PROTOCOL PS0017 AMENDMENT 4

PHASE 2/3, MULTICENTER, RANDOMIZED, DOUBLE-BLIND, PARALLEL-GROUP, PLACEBO-CONTROLLED STUDY TO EVALUATE THE EFFICACY AND SAFETY OF CERTOLIZUMAB PEGOL IN JAPANESE SUBJECTS WITH MODERATE TO SEVERE CHRONIC PSORIASIS

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ACR20/50/70	American College of Rheumatology 20%/ 50%/70% response criteria
AE	adverse event
ALP	alkaline phosphatase
ALT	alanine aminotransferase
AST	aspartate aminotransferase
BSA	body surface area
CDMS	clinical data management system
CGI-I	Clinical Global Impressions - Improvement
CES	Cohort Enrolled Set
CFAS	Cohort Full Analysis Set
CPKS	Cohort Pharmacokinetics Set
CPM	Clinical Project Manager
CPMP	Committee for Proprietary Medicinal Products
CRO	contract research organization
CRS	Cohort Randomized Set
CSS	Cohort Safety Set
CZP	certolizumab pegol
DAS28(CRP)	Disease Activity Score 28 joint count C-reactive protein
DLQI	Dermatology Life Quality Index
DNA	deoxyribonucleic acid
ECG	electrocardiogram
eCRF	electronic Case Report form
EPS	Erythrodermic Psoriasis Set
ES	Enrolled Set
EMA/EMEA	European Medicines Agency
FAS	Full Analysis Set
FDA	Food and Drug Administration
GCP	Good Clinical Practice
GMP	Good Manufacturing Practice
GPPS	Generalized Pustular Psoriasis Set
HAQ-DI	Health Assessment Questionnaire-Disability Index

HBc	hepatitis B core
HBs	hepatitis B surface
HBV	hepatitis type B virus
HCV	hepatitis type C virus
HIV	human immunodeficiency virus
HLA	human leukocyte antigen
IB	Investigator's Brochure
ICH	International Council for Harmonisation
IGRA	interferon-gamma release assay
IMP	investigational medicinal product
IRB	Institutional Review Board
IRT	interactive response technology
ITT	Intent-to-Treat
JDA	Japanese Dermatological Association
LTBI	latent tuberculosis infection
MCID	minimal clinically important difference
MCMC	Markov Chain Monte Carlo
mNAPSI	Modified Nail Psoriasis Severity Index
NAPSIS	Nail Psoriasis Severity Index Set
NRI	nonresponse imputation
NSAID	nonsteroidal anti-inflammatory drug
NTMB	nontuberculous mycobacterium
PASI	Psoriasis Activity and Severity Index
PBO	placebo
PDILI	potential drug-induced liver injury
PEG	polyethylene glycol
PFS	prefilled syringe
PGA	Physician's Global Assessment
PGADA	Patient's Global Assessment of Disease Activity
PhGADA	Physician's Global Assessment of Disease Activity
PK	pharmacokinetic(s)
PK-PPS	Pharmacokinetics Per-Protocol Set

PPS	Per-Protocol Set
PS	Patient Safety
PsA	psoriatic arthritis
PsAS	Psoriatic Arthritis Set
PSO	psoriasis
Q2W	every 2 weeks
RS	Randomized Set
SAE	serious adverse event
sc	subcutaneous
SFU	Safety Follow-Up
SOP	Standard Operating Procedure
SS	Safety Set
SPC	Summary of Product Characteristics
TB	tuberculosis
TEAE	treatment-emergent adverse event
TNF	tumor necrosis factor
ULN	upper limit of normal
VAS	visual analog scale
WBC	white blood cell

1 SUMMARY

PS0017 is a randomized, double-blind, parallel group, placebo (PBO)-controlled, multicenter study designed to evaluate the efficacy and safety of certolizumab pegol (CZP) in adult Japanese subjects with moderate to severe chronic plaque psoriasis (PSO). In addition, a cohort of subjects with generalized pustular PSO or erythrodermic PSO will be eligible for the study. Approximately 125 subjects with moderate to severe chronic plaque PSO, including psoriatic arthritis (PsA), will be randomly assigned in a 2:2:1 ratio at Baseline to either CZP 400mg every 2 weeks (Q2W), CZP 200mg Q2W (loading dose of CZP 400mg at Weeks 0, 2, and 4), or PBO. Study drug will be administered by subcutaneous (sc) injection. Subjects will be followed in a blinded fashion up to Week 52 following randomization.

The treatment from Week 16 through Week 52 for subjects who achieve a Psoriasis Activity and Severity Index (PASI) 50 response will be based on response to double-blind treatment at Week 16. Subjects randomized to CZP 400mg Q2W will remain on their assigned dose. Subjects initially randomized to CZP 200mg Q2W will be rerandomized (1:1) to receive either CZP 200mg Q2W or CZP 400mg Q4W (with PBO administered on alternate dosing weeks to maintain the blind). Subjects randomized to PBO treatment who achieve a PASI50 response at Week 16 will continue on PBO. Subjects who do not achieve a PASI50 response at Week 16 will escape from double-blind treatment and enter the open-label arm of the study.

Subjects who do not achieve a PASI50 response at the Week 16, 24, 32, or 40 visit will escape from double-blind treatment and enter the open-label arm of the study. These subjects will receive open-label CZP (400mg Q2W as 3 loading doses followed by CZP 200mg Q2W) from the visit the response criterion is not met. Subjects receiving open-label CZP 200mg Q2W in the escape arm and not achieving a PASI50 response will be allowed to have their dose increased to CZP 400mg Q2W, at the discretion of the Investigator. If, in the opinion of the Investigator, the subject is not receiving benefit (eg, a PASI50) at the 400mg Q2W dose, the subject should be withdrawn from the study.

A cohort of subjects with generalized pustular PSO or erythrodermic PSO will be eligible for the study. At least 10 subjects with generalized pustular PSO or erythrodermic PSO will be randomly assigned in a 1:1 ratio at Baseline to open-label CZP 400mg Q2W or CZP 200mg Q2W (loading dose of CZP 400mg at Weeks 0, 2, and 4). Study drug will be administered by sc injection.

The treatment from Week 16 through Week 52 for the cohort of subjects with generalized pustular PSO or erythrodermic PSO will be based on response to open-label treatment at Week 16. Subjects achieving a "much improved," "very much improved," or PASI50 will continue to receive the same treatment as randomized. Subjects in the CZP 200mg Q2W group who are not in response (not achieving "much improved" or "very much improved" in the Global Improvement Score [for subjects with generalized pustular PSO] or a PASI50 response [for subjects with erythrodermic PSO]) will be allowed to have their dose increased to CZP 400mg Q2W, at the discretion of the Investigator. Subjects randomized to CZP 400mg Q2W will continue to receive CZP 400mg Q2W at the discretion of the Investigator. If, in the opinion of the Investigator, the subject is not receiving benefit at the 400mg Q2W dose, the subject could be withdrawn from the study. Per the Withdrawal Criteria (Section 6.3),

subjects who develop an aggravation of the primary disease or concomitant disease with hospitalization in the opinion of the Investigator must be withdrawn from the study.

All subjects, including those withdrawn from the study treatment, will have a Safety Follow-Up (SFU) Visit 10 weeks after their final dose of study medication.

The primary objective of the study is to demonstrate the efficacy of CZP administered sc at the doses of CZP 400mg Q2W and CZP 200mg Q2W (after a loading dose of CZP 400mg at Weeks 0, 2, and 4) in the treatment of moderate to severe chronic plaque PSO in Japanese subjects.

2 INTRODUCTION

Psoriasis is a common, chronic inflammatory disease characterized by a series of linked cellular changes in the skin: hyperplasia of epidermal keratinocytes, vascular hyperplasia and ectasia, and infiltration of T lymphocytes, neutrophils, and other types of leucocytes in affected skin. Although 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 (Kreuger and Ellis, 2005).

Psoriasis has a variety of forms including plaque, guttate, pustular, erythrodermic, and PsA. Plaque PSO is the most common, comprising approximately 80% to 90% of all cases. Approximately 17% of those with PSO have moderate to severe disease (Kurd et al, 2008).

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).

A number of comorbidities have been associated with PSO, especially with more severe PSO. Psoriatic arthritis, cardiovascular disease, metabolic syndrome, chronic pulmonary disease, peptic ulcer disease, renal disease, and diabetes have all been demonstrated to have an increased prevalence in PSO patients (Yeung et al, 2013; Christophers et al, 2010; Gisondi et al, 2007; Gelfand et al, 2006). The development of PsA is a sequelae to the development of PSO in approximately 30% of patients (Christophers et al, 2010). On the other hand, generalized pustular PSO is the most severe type, producing sterile pustules over a wide area of the body and occasionally causes fatal systemic symptoms. It is characterized by repeating recurrence or worsening. Erythrodermic PSO is another severe form characterized by diffuse redness and scaling covering nearly the whole body, potentially leading to fatal symptoms.

