in Dermatology Life Quality Index (DLQI) score at OP 2.
- Change from Baseline in DLQI score at OP 4.
- Percentage of patients achieving PASI75 at OP 4.
- Percentage of patients achieving PASI90 at OP 2.
• Percentage of patients achieving PASI90 at OP 4.

4.3 Other variables

The other variables are:

• Percentage of patients achieving and/or maintaining PASI50, PASI75, PASI90, and PASI100 over time.

• Absolute and percent change from Baseline in PASI score at OP 2, OP 3, and OP 4

• Change from Baseline in DLQI mean scores at OP 2, OP 3, and OP 4.

• Percentage of patients achieving minimal clinically important difference (MCID; ≥4-point reduction in the DLQI score) in DLQI at OP 2, OP 3, and OP 4.

• Percentage of patients achieving DLQI remission (absolute score of ≤1) at OP 2, OP 3, and OP 4.

• Percentage of patients on prescribed maintenance dose CZP 400mg Q2W or CZP 200mg Q2W at OP 3.

• Percentage of patients with change in prescribed maintenance CZP dose over time from OP 2 to OP 4.

• Percentage of patients continuing on CZP up to OP 4.

• Self-injection assessment questionnaire (SIAQ) scores at OP 2 per the CZP drug delivery presentation used (PFS, AI, or DDC and ava electronic device).

• All reports of adverse events (AEs) (including AEs of interest and adverse drug reactions [ADRs]) will be collected and summarized.

5 STUDY DESIGN

This is a multicenter NIS in patients with moderate to severe plaque PSO who have been newly prescribed CZP. A total of approximately 650 patients with moderate to severe plaque PSO will be followed in this study. Sample size rationale is discussed in Section 13.4. Patients will be followed for approximately 48 weeks.

The decision to prescribe a CZP drug delivery presentation for a patient with moderate to severe plaque PSO is made independently by the treating physician in the regular course of practice and is not influenced by this NIS protocol. The physician will not be asked to perform any additional examinations or investigations. Along with following the routine clinical practice for moderate to severe plaque PSO existing in his/her site/country, the physician should also follow the safety reporting criteria specified in this protocol.

There will be 4 OPs for data collection: OP 1 at Week 0 (Baseline; start of first CZP dose), OP 2 at approximately Week 12 (Week 11 through Week 18), OP 3 at approximately Week 24 (Week 19 through Week 37), and OP 4 at approximately Week 48 (Week 38 through Week 56). None of these visits are required as part of this NIS observational plan; all visits will be scheduled and conducted according to routine clinical practice.
Patients will be asked per routine clinical practice to complete a DLQI questionnaire at each OP and to provide data on the satisfaction with the self-injection of the prescribed CZP drug delivery presentation at OP 2.

Before any data are transferred from the existing medical records to the electronic Case Report form (eCRF), a Patient Data Consent form (PDCF) will be signed and dated by the patient.

5.1 Recommended schedule of study assessments

An overview of the study assessments is provided in Table 5-1.
## Table 5-1: Recommended schedule of study assessments

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<tr>
<td></td>
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<tr>
<td><em>Baseline Week 0</em> (Start of first CZP dose)</td>
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<tr>
<td>Verification of selection criteria^c</td>
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<tr>
<td>PDCF^c</td>
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<tr>
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<td>PSO history^e</td>
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</tr>
<tr>
<td>DLQI</td>
<td>X^f</td>
</tr>
<tr>
<td>Post-SIAQ version 2.1 (for self-injection only)^g</td>
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<tr>
<td>Recording of CZP drug delivery presentation in use</td>
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<tr>
<td>Drug administration</td>
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<td>Collection of AEs/DRS^h</td>
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<tr>
<td>Collection of ADEs/DDs (for ava electronic device)^i</td>
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Table 5-1: Recommended schedule of study assessments

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<thead>
<tr>
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<tbody>
<tr>
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<td>Baseline</td>
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<tr>
<td></td>
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<td>Approx. Week 48</td>
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<td>(Week 38 to Week 56)</td>
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ADE=adverse device effect; ADR=adverse drug reaction; AE=adverse event; Approx.=approximately; CZP=certolizumab pegol; DD=device deficiency; DLQI=Dermatology Life Quality Index; PASI=Psoriasis Area and Severity Index; PDCF=Patient Data Consent form; OP=observational point; PSO=psoriasis; SIAQ=Self-injection Assessment Questionnaire

a All procedures are done only if they reflect the routine clinical practice and do not include any additional diagnostic or therapeutic measures.
b Observational point scheduling should reflect routine clinical practice; no OPs are required as part of the observational plan.
c Eligibility assessments and PDCF should be completed at the same time up to OP 2.
d Includes gender, year of birth, child bearing potential (Yes/No, as applicable), breastfeeding status (Yes/No, as applicable), height, weight, and comorbidities.
e Includes date of diagnosis, date of first symptoms, prior systemic(s) and biologic(s) treatment history (document reason for discontinuation).
f PASI and DLQI should be collected up to 4 weeks prior to the first dose of CZP.
g Patients who are self-injecting CZP will be asked to complete Post-SIAQ version 2.1. If the injection is performed by the physician, nurse, or caregiver, then Post-SIAQ version 2.1 must not be completed by the patient.
h Collection of AEs/ADRs in the study will begin after the patient signs the PDCF.
i Collection of ADEs/DDs is only required for patients using the ava electronic device. Collection of ADEs/DDs in the study will begin after the patient signs the PDCF.

5.2 Study schematic

A study schematic is provided in Figure 5-1.

Figure 5-1: Study schematic

CZP=certolizumab pegol; OP=observational point; PSO=psoriasis
6 EXPECTED STUDY DURATION AND PLANNED NUMBER OF PATIENTS AND SITES

This NIS is expected to enroll approximately 650 patients at approximately 100 sites. The expected enrollment period is 18 months. The overall duration of observation per patient will be approximately 48 weeks. The observation of the first patient will start following Independent Ethics Committee (IEC) approval of the study (if required by country-specific regulations) and after the patient signs the PDCF. The documentation period for each patient will end with OP 4 (approximately Week 48).