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. Patients with more severe disease are often treated with chemophototherapy, methotrexate, or biologic agents, such as tumor necrosis factor (TNF) antagonists, IL-12/23 inhibitors, and IL-17 inhibitors. The effectiveness of TNF inhibitors in the treatment of PSO has been demonstrated in many Phase 3 clinical studies and has led to the approval by the Food and Drug Administration (FDA) and also by the minister of Ministry of Health, Labour, and Welfare (MHLW) in Japan of multiple TNF inhibitors for use in patients with moderate to severe PSO. Interleukin inhibitors

include secukinumab and ixekizumab, IL-17A inhibitors approved for treatment of moderate to severe PSO. Brodalumab, an IL-17 receptor antagonist, has completed pivotal Phase 3 studies in PSO. Standard therapies for PSO are listed below:

- Topical steroids (eg, triamcinolone, mometasone, clobetasol, betamethasone, hydrocortisone) are generally used as first-line treatment of PSO. High-strength steroids are typically reserved for use on the arms and legs. Areas such as the face and skin folds (axillary, inguinal regions, etc) are usually treated with a low potency steroid. Chronic use of topical steroids can lead to tachyphylaxis and corticosteroid-related side effects, such as skin atrophy and fragility, and is generally discouraged.
- Topical vitamin D analogs (eg, calcipotriol and tacalcitol) are commonly used to treat mild to moderate PSO, and work best within the patients with mild disease. They are safe but lack efficacy for many patients with moderate to severe disease.
- Phototherapy is a frequent option for moderate to severe patients, but the inconvenience of multiple treatment visits and varying efficacy limits its use in the market. The use of photosensitizing agents, such as 8-methoxypsoralen, followed by ultraviolet A (UVA) exposure (so-called, chemophototherapy or phototherapy) has proven to be effective in extensive forms of the disease (Parrish et al, 1981; Henseler et al, 1981).
- Systemic immunosuppressants such as cyclosporine are used in moderate to severe patients. Toxicity concerns are limitations to treatment and include nausea, vomiting, diarrhea, oral ulcers, loss of appetite, low blood counts, infection, and hepatoxicity and/or nephrotoxicity.
- Biologics, including but not limited to TNFα inhibitors (infliximab, adalimumab), are the treatment options of choice for patients with moderate to severe plaque PSO who are candidates for systemic therapy or chemophototherapy. These products are injected subcutaneously or delivered via intravenous infusion and while effective, not all patients respond to current therapies and loss of response often occurs over time (Menter et al, 2011; Piaserico et al, 2014). In addition to loss of response, not all patients respond to currently available therapies; therefore, other treatment options are needed.

The efficacy of TNFα inhibitors in treating PSO has been attributed to their inhibition of Th17 T-cells (Menter et al, 2011). Different from the traditional systemic drugs that impact the entire immune system, biologics target specific parts of the immune system. The efficacy and safety of these molecules is now well established and accepted in the management of the disease, yet a recent study has shown that patients who switched to a different TNFα inhibitor as a result of secondary loss of efficacy, adverse events (AEs), or intolerance were more likely to reach a PASI75 response than those who switched as a result of primary inefficacy (Piaserico et al, 2014). Data consistently demonstrate that >50% of severely affected patients are dissatisfied with current treatments and up to 30% of severe patients are not receiving treatment in accordance with accepted therapy guidelines (Armstrong et al, 2013; Menter et al, 2011).

Certolizumab pegol (CDP870, CZP), the drug substance of Cimzia®, is a recombinant, humanized, antibody Fab′ fragment with specificity for human TNFα. The Fab′ fragment is manufactured in E. coli, purified, and conjugated via a maleimide group to polyethylene glycol (PEG) in order to extend its plasma half-life to that of the whole antibody. Certolizumab pegol is an inhibitor of TNFα, which is a pro-inflammatory cytokine with multiple biologic actions. A unique feature of CZP among TNF antagonists is the lack of an Fc (fragment crystallizable)

region, thereby the molecule cannot initiate potential Fc-mediated effects such as complement-mediated cytotoxicity or antibody dependent, cell-mediated cytotoxicity (Mease, 2011).

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 Q2W (with a 400mg loading dose at Week 0) or 400mg Q2W improved the signs and symptoms of PSO as measured by PASI75 and Physician's Global Assessment (PGA), with up to 82.8% of subjects responding to treatment (PASI75) at the higher dose. A second Phase 2 study, C87044, provided safety and efficacy data on the withdrawal and retreatment of subjects who responded to their initial treatment course in study C87040.

Based on the positive safety and efficacy results from Phase 2, and the need for new treatment options for PSO, three Phase 3 studies are ongoing (PS0002, PS0003, and PS0005). These Phase 3 studies will study the efficacy of CZP in subjects with moderate to severe plaque PSO compared to PBO treatment (PS0002 and PS0005) and to an active comparator (etanercept) and PBO treatment (PS0003). The proposed study in Japan will study the efficacy of CZP in subjects with moderate to severe plaque PSO compared to PBO treatment, and an exploratory evaluation of this study will be performed in regard to efficacy on joint symptoms in patients with PsA who are enrolled having plaque eruptions and joint symptoms.

In addition, the efficacy and safety of CZP in Japanese patients with generalized pustular PSO and erythrodermic PSO will be also assessed. As described above, plaque PSO is the most common form, but more severe variants include generalized pustular PSO and erythrodermic PSO. Patients with generalized pustular PSO or erythrodermic PSO are often refractory to currently available therapies, and there is a need for effective treatment for these types of PSO. Certolizumab pegol is a biological product that may be desirable to develop as a drug for PSO including these types of PSO. However, considering the very small population, the evaluation of generalized pustular PSO and erythrodermic PSO in a double-blind manner is not possible. Consequently, the efficacy and safety of CZP in these populations will be evaluated in an open-label design in an exploratory fashion.

3 STUDY OBJECTIVES

3.1 Primary objective

The primary objective of the study is to demonstrate the efficacy of CZP administered sc at the doses of CZP 400mg Q2W and CZP 200mg Q2W (after a loading dose of CZP 400mg at Weeks 0, 2, and 4) in the treatment of moderate to severe chronic plaque PSO in Japan.

3.2 Secondary objectives

The secondary objectives of the study are to assess:

- The optimal initial treatment dose for the treatment of moderate to severe chronic plaque PSO
- Durability of the clinical response with maintenance treatment
- The safety and tolerability of CZP
- Improvement of skin-related quality of life

- Change from Baseline in Itch Numeric Rating Scale at Week 16

3.3 Other objectives

The other objectives of the study are to demonstrate the effects of CZP on other aspects of disease:

- Efficacy for PsA disease in the subgroup of affected subjects at Baseline
- Efficacy for psoriatic nail disease in the subgroup of subjects with nail disease at Baseline
- Efficacy and safety in a cohort of patients with generalized pustular PSO or erythrodermic PSO
- Safety and efficacy of long-term use of CZP
- Pharmacokinetics and immunogenicity of CZP

4 STUDY VARIABLES

4.1 Efficacy variables

4.1.1 Primary efficacy variable

The primary efficacy variable for subjects with moderate to severe chronic plaque PSO is:

- PASI75 at Week 16

For subjects with generalized pustular PSO or erythrodermic PSO, no primary efficacy variables are planned.

4.1.2 Secondary efficacy variables

The secondary efficacy variables for subjects with moderate to severe chronic plaque PSO are:

- Physician's Global Assessment clear or almost clear (with at least 2-category improvement) at Week 16
- PASI90 at Week 16
- Change from Baseline in Dermatology Life Quality Index (DLQI) at Week 16
- Change from Baseline in Itch Numeric Rating Scale at Week 16

For subjects with generalized pustular PSO or erythrodermic PSO, no secondary efficacy variables are planned.

4.1.3 Other efficacy variables

The other efficacy variables are listed below and will be evaluated as per the schedule of assessments in Table 5–1. This excludes the primary and secondary variables as specified in Sections 4.1.1 and 4.1.2.

4.1.3.1 For subjects with moderate to severe chronic plaque PSO

4.1.3.1.1 Double-Blind Overall population

- PASI75 at Week 24 and Week 52
- PASI50, PASI75, PASI90, and PASI100

- PGA clear or almost clear (with at least 2-category improvement)
- Absolute and percent change from Baseline in PASI score
- PGA score distribution
- Time to onset of action, defined as the time to PASI50
- Time to onset of action, defined as the time to PASI75
- Time to onset of action, defined as the time to PASI90
- Time to onset of action, defined as the time to PASI100
- Absolute and percent change from Baseline in the body surface area (BSA) affected by PSO
- Change from Baseline in DLQI mean scores, percent of subjects achieving minimal clinically important difference (MCID), and percent achieving DLQI remission
- Change from Baseline in Itch Numeric Rating Scale mean scores and percent of subjects achieving MCID

4.1.3.1.2 Double-Blind PsA population

- American College of Rheumatology 20, 50, 70% response criteria (ACR20, 50, 70) and change from Baseline in all individual ACR core components in the subpopulation of subjects with PsA at Baseline
- Change from Baseline in DAS28(CRP)

4.1.3.1.3 Double-Blind NAPSI population

- Change from Baseline in Modified Nail Psoriasis Severity Index (mNAPSI) in the subpopulation of subjects with nail disease at Baseline

4.1.3.1.4 Escape treatment population

- PASI50, PASI75, PASI90, and PASI100
- PGA clear or almost clear (with at least 2-category improvement)
- Absolute and percent change from Baseline in PASI score
- PGA score distribution
- Absolute and percent change from Baseline in the BSA affected by PSO
- Change from Baseline in DLQI mean scores, percent of subjects achieving MCID, and percent achieving DLQI remission

4.1.3.2 For subjects with generalized pustular PSO or erythrodermic PSO

4.1.3.2.1 Cohort overall population

- Clinical Global Impressions of Improvement (CGI-I)
- Change from Baseline in DLQI mean scores, percent of subjects achieving MCID, and percent achieving DLQI remission

- Change from Baseline in Itch Numeric Rating Scale mean scores and percent of subjects achieving MCID

4.1.3.2.2 Cohort generalized pustular PSO population

- Global Improvement Score
- Japanese Dermatological Association (JDA) severity index score

4.1.3.2.3 Cohort erythrodermic PSO population

- PASI50, PASI75, PASI90, and PASI100
- PGA clear or almost clear (with at least 2-category improvement)
- Absolute and percent change from Baseline in PASI score
- PGA score distribution
- Absolute and percent change from Baseline in the BSA affected by PSO

4.2 Pharmacokinetic and pharmacodynamic variable

- Plasma CZP concentration prior to and during study treatment

4.3 Immunological variable

- Plasma anti-CZP antibody levels prior to and during study treatment

4.4 Safety variables

Safety variables to be assessed are:

- AEs
- Blood pressure
- Physical examination
- Clinical laboratory values (hematology, biochemistry, and urinalysis)
- Interferon-gamma release assay (IGRA) test for tuberculosis (TB)

5 STUDY DESIGN

5.1 Study description

This is a Phase 2/3, multicenter, randomized, double-blind, PBO-controlled, parallel-group study designed to evaluate the efficacy and safety of CZP in adult subjects with moderate to severe chronic PSO, including PsA, in Japanese subjects. In addition, a cohort of subjects with generalized pustular PSO or erythrodermic PSO will be eligible to receive open-label treatment in the study.

If the Investigator determines that the subject is no longer benefiting from CZP treatment, the subject should complete the Early Withdrawal Visit and return to the site for a SFU Visit 10 weeks after his/her final dose of study drug.

After the Week 24 Visit of the final subject, the database will be locked and an interim study report will be written.

The study includes 4 periods.

5.1.1 Study design for subjects with moderate to severe chronic plaque PSO

5.1.1.1 Period 1: Screening

The Screening Period of 2 to 5 weeks will be used to confirm eligibility; obtain laboratory data; verify that the doses of nonsteroidal anti-inflammatory drugs (NSAIDs) and other pain relievers, such as acetaminophen, paracetamol, or mild opiates, if used to treat PsA are stable; and enable washout of any medications not permitted for use during the study.

5.1.1.2 Period 2: Week 0 to Week 16

Eligible subjects will be allocated to the following study treatments in a 2:2:1 ratio:

- CZP 400mg (n=50): CZP administered sc at the dose of CZP 400mg Q2W
- CZP 200mg (n=50): CZP administered sc at the dose of CZP 400mg at Weeks 0, 2, and 4, followed by CZP 200mg Q2W (starting at Week 6)
- PBO (n=25): PBO administered sc Q2W

Study treatments (including PBO) will be administered by dedicated, unblinded, trained site personnel at Baseline and Q2W thereafter to Week 16.

5.1.1.3 Period 3: Week 16 to Week 52

The treatment received in Period 3 will be based on response to double-blind treatment at Week 16. All CZP and PBO treatments will be administered by dedicated unblinded site personnel at site visits, excluding the escape treatment.

Subjects who achieve a PASI50 response at Week 16 will continue therapy as follows:

- Subjects initially randomized to CZP 400mg Q2W will continue to receive CZP 400mg Q2W.
- Subjects initially randomized to CZP 200mg Q2W will be re-randomized (1:1) to receive either CZP 200mg Q2W or CZP 400mg Q4W (with PBO administered on alternate dosing weeks to maintain the blind).
- Subjects initially randomized to PBO will be continue to receive PBO.
- Subjects who do not achieve a PASI50 response at Week 16, 24, 32, or 40 will escape from double-blind treatment and receive open-label CZP treatment (400mg Q2W as 3 loading doses followed by CZP 200mg Q2W) from the visit the response criterion is not met. Subjects receiving open-label CZP 200mg Q2W in the escape arm and not achieving a PASI50 response will be allowed to have their dose increased to CZP 400mg Q2W at the visit the criterion is not met, at the discretion of the Investigator. If, in the opinion of the Investigator, the subject is not receiving benefit (eg, a PASI50) at the 400mg Q2W dose, the subject should be withdrawn from the study.

Subjects who do not achieve a PASI50 response at Week 16 will escape from double-blind treatment and receive treatment as follows:

- Escape treatment: Subjects entering the escape arm of the study will receive open-label CZP treatment (400mg Q2W as 3 loading doses followed by CZP 200mg Q2W). Subjects receiving open-label CZP 200mg Q2W in the escape arm and not achieving a PASI50 response will be allowed to have their dose increased to CZP 400mg Q2W, at the discretion of the Investigator. If, in the opinion of the Investigator, the subject is not receiving benefit (eg, a PASI50) at the CZP 400mg Q2W dose, the subject should be withdrawn from the study.

5.1.1.4 Period 4: Safety Follow-up: Week 52 to Week 60

All subjects, including those withdrawn from study treatment, will have a Safety Follow-Up Visit 10 weeks after their final dose of study medication.

5.1.2 Study design for subjects with generalized pustular PSO or erythrodermic PSO

5.1.2.1 Period 1: Screening

The Screening Period of 2 to 5 weeks will be used to confirm eligibility and obtain laboratory data.

5.1.2.2 Period 2: Week 0 to Week 16

At least 10 subjects in the cohort with generalized pustular PSO or erythrodermic PSO will be allocated in a 1:1 ratio to the following open-label study treatments:

- CZP 400mg (n ≥5): CZP administered sc at the dose of CZP 400mg Q2W
- CZP 200mg (n ≥5): CZP administered sc at the dose of CZP 400mg at Weeks 0, 2, and 4, followed by CZP 200mg Q2W (starting at Week 6)

5.1.2.3 Period 3: Week 16 to Week 52

The treatment received in Period 3 will be based on the initial study treatment and on response to open-label treatment at Week 16:

- Subjects achieving a "much improved" or "very much improved" in the Global Improvement Score (for subjects with generalized pustular PSO) or a PASI50 response (for subjects with erythrodermic PSO) will continue to receive the same treatment as randomized.
- Subjects in the CZP 200mg Q2W group who are not in response (not achieving "much improved" or "very much improved" in the Global Improvement Score [for subjects with generalized pustular PSO] or a PASI50 response [for subjects with erythrodermic PSO]) will be allowed to have their dose increased to CZP 400mg Q2W, at the discretion of the Investigator. Subjects randomized to CZP 400mg Q2W will continue to receive CZP 400mg Q2W at the discretion of the Investigator. If, in the opinion of the Investigator, the subject is not receiving benefit at the 400mg Q2W dose, the subject could be withdrawn from the study. Per the Withdrawal Criteria (Section 6.3), subjects who develop an aggravation of the primary disease or concomitant disease with hospitalization in the opinion of the Investigator must be withdrawn from the study.

5.1.2.4 Period 4: Safety Follow-up: Week 52 to Week 60

All subjects, including those withdrawn from study treatment, will have a Safety Follow-Up Visit 10 weeks after their final dose of study medication.

5.1.3 Study duration per subject

The study duration for each subject is estimated to be up to 65 weeks as follows:

- Up to 5 weeks of Screening
- 16 weeks in the Initial Treatment Period
- 36 weeks in the Maintenance Treatment Period
- Safety Follow-Up Visit 10 weeks after final dose of study drug

The end of the study is defined as the date of the final visit of the final subject in the study.

5.1.4 Planned number of subjects and site(s)

Approximately 125 subjects with moderate to severe chronic plaque PSO will be randomized. In addition, a cohort of ≥10 subjects with generalized pustular PSO or erythrodermic PSO will be enrolled. The planned number of study sites is approximately 35.

The study end is defined as the point at which the final subject completes the final visit.

5.1.5 Anticipated regions and countries

Study sites will be located in Japan.

5.2 Schedule of study assessments

Table 5–1: Schedule of study assessments

Visit/ Week (Wk)			Treatment Period																										
Protocol Activity	V1/Screening	V2/Baseline	V3/Wk 2	V4/Wk 4	V5/Wk 6	V6/Wk 8	V7/Wk 10	V8/Wk 12	V9/Wk14	V10/Wk16	V11/Wk 18	V12/Wk 20	V13/Wk 22	V14/Wk 24	V15/Wk 26	V16/Wk 28	V17/Wk 30	V18/Wk 32	V19/Wk 34	V20/Wk 36	V21/Wk 38	V22/Wk 40	V23/Wk42	V24/Wk 44	V25/Wk 46	V26/Wk 48	V27/Wk 50	Wk 52/ EWD	SFU Visit
Inclusion/exclusion	X	X																											
Informed consent	X																												
Demographic data	X																												
Psoriasis history	X																												
Significant past medical history and concomitant diseases	X																												
Blood pressure	X	X	X	X		X		X		X		X		X		X		X				X						X	X
Temperature, pulse	X																												
Height	X																												
Weight	X	X								X															X		X		
12-lead ECG	X													X													X		
Hematology/ biochemistry	X	X	X	X	X	X	X	X	X	X		X		X		X		X		X		X		X		X		X	X
Beta-D-glucan	X			X				X						X														X	
Sialylated carbohydrate antigen KL-6	X													X														X	
Urine[a]	X	X	X	X	X	X	X	X	X	X				X				X				X				X		X	X
Pregnancy testing[b]	X	X		X		X		X		X		X		X		X		X		X		X		X		X		X	X
Hepatitis B and C testing, HIV testing; HTLV-1 testing[c]	X																												
Plasma for CZP concentration and anti-CZP antibodies[d]		X	X	X	X	X		X		X				X				X				X						X	X

Table 5–1: Schedule of study assessments

Visit/ Week (Wk) / Protocol Activity	V1/Screening	V2/Baseline	Treatment Period																										SFU Visit
			V3/Wk 2	V4/Wk 4	V5/Wk 6	V6/Wk 8	V7/Wk 10	V8/Wk 12	V9/Wk14	V10/Wk16	V11/Wk 18	V12/Wk 20	V13/Wk 22	V14/Wk 24	V15/Wk 26	V16/Wk 28	V17/Wk 30	V18/Wk 32	V19/Wk 34	V20/Wk 36	V21/Wk 38	V22/Wk 40	V23/Wk42	V24/Wk 44	V25/Wk 46	V26/Wk 48	V27/Wk 50	Wk 52/ EWD	
Physical exam[e]	X	X								X				X														X	X
Chest x-ray	X[t]							X						X														X	
IGRA	X													X														X	
TB Questionnaire	X	X						X		X				X				X										X	
PASI[g]	X	X	X	X		X		X		X		X		X		X		X		X		X		X		X		X	
PGA[g]	X	X	X	X		X		X		X		X		X		X		X		X		X		X		X		X	
Itch Numeric Rating Scale		X	X	X		X		X		X		X		X		X		X		X		X		X		X		X	
BSA affected by PSO[g]	X	X								X																		X	
DLQI		X	X			X		X		X				X				X				X				X		X	
mNAPSI[h]		X	X			X		X		X				X				X				X				X		X	
Subject PsA assessments[i]	X	X	X	X		X		X		X		X		X		X		X		X		X		X		X		X	
Physician PsA assessments[j]	X	X	X	X		X		X		X		X		X		X		X		X		X		X		X		X	
Pustular and erythrodermic PSO assessments[g]	X	X	X	X		X		X		X		X		X		X		X		X		X		X		X		X	
Medical procedures	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Concomitant medication	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Adverse events[k]	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
IRT	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X		
CZP or PBO administration[l]		X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X		