7 ANTICIPATED REGIONS AND COUNTRIES

This NIS will be conducted at approximately 100 sites in Europe and Canada.

8 SELECTION AND WITHDRAWAL OF PATIENTS

8.1 Selection criteria

All patients from the study site who satisfy the following selection criteria will be included in the study until the required sample size (Section 13.4) is attained. All patients should fulfil selection criteria at the time of PDCF.

1. The patient is ≥18 years of age at OP 1.
2. The PDCF is signed and dated by the patient before any data can be entered into the eCRF. Patients can sign the PCDF up to OP 2.
3. The patient must have a clinical diagnosis of moderate to severe plaque PSO according to the diagnostic criteria used by the physician in routine clinical practice.
4. The decision by the treating physician to prescribe CZP and drug delivery presentation is made independent from participation in this NIS.
5. The patient has an available PASI assessment prior to the first CZP dose according to the standard of care.
6. The patient must be newly prescribed with CZP (ie, no previous CZP exposure including clinical trials, except the current prescription).
7. The patient is being treated with CZP according to instructions in locally approved prescribing information (ie, SmPC in Europe or Product Monograph in Canada).
8. The patient is considered by the treating physician to be reliable and capable of adhering to the observational plan (ie, able to understand and complete questionnaires).
9. If a patient is participating in an ongoing investigational study, then he/she will not be able to take part in this study.

8.2 Withdrawal criteria

Patients are free to withdraw their consent from this NIS at any time, without prejudice to their continued care.
8.2.1 Instructions for patient withdrawal

In the case of withdrawal or discontinuation, the physician should attempt to obtain relevant withdrawal information from the patient. The primary reason for withdrawal or discontinuation (e.g., AE, lack of effectiveness, lost to follow-up, disease remission, consent withdrawn, or other specified reason) must be documented in the eCRF. When the primary reason for withdrawal is lack of effectiveness or an AE, the AE must be reported as described in Section 11.4.

9 PRESCRIBED TREATMENT

The decision to prescribe CZP will be made by the treating physician independent of the decision to include the patient in the study. The CZP dose and administration schedule will be determined according to locally approved prescribing information for PSO.

Certolizumab pegol or any other medications will not be provided nor paid for by the Sponsor.

Each patient will receive a 5-digit number assigned when entering the study that serves as the patient identifier throughout the study.

10 ASSESSMENT OF EFFECTIVENESS

10.1 Psoriasis Area Severity Index

The PASI is a scoring system which averages the redness, thickness, and scaliness of the psoriatic lesions (graded on a 0 to 4 scale), and weights the resulting score by the area of skin involved.

The physician will assess the body for PSO in patients by:

1. Dividing the body into 4 areas: head, arms, trunk to groin, and legs to top of buttocks.
2. Assigning an average score for the erythema, thickness, and scaling for each of the 4 body areas with a score of 0 (clear) to 4 (very marked).
3. Determining the percentage of skin covered with PSO for each of the body areas and convert that to a 0 to 6 scale (0=0%; 1=<10%; 2=10% to <30%; 3=30% to <50%; 4=50% to <70%; 5=70% to <90%; 6=90% to 100%).

The PASI at OP 1 should be collected up to 4 weeks prior to the first dose of CZP. Scores will be entered into the eCRF as outlined in the Schedule of Study Assessments (Table 5-1).

10.2 Dermatology Life Quality Index

The DLQI is a questionnaire designed for use in adult patients with PSO. The DLQI is a skin disease-specific questionnaire aimed at the evaluation of how symptoms and treatment affect patients’ health-related quality of life (HRQoL). This instrument asks patients about symptoms and feelings, daily activities, leisure, work and school, personal relationships, and treatment. It has been shown to be valid and reproducible in PSO patients. The DLQI score ranges from 0 to 30 with higher scores indicating lower HRQoL. A ≥4-point reduction in the DLQI score (DLQI response) has been reported to be meaningful for the patient (within-patient minimal important difference); a DLQI absolute score of ≤1 indicates DLQI remission (ie, no or small impact of the disease on HRQoL) (Basra et al, 2015).
The DLQI should be collected up to 4 weeks prior to the first dose of CZP. Responses to the DLQI will be obtained as part of routine clinical practice, and study staff should respond in the eCRF whether or not the assessment was completed as outlined in the Schedule of Study Assessments (Table 5-1).

11 ASSESSMENT OF SAFETY

11.1 Relevant safety information to be collected and reported

The relevant safety information to be collected by the treating physician and reported to UCB includes reports of:

- (Serious) adverse events ([S]AEs) and/or (serious) adverse drug reactions ([S]ADRs), including (serious) adverse events of interest.
- Pregnancy/lactation exposure.
- Medication errors, overdose, abuse, misuse, or occupational exposure.
  - Medication error: any unintentional error in prescribing, dispensing, or administration of the UCB product while in the control of the healthcare professional, patient, or consumer.
  - Overdose: administration of a quantity of the UCB product given per administration or cumulatively that is above the maximum recommended dose according to the authorized product information. Clinical judgment should always be applied (see Section 11.7).
  - Abuse: persistent or sporadic, intentional excessive use of the UCB product, which is accompanied by harmful physical or psychological effects.
  - Misuse: situation in which the UCB product is intentionally and inappropriately used not in accordance with the authorized product information.
  - Occupational exposure: exposure to the UCB product as a result of one’s professional or nonprofessional occupation.
- Lack of therapeutic effectiveness.
- Suspected transmission of an infectious agent via a UCB product.
- Off-label use of UCB products: situation in which the UCB product is intentionally used for a medical purpose not in accordance with the authorized product information.
- Unexpected therapeutic benefit.
- Suspect AE/ADR associated with a suspected or confirmed falsified medicinal drug product or quality defect (combined complaint) of a UCB drug product.
- (Serious) adverse device effects ([S]ADEs) (for patients using ava electronic device only).
- Device deficiencies (DDs) (for patients using ava electronic device only).
11.2 Definitions

11.2.1 Adverse event

An AE is any untoward medical occurrence in a patient administered a medicinal product that does not necessarily have a causal relationship with this treatment. An AE can, therefore, be any unfavorable and unintended sign (including an abnormal laboratory finding), symptom, or disease temporally associated with the use of a medicinal product, whether or not related to the medicinal product.