BSA=body surface area; CGI-I= Clinical Global Impression-Improvement; CZP=certolizumab pegol; DLQI=Dermatology Life Quality Index; DNA=deoxyribonucleic acid; ECG=electrocardiogram; EWD=Early Withdrawal Visit; HAQ-DI=Health Assessment Questionnaire-Disability Index; HBV=hepatitis Type B virus; HIV=human immunodeficiency virus; HTLV-1=human T-cell lymphotropic virus type-1; IGRA=interferon-gamma release assay; IMP=investigational medicinal product; IRT=interactive response technology; JDA=Japanese Dermatological Association; mNAPSI=modified Nail Psoriasis

Table 5–1: Schedule of study assessments

Visit/ Week (Wk) / Protocol Activity	V1/Screening	V2/Baseline	Treatment Period																										SFU Visit
			V3/Wk 2	V4/Wk 4	V5/Wk 6	V6/Wk 8	V7/Wk 10	V8/Wk 12	V9/Wk14	V10/Wk16	V11/Wk 18	V12/Wk 20	V13/Wk 22	V14/Wk 24	V15/Wk 26	V16/Wk 28	V17/Wk 30	V18/Wk 32	V19/Wk 34	V20/Wk 36	V21/Wk 38	V22/Wk 40	V23/Wk42	V24/Wk 44	V25/Wk 46	V26/Wk 48	V27/Wk 50	Wk 52/ EWD	

Severity Index; PASI=Psoriasis Area and Severity Index; PBO=placebo; PGA=Physician's Global Assessment; PhGADA=Physician's Global Assessment of Disease Activity; PGADA=Patient's Global Assessment of Disease Activity; PsA=psoriatic arthritis; PSO=psoriasis; SFU=Safety Follow-Up; TB=tuberculosis; V=visit; VAS=visual analog scale; WBC=white blood cells; Wk=week

Note: The Screening Visit should occur between Week -5 and Week -2. The period between the Screening and Baseline Visits should not exceed 5 weeks.

[a] Urine dipstick to be performed every 2 months after Week 16. If blood or WBC are present, a microscopic examination should be performed.

[b] Pregnancy testing will be serum testing at Screening, and urine at all other visits.

[c] HBV DNA to be performed at Screening. If the subject is either hepatitis B surface antibody-positive or hepatitis B core antibody-positive at Screening, quantitative measurement of HBV-DNA should be performed every 4 weeks from Baseline to Week 52 and at SFU.

[d] Subjects who are on escape treatments should have samples taken for plasma CZP concentration and anti-CZP antibodies at the time of escape from double-blind treatment and 10 weeks after the final study drug administration.

[e] Includes evaluation of signs and symptoms of active TB and risk for exposure to TB.

[f] Screening chest x-ray must have been performed within 3 months prior to the Screening Visit.

[g] PASI, PGA, and BSA will not be performed for subjects with generalized pustular PSO. The Global Improvement Score, JDA Severity Index, and CGI-I will be performed for subjects with generalized pustular PSO. For subjects with erythrodermic PSO, the CGI-I will be performed. Note: The CGI-I and Global Improvement Score will not be performed at Screening or Baseline.

[h] For subjects with psoriatic nail disease only

[i] Only for chronic plaque PSO subjects with PsA: HAQ-DI, Patient's Assessment of Arthritis Pain (VAS), and PGADA (VAS)

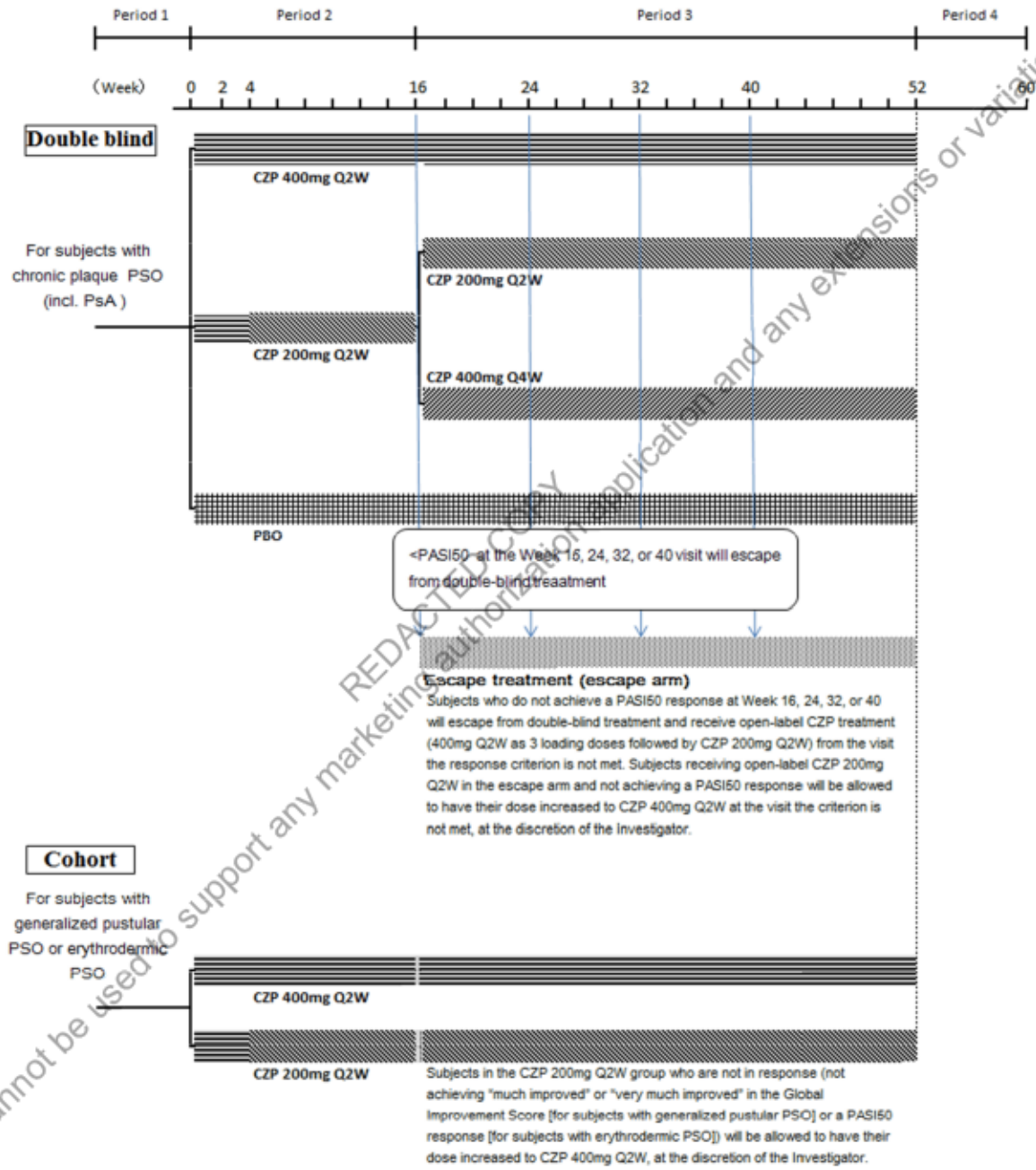
[j] Only for chronic plaque PSO subjects with PsA: swollen and tender joint counts and PhGADA (VAS)

[k] Adverse events should be reported only if they occur after signing the Informed Consent form.

[l] IMP administration of the IMP will occur after all other visit assessments have been completed.

5.3 Schematic diagram

Figure 5–1: Schematic diagram



CZP=certolizumab pegol; PASI=Psoriasis Area and Severity Index; PBO=placebo; PsA=psoriatic arthritis; PSO=psoriasis; Q2W=every 2 weeks; Q4W=every 4 weeks

5.4 Rationale for study design and selection of dose

The dose regimens will be the same as those in the global Phase 3 studies (PS0002, PS0003, and PS0005); CZP 400mg Q2W and CZP 200mg Q2W with a loading dose of CZP 400mg at Weeks 0, 2, and 4. The dose rationale for the global Phase 3 studies is as follows.

Two Phase 2 clinical studies, C87040 and C87044, with CZP have been completed in subjects with PSO. C87040 demonstrated that CZP at 400mg Q2W or 200mg Q2W (with a 400mg loading dose at Week 0) improved the signs and symptoms of PSO as measured by PASI75 and PGA. C87044 provides efficacy and safety data on the withdrawal and retreatment of subjects who responded to their initial treatment course in study C87040. These studies support the choice of doses to be evaluated in the global Phase 3 program.

In C87040, CZP at doses of 200 mg Q2W with a single loading dose of 400mg at Week 0, and 400mg Q2W were evaluated in a 12-week, multicenter, randomized, PBO-controlled study. The study had co-primary endpoints: (1) a comparison of the percentage of subjects who achieved the PASI75 response; and (2) the percentage of subjects who achieved the state of Clear or Almost Clear using the PGA. Both primary endpoints were achieved at Week 12 in both CZP treatment groups relative to PBO (Table 5–2).

Table 5–2: Percentage of subjects achieving endpoint at 12 weeks in C87040

	Placebo	CZP 200mg Q2W	CZP 400mg Q2W
PASI75	6.8%	74.6%[a]	82.8%[a]
PGA clear or almost clear	1.7%	52.5%[a]	72.4%[a]

CZP=certolizumab pegol; PASI75=Psoriasis Activity and Severity Index 75 response; PGA=Physician's Global Assessment; Q2W=every 2 weeks

[a] $p<0.001$ v placebo

Although the study was not designed to show a difference between the 2 active treatment arms, the 400mg Q2W group trended toward greater response, particularly in PGA.

Subjects who achieved a PASI75 at Week 12 in C87040 were observed for up to 24 weeks after discontinuing study drug. Those that lost response (ie, relapsed), defined as a loss of 50% of response during the observation period, were retreated for 12 weeks in C87044. The primary endpoint was the difference in the PASI score at the 12-week time point after retreatment, relative to the 12-week time point after initial treatment in the Intent-to-Treat population.

Table 5–3: PASI response rates after retreatment

	CZP 200mg Q2W	CZP 400mg Q2W
PASI at Initial Baseline (SD)	21.89 (7.52)	22.99 (8.79)
PASI at 12 Weeks in Initial Treatment [Median (95% CI)]	1.60 (0.90, 2.70)	1.80 (1.20, 2.60)
PASI at 12 Weeks in Retreatment [Median (95% CI)]	3.35 (1.40, 6.30)	2.00 (0.60, 3.30)
Median difference in PASI at 12 Weeks [Initial Treatment – Retreatment (95% CI)]		
ITT Population (N=34; N=37)	1.25 (0.10, 4.40)	0.20 (0.00, 0.70)
Per Protocol Population (N=23; N=25)	1.00 (-0.60, 5.80)	0.00 (-0.50, 0.70)

CI=confidence interval; CZP=certolizumab pegol; ITT=Intent-to-Treat; PASI=Psoriasis Area and Severity Index; Q2W=every 2 weeks; SD=standard deviation

After 12 weeks of retreatment, considerable reduction in median PASI scores was observed for both CZP doses. The primary analysis based on the ITT population indicated a modest decrease in response after 12 weeks of retreatment as compared to the initial 12 weeks of treatment at the 200mg dose (the 95% CI did not contain 0). However, no statistical difference in median PASI scores was observed in sensitivity analyses based on the Per Protocol population. There was no significant change in median PASI scores at the 400mg dose in either the primary analysis based on the ITT population or the sensitivity analyses.

Overall, both doses showed clear efficacy and an acceptable tolerability profile for 12 weeks. The higher dose appeared to be numerically more effective both for initial treatment up to Week 12 and after retreatment without safety concerns at the 400mg Q2W dose. The 200mg Q2W and 400mg Q2W doses will be further evaluated and confirmed in the proposed global Phase 3 studies where the efficacy and safety can be assessed for a longer duration of time and also this study.

6 SELECTION AND WITHDRAWAL OF SUBJECTS

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

6.1 Inclusion criteria

6.1.1 Inclusion criteria for all subjects

1. An Institutional Review Board (IRB)-approved written Informed Consent form is signed and dated by the subject.
2. Subject is considered reliable and capable of adhering to the protocol, visit schedule, or medication intake according to the judgment of the Investigator.
3. Subject is male and female, ≥20 years of age.
4. Female subjects must be either postmenopausal (defined as 12 months with no menses without an alternative medical cause), surgically incapable of childbearing, or effectively practicing an acceptable method of contraception (including oral hormonal contraceptives, intrauterine device or barrier and spermicide or contraception methods that are considered as

at least as safe for contraception). Abstinence only is not an acceptable method. Subjects must agree to use adequate contraception during the study and for at least 5 months (in accordance with the Summary of Product Characteristics, SPC) after the last dose of study treatment. Male subjects must agree to ensure they or their female partner(s) use adequate contraception during the study and for at least 5 months (in accordance with the SPC) after the subject receives their last dose of study treatment.

6.1.2 Inclusion criteria for subjects with moderate to severe chronic plaque PSO

5. Have a diagnosis of chronic plaque PSO for at least 6 months.
6. Baseline PASI ≥12 and BSA affected by PSO ≥10% and PGA score of 3 or higher.
7. Candidates for systemic PSO therapy and/or phototherapy and/or chemophototherapy.

6.1.3 Inclusion criteria for subjects with generalized pustular PSO or erythrodermic PSO

8. Have a diagnosis of generalized pustular PSO or erythrodermic PSO at Screening. A diagnosis of generalized pustular PSO must be classified on the basis of the criteria for diagnosis of generalized pustular PSO by the JDA.
9. Have a history of plaque-type PSO if subjects have a diagnosis of erythrodermic PSO.
10. Baseline BSA affected by PSO ≥80% if subjects have a diagnosis of erythrodermic PSO.

6.2 Exclusion criteria

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

6.2.1 Exclusion criteria for all subjects

1. Female subject who is breastfeeding, pregnant, or plans to become pregnant during the study or within 5 months following last dose of study drug. Male subject who is planning a partner pregnancy during the study or within 5 months following the last dose of study drug.
2. Subject has previously participated in a CZP clinical study or has received CZP treatment outside of a clinical study.
3. Subject participated in another study of a medication or a medical device under investigation within the last 3 months or currently participating in another study of a medication or medical device under investigation.
4. Subject has a known hypersensitivity to any excipients of CZP or with a history of an adverse reaction to polyethylene glycol (PEG).

Psoriasis exclusion criteria

5. Subject has guttate PSO or drug-induced PSO.

Prior medical history exclusions

6. Subject has a history of chronic or recurrent infections (more than 3 episodes requiring antibiotics/antivirals during the preceding year), recent serious or life-threatening infection within the 6 months prior to the Baseline Visit (including herpes zoster), hospitalization for

any infection in the last 6 months, or any current sign or symptom that may indicate an infection.

7. Subject has concurrent acute or chronic viral hepatitis B or C or with known human immunodeficiency virus infection (HIV) or T-cell lymphotropic virus type-1 (HTLV-1) infection.
8. Subject has a known history of or current clinically active infection with Histoplasma, Coccidiodes, Paracoccidioides, Pneumocystis, nontuberculous mycobacteria, Blastomyces, or Aspergillus.
9. Subject has a history of an infected joint prosthesis at any time with that prosthesis still in situ.
10. Subject received any live (includes attenuated) vaccination within the 8 weeks prior to Baseline (eg, inactivated influenza and pneumococcal vaccines are allowed but nasal influenza vaccination is not permitted).
11. Subject has a high risk of infection in the Investigator's opinion (eg, subjects with leg ulcers, indwelling urinary catheter, persistent or recurrent chest infections, subjects who are permanently bedridden or wheelchair bound).
12. Subject has a history of a lymphoproliferative disorder including lymphoma or current signs and symptoms suggestive of lymphoproliferative disease.
13. Subject has concurrent malignancy or history of malignancy except for the following specific exceptions will be excluded. Subjects who meet the following criteria may be included:
    a. ≤3 excised, or ablated, basal cell carcinomas of the skin
    b. One squamous cell carcinoma (stage T1 maximum) of the skin successfully excised, or ablated, with no signs of recurrence or metastases for more than 2 years prior to screening (other treatments, ie, chemotherapy) are excluded
    c. Actinic keratosis (-es)
    d. Squamous cell carcinoma-in-situ of the skin successfully excised, or ablated, more than 6 months prior to Screening
    e. Uterine cervical carcinoma in situ successfully surgically treated with no signs of recurrence or metastases for more than 5 years prior to Screening
14. Subject has class III or IV congestive heart failure as per the New York Heart Association 1964 criteria.
15. Subject has a history of, or suspected, demyelinating disease of the central nervous system (eg, multiple sclerosis or optic neuritis).
16. Subject had major surgery (including joint surgery) within the 8 weeks prior to Screening, or having planned surgery within 6 months after entering the study.
17. Subject has a current or recent history, as determined by the Investigator, of severe, progressive, and/or uncontrolled renal, hepatic, hematological, endocrine, pulmonary, cardiac, or neurological disease.

18. Subject has any of the following clinically significant laboratory abnormalities at the Screening:
    a. Aspartate aminotransferase (AST) ≥3 x upper limit of normal (ULN)
    b. Alanine aminotransferase (ALT) ≥3 x ULN
    c. Alkaline phosphatase (ALP) ≥3 x ULN
    d. Creatinine >ULN
    e. White blood cell (WBC) <3.0 x10^9/L
    f. Hepatitis B surface (HBs) antigen, hepatitis B core (HBc) antibody, hepatitis B surface (HBs) antibody, Hepatitis type B virus (HBV) DNA assay: Positive to any of these (However, patients with negative HBs antigen and HBV-DNA and positive HBc antibody and/or HBs antibody may be included provided that they undergo a HBV-DNA assay every 4 weeks (from Baseline to Week 52) and then at SFU.
    g. Hepatitis type C virus (HCV) antibody: Positive
    h. Human immunodeficiency virus (HIV) antigen or antibody: Positive to either test
    i. T-cell lymphotropic virus type-1 (HTLV-1) antibody: Positive
19. Subject has >ULN total bilirubin (≥1.5xULN total bilirubin if known Gilbert's syndrome). If subject has elevations only in total bilirubin that are >ULN and <1.5xULN, fractionate bilirubin to identify possible undiagnosed Gilbert's syndrome (ie, direct bilirubin <35%).
20. Subject has a diagnosis of any other inflammatory arthritis other than PsA, eg, rheumatoid arthritis, sarcoidosis, systemic lupus erythematosus, or a diagnosis of fibromyalgia.
21. Subject has any other condition which, in the Investigator's judgment, would make the subject unsuitable for inclusion in the study.
22. Subject with known TB infection, at high risk of acquiring TB infection, or with untreated LTBI (ie, pending anti-TB prophylactic course) or current or history of nontuberculous mycobacterial (NTMB) infection.
    a. Known TB infection whether present or past is defined as:
        - Active TB infection or clinical signs and symptoms suspicious for TB (pulmonary or extra-pulmonary)
        - History of active TB infection involving any organ system or findings in other organ systems consistent with TB infection unless adequately treated and proven to be fully recovered upon consult with a TB specialist.
        - Any evidence by radiography or other imaging modalities consistent with previously active TB infection that is not reported in the subject's medical history

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

- Known close exposure (eg, sleeping in the same room) to another person with active TB infection within the 3 months prior to Screening
- Time spent in a healthcare delivery setting or institution where individuals infected with TB are housed and where the risk of transmission of infection is high

c. LTBI is defined as an infection by mycobacteria TB with:

- A positive IGRA (or 2 indeterminate IGRAs) AND
- Chest imaging (or other imaging) negative for TB infection, AND
- Absence of signs, symptoms (eg, evidence of organ-specific involvement), or physical findings suggestive of TB infection.