11.2.2 Adverse drug reaction

An ADR is a response to a medicinal product which is noxious and unintended. “Response” in this context means that a causal relationship between a medicinal product and an AE is at least a reasonable possibility.

This includes ADRs that arise from:

- The use of a medicinal product within the terms of the marketing authorization.
- The use of a medicinal product outside the terms of the marketing authorization, including overdose, off-label use, misuse, abuse, and medication errors.
- Occupational exposure (see definition in Section 11.1).

11.2.3 Serious adverse event/serious adverse drug reaction

An AE or ADR is serious if 1 or more of the following criteria are met:

- Death.
- Life threatening: An event in which the patient 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.
- Inpatient hospitalization or prolongation of existing hospitalization: If a hospitalization is planned prior to the patient receiving the first dose of medicinal product, it is not classified as serious. However, if a hospitalization is unplanned and is a result of an adverse experience, this is considered an SAE.
- Persistent or significant disability/incapacity.
- Congenital anomaly or birth defect.
- An important medical event or an event requiring significant intervention: Medical and scientific judgment must be exercised 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 patient or may require intervention to prevent 1 of the other outcomes listed in the above definition. These are usually considered serious.

11.2.4 Adverse event of interest

An AE of interest is any AE which is listed in a Risk Management Plan, or meets another commitment requiring nonstandard expedited reporting, even if the AE does not fulfill the
expedited reporting criteria of “serious,” “unexpected,” and “associated with the use of the
drug.” Adverse events of interest for CZP include:

- Serious infections including opportunistic infections infections (note that latent tuberculosis
  is not considered an opportunistic infection, and therefore is not an adverse event of interest,
  unless it is a serious adverse event)
- 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, erythema
  multiforma)

11.2.5 Definitions for patients using the ava electronic device

Adverse device effects, SADEs, and DDs should be reported, if they occur, only for patients
using the ava electronic device and not for patients using other drug delivery presentations of
CZP.

11.2.5.1 Adverse device effect

An ADE is an AE related to the use of a device presentation. An ADE must meet one or more of the
following criteria:

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

11.2.5.2 Unanticipated adverse device effect

An unanticipated ADE is an ADE which by its nature, incidence, severity, or outcome has not
been previously identified at UCB.

11.2.5.3 Serious adverse device effect

An SADE is an ADE that has resulted in any of the consequence characteristics of an SAE (see
Section 11.2.3).

11.2.5.4 Anticipated and unanticipated serious adverse device effect

An anticipated SADE is an SADE which by its nature, incidence, severity, or outcome has been
identified in the risk analysis report issued by the Sponsor.

An unanticipated serious adverse device effect (USADE) is an SADE which by its nature,
incidence, severity, or outcome has not been identified in the current version of the risk analysis
report.
The Sponsor will determine if an SADE qualifies as an USADE.

11.2.5.5 Device deficiency

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

11.3 Identification and description of (serious) adverse events/(serious) adverse drug reactions and other relevant safety information

The treating physician is requested to inform participating patients of the need to inform their treating physician of any (S)AE/(S)ADR and other relevant safety information during the study. The patient will be given the opportunity to report (S)AEs/(S)ADRs and other relevant safety information spontaneously. A general prompt will also be given at each study visit to detect (S)AEs/(S)ADRs or other relevant safety information; for example:

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

In addition, the treating physician should review any self-assessment procedures (eg, questionnaires) employed.

In order to ensure complete safety data collection, all AEs/ADRs and other relevant safety information occurring during the study (ie, after signing the PCDF) including any posttreatment periods required by this NIS protocol (when applicable), must be reported. This includes all AEs/ADRs not present prior to the initial visit and all AEs/ADRs that recurred or worsened after the initial visit (eg, underlying or previous concomitant disease) or that resulted in discontinuation of the prescribed treatment.

Signs or symptoms of the condition/disease for which the prescribed treatment is being studied should be recorded as AEs/ADRs only if their nature changes considerably or their frequency or intensity increases in a clinically significant manner as compared with the clinical profile known to the treating physician from the patient’s history or OP 1.

When recording an (S)AE/(S)ADR or any other relevant safety information, the treating physician should use the overall diagnosis or syndrome using standard medical terminology, rather than recording individual symptoms, signs, or medical procedures. The Adverse Event Report form and source documents should be consistent.

11.4 Reporting of (serious) adverse events/(serious) adverse drug reactions and other relevant safety information

All reports of SAEs, SADRs, and AEs of interest should be transmitted to UCB in English within 1 working day of acknowledgement of the safety information using the Adverse Event Report form for NIS. All other AEs, ADRs, pregnancies/lactation exposure (see Section 11.6), and other relevant safety information should be reported within 5 working days. The fax/email where reports must be returned to are described in the section “Contact Details for the Transmission of (S)AE/(S)ADR, (S)ADE, and Other Relevant Safety Information to UCB.”
The Adverse Event Report form for NIS should be duly completed, even if the data are incomplete or if it is obvious that more data will be needed in order to draw any conclusions. However, attempts should be made to provide information as completely as possible. When this is not possible or information is not readily available, attempts should be made to obtain missing or incomplete information.

The causal relationship between CZP and an AE must be assessed by the treating physician for each AE.

Information recorded on the Adverse Event Report form for NIS will be entered into the global safety database of UCB. Additional information (eg, autopsy or laboratory reports) received by the treating physician must be provided to UCB within 1 working day for SAEs, SADRs, and AEs of interest and within 5 working days for other AEs, ADRs, pregnancies/lactation exposure, and other relevant safety information.

11.4.1 Follow up on (serious) adverse events/(serious) adverse drug reactions and other relevant safety information

The treating physician will cooperate with UCB in providing any clarification that may be needed regarding the safety aspects of the reported cases.

An (S)AE/(S)ADR should be followed until it has resolved, has a stable sequelae, the treating physician determines that it is no longer clinically significant, or the patient is lost to follow-up.

If an (S)AE/(S)ADR is still ongoing at the end of the study for a patient, follow-up should be provided until resolution/stable level of sequelae, or until the treating physician no longer deems that it is clinically significant, or until the patient is lost to follow-up.

For certain (S)AEs/(S)ADRs, standardized follow-up forms may be provided by UCB. Every effort should be made to provide as much information as possible on the form and return it to UCB.

11.5 Reporting of (serious) adverse device effects and device deficiencies for patients using the ava electronic device

Adverse device effects, SADEs, and DDs should be reported, if they occur, only for patients using the ava electronic device and not for patients using other drug delivery presentations of CZP.

11.5.1 Reporting of adverse device effects

All reports of ADEs should be transmitted to UCB using the Adverse Event and Device Deficiency form provided to the treating physician. The form must be completed in English.

Treating physicians or (or designees) shall report all ADEs to UCB within 5 working days after knowledge of the event using the appropriate forms. When required by national or local regulations, the treating physician shall also notify the IEC and regulatory agencies of all reportable events according to national regulations in acceptable timely conditions, and may also be requested by IECs to provide annual reports (if applicable).

11.5.2 Reporting of serious adverse device effects

If an SADE is reported, UCB must be informed within 1 working day of receipt of this information by the site. The treating physician (or designee) must complete a corresponding SAE
Report form for Medical Device, even if the data are incomplete, or if it is obvious that more data will be needed to draw any conclusions. The form must be completed in English.

Additional information (eg, autopsy or laboratory reports) received by the treating physician must be provided within 1 working day. All documents in the local language must be accompanied by a translation in English, or the relevant information included in the same document must be summarized in the SAE Report form for Medical Device.

The treating physician is specifically requested to collect and report to UCB (or designee) any ADEs or SADEs until end of this NIS for each patient, and to also inform participating patients of the need to inform the treating physician of any ADEs or SADEs within this period. Serious adverse events that the treating physician thinks may be associated with the ava electronic device use must be reported to UCB regardless of the time between the event and the end of the study. Upon receipt of the SAE Report Form for Medical Device, UCB will perform an assessment of whether the SADE is anticipated based on the current version of the risk analysis report.

11.5.3 Reporting of device deficiencies

If a DD related to identity, quality, durability, reliability, safety, or performance of the ava electronic device is reported (even if the device was not used), UCB must be informed within 1 working day of receipt of this information by the site. The treating physician (or designee) must complete the UCB Medical Device section of the Adverse Event and Device Deficiency Form and then also contact UCB Cares. UCB Cares will then complete the Product Complaint Form with the physician. It is important for the treating physician, when completing the forms, to include an assessment and documentation of whether the DD could have led to an SADE if any of the following occurred: suitable action had not been taken, intervention had not been made, and/or circumstances had been less fortunate. The forms must be completed in English.

11.5.4 Rule for repetition of a (serious) adverse device effect

An increase in the intensity of an ADE or SADE should lead to the repetition of the ADE or SADE being reported with:

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

11.5.5 Follow up of (serious) adverse device effects

All ADEs and SADEs should be followed until they have resolved, have stable sequelae, the treating physician determines that they are no longer clinically significant, or the patient is lost to follow up. If an ADE or SADE is ongoing at the end of the study for a patient, follow up should be provided until resolution/stable level of sequelae is achieved, until the treating physician no longer deems that it is clinically significant, or until the patient is lost to follow up. If no follow up is provided, the treating physician must provide a justification.

Information on SADEs obtained after clinical database lock will be captured through the Patient Safety database without limitation of time.
11.6 Pregnancy and breastfeeding

Pregnant women may participate in this NIS if CZP is prescribed in accordance with local prescribing information.

Treating physicians are requested to report pregnancy of a patient, pregnancy of a patient’s partner, and a patient who is breastfeeding using the Pregnancy Report and Outcome Form for Postmarketing Cases. The procedure for reporting a pregnancy or breastfeeding is identical to the procedure for reporting relevant safety information (see Section 11.4).

The progression of the pregnancy and the eventual birth (if applicable) must be followed up using the same form in which the treating physician has to report on the health of the mother and of the child. Every reasonable attempt should be made to follow the development and health of the child for at least 30 days after birth for any significant medical issues or development delay.

If the patient is lost to follow-up and/or refuses to give information, written documentation of attempts to contact the patient needs to be provided by the treating physician and filed at the site.

In cases where the partner of a male patient enrolled in a NIS becomes pregnant, the treating physician or designee is asked to contact the patient to request consent of the partner via the Partner Pregnancy Consent form that should be available in the treating physician’s site file. The treating physician will complete the Pregnancy Report and Outcome form for Postmarketing Cases and send it to UCB only after the partner has agreed that additional information can be captured and has provided the signed Partner Pregnancy Consent form.

11.7 Overdose of prescribed treatment

Excessive dosing (beyond the maximum recommended intake per day and/or per month according to marketing authorization for patients with moderate to severe plaque PSO in the respective country) should be reported on the Adverse Event Report form for NIS, independent of whether there is an (S)AE/(S)ADR associated with the excessive dosing or not.

Any (S)AE/(S)ADR associated with excessive dosing must be reported separately and followed as any other (S)AE/(S)ADR.