Exceptions for considering subjects for study participation despite identification of LTBI:

- Subject who has recently (no more than 12 months prior to Screening) completed full treatment course of prophylaxis for LTBI.
- Subject who has started prophylactic therapy (as defined above) for LTBI at least 4 weeks prior to receiving the study medication and are committed to completing the full course of therapy may be considered for study participation.

d. NTMB is defined as a group of lung infections caused by mycobacteria different from mycobacterium TB infections.

6.2.2 Exclusion criteria for subjects with moderate to severe chronic plaque PSO

Psoriasis exclusion criteria

23. Subject has with erythrodermic or pustular form of PSO.

Prior medications exclusions

24. Subject has been exposed to more than 2 biological response modifiers (including anti-TNF) for PsA or PSO prior to Baseline Visit. Prior use must be in accordance to Table 6–1.
    - Subjects must not have been a primary failure to any prior biologic therapy (primary failure defined as no response within the first 12 weeks of treatment with the biologic) and may have been a secondary failure (ie, subject initially responded to therapy and then stopped treatment due to loss of response after Week 12) to no more than 2. Subjects who stopped biologic therapy for intolerance or reasons unrelated to efficacy are not considered secondary failures.
25. Subject used the following medications in the manner as detailed by the exclusion criteria in Table 6–1.

Table 6–1: Exclusions for prior treatments for subjects with moderate to severe active plaque PSO

Drug class	Dose	Exclusion criteria relative to Baseline Visit
Systemic retinoids	Any dose	12 weeks
Systemic treatment (nonbiological) Systemic immunosuppressants agents (eg, methotrexate, cyclosporine, azathioprine) Systemic corticosteroids Phototherapy or chemophototherapy	Any dose	4 weeks
Anti-TNFs Infliximab (including biosimilar) Adalimumab Etanercept Golimumab	Any dose	12 weeks for infliximab (including biosimilar), adalimumab, and golimumab 4 weeks for etanercept
Other biologicals and other systemic therapies Ustekinumab Secukinumab Brodalumab Ixekizumab Rituximab	Any dose	2 years for rituximab 24 weeks for ustekinumab, secukinumab, brodalumab and ixekizumab
Any other antipsoriatic agent (systemic) under investigation (or approved after the protocol is approved)	Any dose	24 weeks
Topical agents Any other antipsoriatic agent (topical) under investigation (or approved after the protocol is approved)	Any dose	4 weeks
Topical corticosteroids for dermatologic use Vitamin D analogues and topical retinoids Keratolitic and coal tar	Any dose	2 weeks

Other Exclusion Criteria

26. Subject takes PsA medications. Subjects are allowed to take stable doses of NSAIDs to treat their PsA symptoms during the study. Subjects are allowed as needed use of acetaminophen, paracetemol, or pain medications

6.2.3 Exclusion criteria for subjects with generalized pustular PSO or erythrodermic PSO

Psoriasis exclusion criteria

27. Subject has a total score on the JDA severity index for generalized pustular PSO ≥14 at Baseline if subjects have a diagnosis of generalized pustular PSO.

28. Subject has a differential diagnosis of the erythroderma (eg, erythroderma caused by lymphoma or drug eruption) other than erythrodermic PSO.

Prior medications exclusions

29. Subject with a primary failure to any prior biologic therapy (primary failure defined as no response within the first 12 weeks of treatment with the biologic).

30. Subject used the following medications and therapies in the manner as detailed by the exclusion criteria in Table 6–2:

Table 6–2: Exclusions for prior treatments for subjects with generalized pustular PSO or erythrodermic PSO

Drug class	Dose	Exclusion criteria relative to Baseline Visit
Systemic treatment (nonbiological)[a] Phototherapy or chemophotoherapy Granulocyte and monocyte adsorption apheresis	-	4 weeks for phototherapy or chemophototherapy 1week for granulocyte and monocyte adsorption apheresis
Anti-TNFs Infliximab (including biosimilar) Adalimumab Etanercept Golimumab	Any dose	12 weeks for infliximab (including biosimilar), adalimumab, and golimumab 4 weeks for etanercept
Other biologicals and other systemic therapies Ustekinumab Secukinumab Brodalumab Ixekizumab Rituximab	Any dose	2 years for rituximab 24 weeks for ustekinumab, secukinumab, brodalumab and ixekizumab
Any other antipsoriatic agent (systemic) under investigation (or approved after the protocol is approved)	Any dose	24 weeks
Topical agents Antipsoriatic agent (topical) under investigation (or approved after the protocol is approved)	Any dose	4 weeks

[a] The use of systemic retinoids, systemic immunosuppressants agents (eg: methotrexate, cyclosporine, azathioprine) and/or systemic corticosteroids (at a daily dose ≤10 mg/day of prednisone or its equivalent) are allowed provided the patient has been using such medication(s) since before starting the study. Dose reduction of these drugs is allowed as well; however, dose increase after dose reduction is limited to the level at the start of the study.

6.3 Withdrawal criteria

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

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

1. Subject develops an illness that would interfere with his/her continued participation.
2. Subject is noncompliant with the study procedures or medications in the opinion of the Investigator.
3. Subject considered as having either a suspected new latent or who develop active TB or NTMB infection during the study (including but not limited to, conversion demonstrated by IGRA or other diagnostic means) must be immediately discontinued from study medication, and an Early Termination Visit must be scheduled as soon as possible, but not later than the next regular visit.

   Confirmed active TB is a serious adverse event (SAE) and must be captured on an SAE report form and provided to the Sponsor in accordance with SAE reporting requirements. As with all SAEs, periodic follow-up reports should be completed as per protocol requirements until such time as the TB infection resolves.

   Subjects who prematurely discontinue treatment for latent TB, or, in the opinion of the Investigator or Sponsor, are noncompliant with anti-TB therapy must discontinue further use of study mediation and be immediately withdrawn.
4. There is confirmation of a positive HBV-DNA assay during the study period, subject with positive HBc antibody and/or HBs antibody at Screening. Appropriate actions such as administration of a nucleic acid analog should be taken after prompt consultation with a hepatologist.
5. Subjects developing aggravation of the primary disease or concomitant disease with hospitalization in the opinion of the Investigator.
6. Subjects with generalized pustular PSO developing a total score on the JDA Severity Index for Generalized Pustular PSO ≥14 at any post-Baseline visit.
7. Subject withdraws his/her consent.
8. There is confirmation of a subject pregnancy during the study, as evidenced by a positive pregnancy test.
9. The Sponsor or a regulatory agency requests withdrawal of the subject.
10. Subjects develops guttate PSO.

Once withdrawn from study treatment, subjects must return for the Early Withdrawal Visit and complete all Early Withdrawal assessments, and complete a final Safety Follow-Up Visit 10 weeks after the last dose of study medication.

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

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

Subjects withdrawn from the study will not be replaced.

6.3.1 Potential drug-induced liver injury IMP discontinuation criteria

Subjects with potential drug-induced liver injury (PDILI) must be assessed to determine if IMP must be discontinued. In addition, all concomitant medications and herbal supplements that are not medically necessary should also be discontinued.

The PDILI criteria below require immediate and permanent discontinuation of IMP:

- Subjects with either of the following:
  - ALT or AST ≥ 8xULN
  - ALT or AST ≥3xULN and coexisting total bilirubin ≥2xULN

The PDILI criterion below requires immediate discontinuation of IMP:

- Subjects with ALT or AST ≥3xULN who exhibit temporally associated symptoms of hepatitis or hypersensitivity. Hepatitis symptoms include fatigue, nausea, vomiting, right upper quadrant pain or tenderness. Hypersensitivity symptoms include fever (without clear alternative cause), rash, or eosinophilia (ie, >5%).

The PDILI criterion below allows for subjects to continue on IMP at the discretion of the Investigator.

- Subjects with ALT or AST ≥3xULN (and ≥2x baseline) and <8xULN, total bilirubin <2xULN, and no eosinophilia (ie, ≤5%), with no fever, rash, or symptoms of hepatitis (eg, fatigue, nausea, vomiting, right upper quadrant pain or tenderness).

Evaluation of PDILI must be initiated as described in Section 12.2.1. If subjects are unable to comply with the applicable monitoring schedule, IMP must be discontinued immediately.

Investigators should attempt to obtain information on subjects in the case of IMP discontinuation to complete the final evaluation. Subjects with PDILI should not be withdrawn from the study until investigation and monitoring are complete. All results of these evaluations and observations, as well as the reason(s) for IMP discontinuation and subject withdrawal (if applicable), must be recorded in the source documents. The CRF must document the primary reason for IMP discontinuation.

7 STUDY TREATMENTS

7.1 Description of investigational medicinal products

The investigational medicinal products (IMPs) used in this study are CZP and PBO. These products will be supplied by the UCB Clinical Supply Unit. Drug and supplies will consist of the following:

Certolizumab pegol is supplied as a sterile, clear, colorless to slightly yellow liquid solution with a pH of approximately 4.7 in 1mL single use glass prefilled syringe (PFS) with a 25G ½-inch thin-wall needle for sc injection. Each syringe contains an extractable volume of 1mL at a

concentration of 200mg/mL of CZP in 10mM sodium acetate buffer and 125mM sodium chloride as a tonicity agent.

Placebo is supplied in a PFS with a 25G ½-inch thin-wall needle, containing an injectable volume of 1mL 0.9% saline for single use. Due to the difference in presentation and viscosity between CZP and PBO, special precautions will be taken in order to ensure maintained blinding of the study (unblinded/blinded site personnel and monitors).

7.2 Treatments to be administered

The study medication is to be administered every 2 weeks by sc injections.

Study injections will be administered by study site staff. Suitable areas for sc injections are the upper arm, lateral abdominal wall, and upper outer thigh. During each dosing visit if 2 injections are being administered, each of the 2 injections should be administered at a separate injection site.