11.8 Safety signal detection

Reported AEs/ADRs from this study will be reviewed periodically, together with other relevant safety information received at UCB, to detect any safety concern(s) related to the treatment as early as possible so that treating physicians, study patients, and regulatory authorities will be informed appropriately and as early as possible.

12 ASSESSMENT OF OTHER VARIABLES

12.1 Self-injection assessment questionnaire

The SIAQ is a validated questionnaire developed by UCB to assess the perceived advantages and the potential limitations of self-injection of an sc medication and is composed of pre-self-injection and post-self-injection modules (Keininger and Coteur, 2011). The Post-SIAQ (version 2.1) is composed of 21 items and has no specific recall period. Items of the Post-SIAQ are summarized into 6 domains as follows:

1. Feelings about injection (3 items)
2. Self-image (1 item)  
3. Self-confidence (3 items)  
4. Pain and skin reactions during or after the injection (2 items)  
5. Ease of use of the self-injection device (5 items)  
6. Satisfaction with self-injection (7 items)  

Patients are asked to answer questions on a 5-point or 6-point semantic scale (eg, not at all, little, moderately, very, and extremely). Each domain is then scored on a scale from 0 to 10 with higher scores representing better experience with self-injection.

Responses to the Post-SIAQ version 2.1 will be obtained as part of routine clinical practice for patients who are self-injecting, and study staff should respond in the eCRF whether or not the assessment was completed as outlined in the Schedule of Study Assessments (Table 5-1).

13 STATISTICS

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

13.1 Definition of analysis sets

For this study, the following definitions will apply:

The Safety Set (SS) will consist of all patients who have received at least 1 dose of CZP and will be used to assess safety variables.

The Full Analysis Set (FAS) will consist of all patients in the SS who have a valid Baseline, and have at least 1 valid post-Baseline measurement for the PASI. The FAS will be used to assess variables describing effectiveness.

The Effectiveness Evaluable Set (EES) will consist of all patients in the FAS but exclude any patients who are not CZP naïve or who are not confirmed as having a diagnosis of moderate to severe plaque PSO.

Patients without valid data consent will be excluded from all analysis sets.

13.2 Planned analyses

The summaries for the effectiveness analyses will be performed in the FAS and for the appropriate subgroups specified in Section 13.2.4. A sensitivity analysis will be performed on the primary variable using the EES.

All of the analyses for the assessment of effectiveness as specified in the primary and secondary objectives will be performed using descriptive methods only; no formal statistical comparisons will be made to test effectiveness.

13.2.1 Analysis of the primary variable

The primary effectiveness variable is PASI75 response at OP 2 (approximately Week 12). A patient will be classified as a PASI75 responder if the PASI score has improved at least 75% from Baseline. The analysis of the primary endpoint will be performed using descriptive
statistics showing the number and percentage of patients with PASI75 response and the 95% 2-sided confidence intervals (CIs) for the percentage.

**13.2.2 Analysis of secondary variables**

The secondary variables of PASI90 (at OP 2 and OP 4), PASI75 at OP 4, and DLQI at OP 2 and OP 4 will be summarized using descriptive statistics, presenting the number of available observations, mean, standard deviation, minimum, median, maximum, interquartile range (Q1, Q3), and 95% 2-sided CIs, as appropriate, for the continuous variables, and the number of available observations, percentage, and 95% 2-sided CIs, as appropriate, for the binary variables.

**13.2.3 Analysis of other variables**

Other variables, as listed in Section 4.3, will be summarized using descriptive statistics as proposed for the secondary variables (Section 13.2.2).

**13.2.3.1 Analysis of safety variables**

The summaries for safety analyses will be performed on the SS. No statistical testing will be conducted on the safety parameters. All AE data will be listed.

All AEs will be coded and classified by system organ class, high level term, and preferred term according to the latest version of the Medical Dictionary for Regulatory Activities (MedDRA).

Adverse events, ADRs, and AEs of interest will be summarized by the frequency and percentage of patients having 1 or more of the events in question and the total number of events.

Supplemental ADE and DD data for the ava electronic device will also be listed.

**13.2.4 Subgroup analyses**

Primary and secondary variables (Section 4.1 and Section 4.2, respectively), as well as select other variables (Section 4.3) to be defined in the SAP, will be assessed for the following subgroups:

- Female/Male
- Biologic pretreatment naïve/pretreated with 1 biologic/pretreated with ≥2 biologics
- Biologic pretreatment naïve/primary failure (nonresponse) to last biologic/secondary failure (loss of response) to last reported biologic
- Without comorbidities/with comorbidities
- Other subgroups to be defined in the SAP, as needed

**13.2.5 Analysis of missing data**

Missing data for the PASI assessment will be imputed using the Markov Chain Monte Carlo method for multiple imputations, with additional analyses performed using nonresponse imputation, and observed cases ignoring the missing data. An assessment of the patterns and reasons for missing data will also be undertaken to ensure results can be interpreted appropriately. Full specifications will be provided in the SAP.
If there are individual missing items in questionnaires or missing components in composite variables, their total score will be set to missing unless specified otherwise. Missing or partial dates will be imputed as described in the SAP.

13.3  Planned interim analysis and data monitoring

No interim analyses are formally planned, but interim analyses may be performed during the course of the study as needed.

13.4  Determination of sample size

The primary endpoint variable is the percentage of patients with a PASI75 response at OP 2 (approximately Week 12). Previous clinical studies (PS0002, PS0003, and PS0005) showed Week 12 and Week 16 PASI75 response rates between 65% and 75%. The PASI75 response rate at Week 48 was between 80% and 85% in these studies.

Assuming a 15% attrition rate by OP 2, an enrolled sample size of 650 patients will provide 550 patients with assessments at OP 2 for the Full Analysis Set. Table 13-1 shows the width of 1 side of the 95% CI for the estimates of 70%, 75%, 80%, and 85% PASI75 response. The table also shows the width of 1 side of the 95% CI for a PASI75 response of 70%, for subgroup sizes of one-third (185), one-half (275), and two-thirds (370) of the patients expected to be included in the FAS.