Injections should be administered with a minimum of 10 days between study injections. Each deviation less than these minimum timeframes must be discussed immediately with the Medical Monitor.

A pharmacy manual will be provided to each site containing instructions regarding drug preparation and dosing.

7.3 Packaging

Certolizumab pegol and PBO are packaged and labelled according to Good Manufacturing Practice (GMP) guidelines and applicable laws or regulations. They are suitably packaged in such a way as to protect the IMPs from deterioration during transportation and storage.

7.4 Labeling

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

7.5 Handling and storage requirements

Investigational medicinal product (IMP) must be stored under the conditions defined in the IMP Handling Manual.

The Investigator (or designee) is responsible for the safe and proper storage of IMP at the site. Investigational medicinal product stored by the Investigator is to be kept in a secured area with limited access.

Appropriate storage conditions must be ensured by controlled temperature and by completion of a temperature log in accordance with local requirements on a regular basis, per Study Manuals, showing minimum and maximum temperatures reached over the time interval.

Study drug will be shipped to the study sites in temperature controlled containers. Out-of-range shipping or storage conditions must be brought to the attention of the Sponsor or designee, immediately. Authorization to use any out-of-range IMP must be documented and received prior to dispensing or administering the IMP at the study site.

7.6 Drug accountability

A Drug Accountability form will be used to record IMP dispensing and return information on a by-subject basis and will serve as source documentation during the course of the study. Details of any IMP lost, damaged (due to breakage or wastage), not used, partially used, disposed of at the study site, or returned to the Sponsor or designee must also be recorded on the appropriate forms. All supplies and pharmacy documentation must be made available throughout the study for UCB (or designee) to review.

All study drug documentation (eg, shipping receipts, drug accountability logs, IRT randomization materials) must be maintained and accessed by unblinded, trained site personnel only. Designated, unblinded site personnel must be appropriately trained and licensed (per country guidelines) to administer injections.

Blinded study staff may be delegated the responsibility to receive, inventory and destroy the used kits. The packaging identifies each kit by a unique number that does not correlate to the contents and therefore, does not unblind study site staff. Unblinded study staff will be responsible for preparation (breaking tamper proof sticker on kit, etc) and administration of the clinical trial material to the subject, including recording the administration information on source documents.

The Investigator (or designee) is responsible for retaining all used, unused, and partially used containers of IMP until returned or destroyed.

The Investigator may assign some of the Investigator's duties for drug accountability at the study site to an appropriate pharmacist/designee.

The Investigator must ensure that the IMP is used only in accordance with the protocol.

Periodically, and/or after completion of the clinical phase of the study, all used (including empty containers)/partially used, unused and unused IMP containers must be reconciled and returned to the Sponsor, or designee, preferably in their original package. Onsite destruction of used kits only may be allowed with prior approval from the Sponsor or designee after reconciliation.

7.7 Procedures for monitoring subject compliance

Study medication will be administered in the clinic and compliance will be determined at the visit by study personnel. Drug accountability must be recorded on the Drug Accountability form.

If a subject is found to be persistently noncompliant (missing 2 or more doses during the first 16 weeks of treatment and missing 3 or more doses from Week 16 thereafter), the Sponsor, in conjunction with the Investigator, will make a decision as to whether the subject should be withdrawn from the study.

7.8 Concomitant medications/treatments

All medications (including over-the-counter drugs, vitamins, antacids) being taken at the time of the Baseline Visit or during study participation will be collected and recorded on the eCRF. Medication entries should be specific to the generic name (if a combination drug, then marketed product name) and will include the dose, unit, and frequency of administration and/or treatment, route of administration, start date, discontinuation date, and indication.

The Investigator should examine the acceptability of all concomitant procedures, medications, topical preparations, and dietary supplements not explicitly prohibited in this study.

In order to ensure that appropriate concomitant therapy is administered, subjects will be instructed to consult with the Investigator prior to taking any medication (either self-administered nonprescription drugs or prescription therapy prescribed by another physician).

7.8.1 Permitted concomitant treatments (medications and therapies)

The use of concomitant medications for medical conditions (eg, hypertension, diabetes, acute infections) or treatment of an AE is permitted during this study as long as medications are not explicitly prohibited by the protocol. The following concomitant medication is permitted during the study:

- NSAIDs, acetaminophen, paracetamol and opioids for PsA

7.8.1.1 Permitted concomitant treatments (medications and therapies) for subjects with moderate to severe chronic plaque PSO who escape from double-blind treatment

For subjects who escape from double-blind treatment, the following medications are permitted:

- Moderate potency (class III to V) topical corticosteroids for PSO
- Vitamin D analogues and topical retinoids for PSO
- Keratolytic and coal tar for PSO

7.8.1.2 Permitted concomitant treatments (medications and therapies) for subjects with generalized pustular PSO or erythrodermic PSO

The use of systemic retinoids, systemic immunosuppressants agents (eg, methotrexate, cyclosporine, azathioprine), and/or systemic corticosteroids (at a daily dose ≤10mg/day of prednisone or its equivalent) are allowed provided the subject had been using such medication(s) since before starting the study. Dose reduction of these drugs is allowed as well; however, dose increase after dose reduction is limited to the level at the start of the study.

7.8.2 Prohibited concomitant treatments (medications and therapies)

Prohibited concomitant treatments (medications and therapies) differ based on whether the subject is in the moderate to severe chronic plaque PSO, generalized pustular PSO, or erythrodermic PSO treatment group.

7.8.2.1 Prohibited concomitant treatments (medications and therapies) for subjects with moderate to severe chronic plaque PSO

The following concomitant medications are prohibited for subjects with moderate to severe chronic plaque PSO:

- Systemic retinoids
- Systemic treatments for PSO
  - Systemic immunosuppressants agents (eg, methotrexate, cyclosporine, azathioprine, thioguanine)
  - Systemic corticosteroids
  - Phototherapy or chemophototherapy

- Anti-TNFs: infliximab (including biosimilar), adalimumab, golimumab, etanercept
- Other biologics and systemic therapies: ustekimumab, secukinumab, ixekizumab, and brodalumab
- Any other antipsoriatic agent (systemic) under investigation (or approved after the protocol is approved)
- Rituximab

- Topical agents for dermatologic use:
  - High potency topical corticosteroids (class I and II)
  - Any other antipsoriatic agent (topical) under investigation (or approved after the protocol is approved)
  - Moderate potency (class III to V) topical corticosteroids
  - Vitamin D analogues and topical retinoids
  - Keratolitic and coal tar

7.8.2.2 Prohibited concomitant treatments (medications and therapies) for subjects with generalized pustular PSO or erythrodermic PSO

The following concomitant medications are prohibited for subjects with generalized pustular PSO or erythrodermic PSO:

- Systemic treatments for PSO
  - Phototherapy or chemophototherapy
  - Granulocyte and monocyte adsorption apheresis
  - Anti-TNFs: infliximab (including biosimilar), adalimumab, golimumab, etanercept)
  - Other biologics and systemic therapies: ustekimumab, secukinumab, ixekizumab, and brodalumab
  - Any other antipsoriatic agent (systemic) under investigation (or approved after the protocol is approved)
  - Antipsoriatic agent (topical) under investigation (or approved after the protocol is approved)
  - Rituximab

7.9 Blinding

Due to differences in presentation of the IMP (CZP and PBO), special precautions will be taken to ensure study blinding, and study sites will have blinded and unblinded personnel.

Certolizumab pegol and placebo injections will be prepared and administered at the study sites by unblinded dedicated study personnel who will only be responsible for dosing and drug accountability.

Study sites will be required to have a written blinding plan in place, signed by the Principal Investigator, which will detail the site's steps for ensuring that the double-blind nature of the study is maintained.

During the study, the Sponsor will provide blinded and unblinded site monitors for the purposes of verifying safety, efficacy, and drug administration and documentation records. Blinded study monitors and study site personnel, blinded to treatment assignment, will not discuss or have access to any drug-related information.

When the study is unblinded after the final subject completes the Week 24 Visit, preassigned PS0017 study team members will have access to subject-level data. This operational unblinding to treatment assignment will pertain to preassigned clinical PS0017 study team members, but will not extend to blinded staff at the investigational sites.

While the blinding of Sponsor clinical study team members is important for ensuring the integrity of data collection and analysis in a controlled study, this unblinding is considered acceptable because the primary evaluation of efficacy, upon which sample size calculations were based, will be performed in a blinded manner using Week 24 data. Additionally, because investigational site staff collecting and recording study data remain blinded, those data will not be impacted by the unblinding of selected Sponsor clinical study team members. Finally, to ensure that unblinding of study team members did not impact the primary efficacy outcome, sensitivity analyses will be outlined in the SAP to evaluate what, if any, impact there was on the results based on queries that resulted in changes to the data following the unblinding of Week 24 data.

Further details are provided in the study manuals and site blinding plan.

7.9.1 Procedures for maintaining and breaking the treatment blind

7.9.1.1 Maintenance of study treatment blind

All subject treatment details will be allocated and maintained by the interactive response technology (IRT) system.

7.9.1.2 Breaking the treatment blind in an emergency situation

The integrity of this clinical study must be maintained by observing the treatment blind. In the event of an emergency, it will be possible to determine to which treatment arm and dose the subject has been allocated by contacting the IRT. All sites will be provided with details of how to contact the system for code breaking at the start of the study. The Medical Monitor or equivalent should be consulted prior to unblinding, whenever possible.

The CPM will be informed immediately via the IRT when a code is broken, but will remain blinded to specific treatment information. Any unblinding of the IMP performed by the Investigator must be recorded in the source documents and on the Study Termination CRF page.

7.10 Randomization and numbering of subjects

An IRT will be used for assigning eligible subjects to a treatment regimen (as applicable) based on a predetermined production randomization and/or packaging schedule provided by UCB (or designee). The randomization schedule will be produced by the IRT vendor. Subject treatment assignment will be stratified by prior biologic exposure (yes/no) and psoriatic arthritis (yes/no).