Table 13-1: CI estimates for PASI75 response rates

<table>
<thead>
<tr>
<th>PASI75 response rate</th>
<th>Number of patients</th>
<th>Width of 95% CI</th>
</tr>
</thead>
<tbody>
<tr>
<td>70%</td>
<td>550</td>
<td>4.0%</td>
</tr>
<tr>
<td>75%</td>
<td>550</td>
<td>3.8%</td>
</tr>
<tr>
<td>80%</td>
<td>550</td>
<td>3.5%</td>
</tr>
<tr>
<td>85%</td>
<td>550</td>
<td>3.1%</td>
</tr>
<tr>
<td>70% (subgroup)</td>
<td>185</td>
<td>6.9%</td>
</tr>
<tr>
<td>70% (subgroup)</td>
<td>275</td>
<td>5.7%</td>
</tr>
<tr>
<td>70% (subgroup)</td>
<td>370</td>
<td>4.9%</td>
</tr>
</tbody>
</table>

CI=confidence interval; PASI75=Psoriasis Area and Severity Index 75%

With the proposed patient enrollment numbers for the study, the 95% CI around a PASI75 response of 70% will be estimated as (66.0%, 74.0%). Likewise, for a subgroup with 185 patients, the 95% CI around a PASI75 response of 70% will be estimated as (63.1%, 76.9%) (Table 13-1).

Note that with 650 enrolled patients and an attrition rate of 30% by OP 4 (approximately Week 48), there will be approximately 450 patients with assessments at OP 4.
14 STUDY MANAGEMENT AND ADMINISTRATION

14.1 Monitoring

Monitoring of the study will be delegated by UCB to a contract research organization (CRO). The CRO will monitor the study to meet the CRO’s monitoring standard operating procedures, and applicable regulatory requirements, and to ensure that study initiation, conduct, and closure are adequate.

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

14.1.1 Source data

All source documents must be accurate, clear, unambiguous, permanent, and capable of being audited. They should be made using some permanent form of recording (ink, typing, printing, optical disc). They should not be obscured by correction fluid or have temporary attachments (such as removable self-stick notes). Photocopies of CRFs are not considered acceptable source documents.

14.2 Data handling

14.2.1 Electronic Case Report form completion

The treating physician is responsible for prompt reporting of accurate and complete data in the eCRFs and in all required reports. Data from paper questionnaires completed by patients will be transferred into the eCRF by study personnel.

Any change or correction to the eCRF after saving must be accompanied by a reason for the change. Corrections made after the treating physician’s review and approval (by means of a password/electronic signature) of the completed eCRF will be reapproved by the treating physician.

The treating physician should maintain a list of personnel authorized to enter data into the eCRF. Detailed instructions will be provided in the eCRF Completion Instructions.

14.2.1.1 Database entry and reconciliation

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

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

Medications will be coded with the World Health Organization Drug Dictionary and AEs and ADRs will be coded using MedDRA. In both cases, the version used will be that current to the Sponsor at the time of data capture.

14.2.2 Patient enrollment log/patient identification code list

The patient’s enrollment will be recorded in the patient enrollment log.

The treating physician will keep a patient identification code list. This list remains with the treating physician and is used for unambiguous identification of each patient.

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

14.3 Termination of the study

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

If the study is prematurely terminated or suspended, UCB (or its representative) will inform the treating physicians/institutions and the regulatory authority(ies) (when applicable) of the termination or suspension and the reason(s) for the termination or suspension, in accordance with applicable regulatory requirement(s). The IEC and other institutions as per national legislation should also be informed (when applicable) and provided with reason(s) for the termination or suspension by UCB or by the treating physician/institution, as specified by the applicable regulatory requirement(s).

14.4 Archiving and data retention

The treating physician will maintain adequate records for the study, including eCRFs, medical records, data consent documents, safety reports, and other pertinent data.

All essential documents, including eCRFs, medical records, data consent documents, safety reports, and other pertinent data, are to be retained by the treating physician for at least 5 years after the final study report or first publication of the study results becomes available, whichever comes later. These documents should be retained for a longer period, however, if required by the applicable regulatory requirement(s). The treating physician 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 treating physician will also notify UCB should he/she relocate or move the study-related files to a location other than that specified in UCB’s study master file.

14.5 Audit and inspection

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

The main purposes of an audit or inspection are to confirm that the rights and well-being of the patients enrolled have been protected, that enrolled patients (ie, signing consent) are appropriate for the study, and that all data relevant for evaluation of the prescribed treatment have been processed and reported in compliance with the planned arrangements, the protocol,
investigational site, IEC standard operating procedures (when applicable), and applicable regulatory requirements.

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

15 ETHICS AND REGULATORY REQUIREMENTS

Prior to being initiated, the study will be approved by the IEC, the national competent authority, data protection authorities, and/or local institutions, as applicable by local regulations.

15.1 Data consent

Patient’s data consent must be obtained and documented in accordance with local regulations and the ethical principles that have their origin in the principles of the Declaration of Helsinki.

Prior to obtaining data consent, information on the study must be given in a language and at a level of complexity understandable to the patient in both oral and written form by the treating physician (or designee). Each patient will have the opportunity to discuss the study with the treating physician.

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

If the PDCF is amended during the study, the treating physician (or UCB, if applicable) must follow all applicable regulatory requirements pertaining to the approval of the amended PDCF by the IEC (if applicable) and use of the amended form.

15.2 Independent Ethics Committees

The study will be conducted under the auspices of an IEC if required by country-specific regulations.

The treating physician/UCB (or his/her representative) will ensure that an appropriately constituted IEC that complies with the 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 treating physician/UCB (or his/her representative) will forward copies of the protocol, PDCF, treating physician’s curriculum vitae (if applicable), and all other patient-related documents to be used for the study, to the IEC for its review and approval.

Before initiating a NIS, the treating physician will have written and dated full approval from the responsible IEC for this NIS.

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

15.3 Patient privacy

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

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

15.4 Protocol amendments

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

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

16 STUDY LIMITATIONS

The proposed study is a NIS; therefore, patients are self-selected and may be lost to follow-up. Also, while data may represent the clinics chosen for the study, it may not be representative of the greater PSO population. All data in these analyses are descriptive in nature and consideration for confounding factors should be taken into account during interpretation.

17 REMUNERATION

Any payments to physicians will be in accordance with any local regulations and laws and will compensate only the additional work load related to the conduct of the study. The remuneration shall be regulated in a separate agreement to be concluded between UCB Biopharma SPRL and the participating physician and/or his/her clinic administration.

18 PUBLICATION

Publication rights are addressed in the treating physician and/or CRO agreements, as applicable.

19 REFERENCES


Rationale for the amendment

The purpose of this amendment is the following:

- Revise the recommended time points and visit windows for OP 2, OP 3, and OP 4.

In addition, other minor edits and clarifications were made.

Modifications and changes

Global changes

The following changes were made throughout the protocol:

- OP 2 was changed to approximately Week 12 (Week 11 through Week 18), OP 3 was changed to approximately Week 24 (Week 19 through Week 37), and OP 4 was changed to approximately Week 48 (Week 38 through Week 56).
- Minor editorial revisions were made.

Specific changes

Change #1

Study Contact Information

Added contact details for Italy

Change #2

Section 2, Study type

This is an observational study (NIS) designed to evaluate clinical outcomes in patients with moderate to severe plaque PSO newly prescribed CZP. The overall duration of observation per patient will be approximately 48 weeks under standard clinical practice care.

Has been changed to:

This is an observational, noninterventional study (NIS) designed to evaluate clinical outcomes in patients with moderate to severe plaque PSO newly prescribed CZP. The overall duration of observation per patient will be approximately 48 weeks under standard clinical practice care.

Change #3

Section 3.3, Other objectives

Bullet #1 and #4

The other objectives of this NIS are:
• To assess the effectiveness of CZP in patients with moderate to severe plaque PSO per the continuous reporting of maintenance doses at observational point (OP) 2 (approximately Week 16 [Week 15 through Week 21]), OP 3 (approximately Week 32 [Week 22 through Week 40]), and OP 4 (approximately Week 48 [Week 41 through Week 56]).

• To assess the usage of the prescribed maintenance dose CZP 400mg Q2W or CZP 200mg Q2W in daily practice at OP 2.

**Has been changed to:**

The other objectives of this NIS are:

• To assess the effectiveness of CZP in patients with moderate to severe plaque PSO per the continuous reporting of prescribed maintenance doses at observational point (OP) 2 (approximately Week 12 [Week 11 through Week 18]), OP 3 (approximately Week 24 [Week 19 through Week 37]), and OP 4 (approximately Week 48 [Week 38 through Week 56]).

• To assess the usage of the prescribed maintenance dose CZP 400mg Q2W or CZP 200mg Q2W in daily practice at OP 3.

**Change #4**

**Section 4, Study variables**

**First paragraph**

In this NIS, assessments will be performed per the standard of care, and data will be collected at 4 OPs: OP 1 at Week 0 (Baseline; start of first CZP dose), OP 2 at approximately Week 16 (Week 15 through Week 21), OP 3 at approximately Week 32 (Week 22 through Week 40), and OP 4 at approximately Week 48 (Week 41 through Week 56).

**Has been changed to:**

In this NIS, assessments will be performed per the standard of care, and data will be collected at 4 OPs: OP 1 at Week 0 (Baseline; start of first CZP dose), OP 2 at approximately Week 12 (Week 11 through Week 18), OP 3 at approximately Week 24 (Week 19 through Week 37), and OP 4 at approximately Week 48 (Week 38 through Week 56).

**Change #5**

**Section 4.3, Other variables**

**Bullets #6 and #7**

• Percentage of patients on maintenance dose CZP 400mg Q2W or CZP 200mg Q2W at OP 3.

• Percentage of patients with change in maintenance CZP dose over time from OP 2 to OP 4.

**Has been changed to:**

• Percentage of patients on prescribed maintenance dose CZP 400mg Q2W or CZP 200mg Q2W at OP 3.
• Percentage of patients with change in prescribed maintenance CZP dose over time from OP 2 to OP 4.

Change #6

Section 5, Study design

Third paragraph

There will be 4 OPs for data collection: OP 1 at Week 0 (Baseline; start of first CZP dose), OP 2 at approximately Week 16 (Week 15 through Week 21), OP 3 at approximately Week 32 (Week 22 through Week 40), and OP 4 at approximately Week 48 (Week 41 through Week 56). None of these visits are required as part of this NIS observational plan; all visits will be scheduled and conducted according to routine clinical practice.

Has been changed to:

There will be 4 OPs for data collection: OP 1 at Week 0 (Baseline; start of first CZP dose), OP 2 at approximately Week 12 (Week 11 through Week 18), OP 3 at approximately Week 24 (Week 19 through Week 37), and OP 4 at approximately Week 48 (Week 38 through Week 56). None of these visits are required as part of this NIS observational plan; all visits will be scheduled and conducted according to routine clinical practice.

Change #7

Section 5.1, Recommended schedule of study assessments

Table 5-1, Recommended schedule of study assessments

Table 5-1:  Recommended schedule of study assessments

<table>
<thead>
<tr>
<th>Assessment</th>
<th>OP 1</th>
<th>OP 2</th>
<th>OP 3</th>
<th>OP 4</th>
</tr>
</thead>
<tbody>
<tr>
<td>Baseline 0 Week 0 (Start of first CZP dose)</td>
<td>Approx. Week 12 (Week 15 to Week 21)</td>
<td>Approx. Week 24 (Week 22 to Week 40)</td>
<td>Approx. Week 48 (Week 38 to Week 56)</td>
<td></td>
</tr>
</tbody>
</table>

Has been changed to:
Table 5-1:  Recommended schedule of study assessments

<table>
<thead>
<tr>
<th>Assessments&lt;sup&gt;a&lt;/sup&gt;</th>
<th>Treatment Period&lt;sup&gt;b&lt;/sup&gt;</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>OP 1</td>
</tr>
<tr>
<td>Baseline</td>
<td></td>
</tr>
<tr>
<td>Week 0</td>
<td></td>
</tr>
<tr>
<td>(Start of first</td>
<td></td>
</tr>
<tr>
<td>CZP dose)</td>
<td></td>
</tr>
<tr>
<td>Approx.</td>
<td></td>
</tr>
<tr>
<td>Week 12</td>
<td></td>
</tr>
<tr>
<td>(Week 11 to Week 18)</td>
<td></td>
</tr>
<tr>
<td>Approx.</td>
<td></td>
</tr>
<tr>
<td>Week 24</td>
<td></td>
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<tr>
<td>(Week 19 to Week 37)</td>
<td></td>
</tr>
<tr>
<td>Approx.</td>
<td></td>
</tr>
<tr>
<td>Week 48</td>
<td></td>
</tr>
<tr>
<td>(Week 38 to Week 56)</td>
<td></td>
</tr>
</tbody>
</table>

Change #8

Table 5-1, Recommended schedule of study assessments

Footnote f

The following Footnote f was added, and subsequent footnotes were re-lettered accordingly:
PASI and DLQI should be collected up to 4 weeks prior to the first dose of CZP.
Change #9

Section 5.2, Study schematic

Figure 5-1, Study schematic

Has been changed to:

Change #10

Section 8.1, Selection criteria

All patients from the study site who satisfy the following selection criteria will be included in the study until the required sample size (Section 13.4) is attained.

Has been changed to:

All patients from the study site who satisfy the following selection criteria will be included in the study until the required sample size (Section 13.4) is attained. All patients should fulfil selection criteria at the time of PDCF.

Change #11

Section 9, Prescribed treatment

The decision to prescribe CZP will be made by the treating physician independent of the decision to include the patient in the study. The CZP dose and administration schedule will be determined according to locally approved prescribing information for PSO. Selection of the maintenance dose is entirely at the discretion of the treating physician.
Has been changed to:

The decision to prescribe CZP will be made by the treating physician independent of the decision to include the patient in the study. The CZP dose and administration schedule will be determined according to locally approved prescribing information for PSO.

Change #12

Section 10.1, Psoriasis Area Severity Index

Scores will be entered into the eCRF as outlined in the Schedule of Study Assessments (Table 5-1).

Has been changed to:

The PASI at OP 1 should be collected up to 4 weeks prior to the first dose of CZP. Scores will be entered into the eCRF as outlined in the Schedule of Study Assessments (Table 5-1).

Change #13

Section 10.2, Dermatology Life Quality Index

Responses to the DLQI will be obtained as part of routine clinical practice, and study staff should respond in the eCRF whether or not the assessment was completed as outlined in the Schedule of Study Assessments (Table 5-1).

Has been changed to:

The DLQI should be collected up to 4 weeks prior to the first dose of CZP. Responses to the DLQI will be obtained as part of routine clinical practice, and study staff should respond in the eCRF whether or not the assessment was completed as outlined in the Schedule of Study Assessments (Table 5-1).

Change #14

Section 11.2.4, Adverse event of interest

First bullet

- Serious infections including opportunistic infections infections

Has been changed to:

- Serious infections including opportunistic infections infections (note that latent tuberculosis is not considered an opportunistic infection, and therefore is not an adverse event of interest, unless it is a serious adverse event)
Change #15

Section 11.2.5, Definitions for patients using the ava electronic device

The second paragraph has been removed:

As this NIS is being conducted using a CE marked device within its intended use, the provisions of Section 2.3.5 of Annex X of the Directive 93/42/EEC do not apply. During this NIS, the provisions of the Directive 93/42/EEC concerning information and notification of incidents occurring with the ava electronic device are applicable, and will be performed as per UCB’s standard operating procedures and applicable country-specific regulatory requirements for device presentation.

Change #16

Section 13.2.1, Analysis of the primary variable

The primary effectiveness variable is PASI75 response at OP 2 (approximately Week 16). A patient will be classified as a PASI75 responder if the PASI score has improved at least 75% from Baseline. The analysis of the primary endpoint will be performed using descriptive statistics showing the number and percentage of patients with PASI75 response and the 95% 2-sided confidence intervals (CIs) for the percentage.

Has been changed to:

The primary effectiveness variable is PASI75 response at OP 2 (approximately Week 12). A patient will be classified as a PASI75 responder if the PASI score has improved at least 75% from Baseline. The analysis of the primary endpoint will be performed using descriptive statistics showing the number and percentage of patients with PASI75 response and the 95% 2-sided confidence intervals (CIs) for the percentage.

Change #17

Section 13.4, Determination of sample size

The primary endpoint variable is the percentage of patients with a PASI75 response at OP 2 (approximately Week 16). Previous clinical studies (PS0002, PS0003, and PS0005) showed Week 16 PASI75 response rates of approximately 70%. The PASI75 response rate at Week 52 was between 80% and 85% in these studies.

Has been changed to:

The primary endpoint variable is the percentage of patients with a PASI75 response at OP 2 (approximately Week 12). Previous clinical studies (PS0002, PS0003, and PS0005) showed Week 12 and Week 16 PASI75 response rates between 65% and 75%. The PASI75 response rate at Week 48 was between 80% and 85% in these studies.
SPONSOR DECLARATION

I confirm that I have carefully read and understand this noninterventional study protocol and agree to conduct this noninterventional study as outlined in this protocol.