The IRT will generate individual assignments for subject kits of IMP, as appropriate, according to the visit schedule.

To enroll a subject (Visit 1), the Investigator or designee will contact the IRT and provide brief details about the subject to be enrolled. Each subject will receive a 5-digit number assigned at screening that serves as the subject identifier throughout the study. The subject number will be required in all communication between the Investigator or designee and the IRT regarding a particular subject. Subject numbers and kit numbers will be tracked via the IRT.

To randomize a subject, the Investigator or designee will contact the IRT and provide brief details about the subject to be randomized. The IRT will automatically inform the Investigator or designee of the subject's randomization number. The IRT will allocate kit numbers to the subject based on the subject number during the course of the study. The randomization number must be incorporated into the CRF.

8 STUDY PROCEDURES BY VISIT

After the Baseline Visit, subjects will have study assessments and procedures every 2 weeks through the Week 52 Visit.

- Visit windows of ±3 days on either side of the scheduled dosing are permitted; however, the Investigator should try to keep the subjects on the original dosing schedule. The window of ±3 days is relative to Baseline and applicable for all subsequent visits. Changes to the dosing schedule outside of the 3-day window must be discussed with the Medical Monitor and may result in subject withdrawal.
- For the Safety Follow-up Visit (10 weeks after final dose), the visit should occur no more than 3 days prior to the scheduled visit date and within 14 days after the scheduled visit date (-3 days/+14 days).

8.1 Visit 1 (Screening)

Prior to any study activities, subjects will be asked to read and sign an ICF that has been approved by an IRB and the Sponsor and which complies with regulatory requirements.

The period between the Screening and Baseline Visits should not exceed 5 weeks.

Assessments at the Screening Visit include:

- Confirm informed consent
- Assess inclusion/exclusion criteria
- Demographic data
- Medical history
- Medical procedures
- Concomitant medications
- AEs (only if it occurred after signing informed consent)
- Psoriasis history
- Blood pressure, pulse, and temperature

- 12-lead ECG
- Height
- Weight
- Hematology, biochemistry, and urine for clinical laboratory values, including a serum pregnancy test for women of childbearing potential, hepatitis B and C testing, HIV, HTLV-1 testing, beta-D-glucan, and sialylated carbohydrate antigen KL-6
- Physical examination, including evaluation for signs and symptoms of TB
- Chest x-ray (not necessary if performed within 3 months prior to Screening Visit and report is available)
- IGRA
- Subject TB questionnaire
- PASI (will not be performed in subjects with generalized pustular PSO)
- PGA (will not be performed in subjects with generalized pustular PSO)
- BSA affected by PSO (will not be performed in subjects with generalized pustular PSO)
- Subject PsA assessments (HAQ-DI, Patient's Assessment of Arthritis Pain, and PGADA for subjects with PsA)
- Physician PsA assessments (swollen and tender joint counts and PhGADA for subjects with PsA)
- Pustular and erythrodermic PSO assessments (JDA Severity Index for subjects with generalized pustular PSO)
- IRT for subject screening
- Schedule Baseline visit within 5 weeks

8.2 Visit 2 (Baseline)

Subjects will have the following procedures performed/recorded prior to administration of study drug:

- Review of inclusion/exclusion criteria and confirm study eligibility
- Blood pressure
- Weight
- Hematology, biochemistry, and urine for clinical laboratory values
- Urine pregnancy test for women of childbearing potential
- Plasma for PK and immunogenicity samples
- Physical examination, including evaluation for signs and symptoms of TB
- Subject TB questionnaire

- PASI (will not be performed in subjects with generalized pustular PSO)
- PGA (will not be performed in subjects with generalized pustular PSO)
- Itch Numeric Rating Scale
- BSA (will not be performed in subjects with generalized pustular PSO)
- DLQI
- mNAPSI (for subjects with psoriatic nail disease)
- Subject PsA assessments (HAQ-DI, Patient's Assessment of Arthritis Pain, and PGADA for subjects with PsA)
- Physician PsA assessments (swollen and tender joint counts and PhGADA for subjects with PsA)
- Pustular and erythrodermic PSO assessments (JDA Severity Index for subjects with generalized pustular PSO)
- Medical procedures
- Concomitant medication
- AEs
- IRT to randomize subject and obtain kit number
- Study drug administration (after all other visit assessments completed)

8.3 Visit 3 (Week 2)

Subjects will have the following procedures performed/recorded prior to administration of study drug:

- Blood pressure
- Hematology, biochemistry, and urine for clinical laboratory values
- Plasma for PK and immunogenicity samples
- PASI (will not be performed in subjects with generalized pustular PSO)
- PGA (will not be performed in subjects with generalized pustular PSO)
- Itch Numeric Rating Scale
- DLQI
- mNAPSI (for subjects with psoriatic nail disease)
- Subject PsA assessments (HAQ-DI, Patient's Assessment of Arthritis Pain, and PGADA for subjects with PsA)
- Physician PsA assessments (swollen and tender joint counts and PhGADA for subjects with PsA)

- Pustular and erythrodermic PSO assessments (Global Improvement Score, JDA Severity Index, and CGI-I for subjects with generalized pustular PSO or CGI-I for subjects with erythrodermic PSO)
- Medical procedures
- Concomitant medication
- AEs
- IRT information
- Study drug administration (after all other visit assessments completed)

8.4 Visit 4 (Week 4)

Subjects will have the following procedures performed/recorded prior to administration of study drug:

- Blood pressure
- Hematology, biochemistry, and urine for clinical laboratory values, including beta-D-glucan
- Urine pregnancy test for women of childbearing potential
- Plasma for PK and immunogenicity samples
- PASI (will not be performed in subjects with generalized pustular PSO)
- PGA (will not be performed in subjects with generalized pustular PSO)
- Itch Numeric Rating Scale
- Subject PsA assessments (HAQ-DI, Patient's Assessment of Arthritis Pain and PGADA for subjects with PsA)
- Physician PsA assessments (swollen and tender joint counts and PhGADA for subjects with PsA)
- Pustular and erythrodermic PSO assessments (Global Improvement Score, JDA Severity Index, and CGI-I for subjects with generalized pustular PSO or CGI-I for subjects with erythrodermic PSO)
- Medical procedures
- Concomitant medication
- AEs
- IRT information
- Study drug administration (after all other visit assessments completed)

8.5 Visit 5 (Week 6)

Subjects will have the following procedures performed/recorded prior to administration of study drug:

- Hematology, biochemistry, and urine for clinical laboratory values

- Plasma for PK and immunogenicity samples
- Medical procedures
- Concomitant medication
- AEs
- IRT information
- Study drug administration (after all other visit assessments completed)

8.6 Visit 6 (Week 8)

Subjects will have the following procedures performed/recorded prior to administration of study drug:

- Blood pressure
- Hematology, biochemistry, and urine for clinical laboratory values
- Urine pregnancy test for women of childbearing potential
- Plasma for PK and immunogenicity samples
- PASI (will not be performed in subjects with generalized pustular PSO)
- PGA (will not be performed in subjects with generalized pustular PSO)
- Itch Numeric Rating Scale
- DLQI
- mNAPSI (for subjects with psoriatic nail disease)
- Subject PsA assessments (HAQ-DI, Patient's Assessment of Arthritis Pain, and PGADA for subjects with PsA)
- Physician PsA assessments (swollen and tender joint counts and PhGADA for subjects with PsA)
- Pustular and erythrodermic PSO assessments (Global Improvement Score, JDA Severity Index, and CGI-I for subjects with generalized pustular PSO or CGI-I for subjects with erythrodermic PSO)
- Medical procedures
- Concomitant medication
- AEs
- IRT information
- Study drug administration (after all other visit assessments completed)

8.7 Visit 7 (Week 10)

Subjects will have the following procedures performed/recorded prior to administration of study drug:

- Hematology, biochemistry, and urine for clinical laboratory values
- Medical procedures
- Concomitant medication
- AEs
- IRT information
- Study drug administration (after all other visit assessments completed)

8.8 Visit 8 (Week 12)

Subjects will have the following procedures performed/recorded prior to administration of study drug:

- Blood pressure
- Hematology, biochemistry, and urine for clinical laboratory values, including beta-D-glucan
- Urine pregnancy test for women of childbearing potential
- Plasma for PK and immunogenicity samples
- Chest x-ray
- Subject TB questionnaire
- PASI (will not be performed in subjects with generalized pustular PSO)
- PGA (will not be performed in subjects with generalized pustular PSO)
- Itch Numeric Rating Scale
- DLQI
- mNAPSI (for subjects with psoriatic nail disease)
- Subject PsA assessments (HAQ-DI, Patient's Assessment of Arthritis Pain, and PGADA for subjects with PsA)
- Physician PsA assessments (swollen and tender joint counts and PhGADA for subjects with PsA)
- Pustular and erythrodermic PSO assessments (Global Improvement Score, JDA Severity Index, and CGI-I for subjects with generalized pustular PSO or CGI-I for subjects with erythrodermic PSO)
- Medical procedures
- Concomitant medication
- AEs
- IRT information
- Study drug administration (after all other visit assessments completed)

8.9 Visit 9 (Week 14)

Subjects will have the following procedures performed/recorded prior to administration of study drug:

- Hematology, biochemistry, and urine for clinical laboratory values
- Medical procedures
- Concomitant medication
- AEs
- IRT information
- Study drug administration (after all other visit assessments completed)

8.10 Visit 10 (Week 16)

Subjects will have the following procedures performed/recorded prior to administration of study drug:

- Blood pressure
- Weight
- Hematology, biochemistry, and urine for clinical laboratory values
- Urine pregnancy test for women of childbearing potential
- Subject TB questionnaire
- Plasma for PK and immunogenicity samples
- Physical examination, including evaluation for signs and symptoms of TB
- PASI (will not be performed in subjects with generalized pustular PSO)
- PGA (will not be performed in subjects with generalized pustular PSO)
- Itch Numeric Rating Scale
- DLQI
- mNAPSI (for subjects with psoriatic nail disease)
- BSA affected by PSO (will not be performed in subjects with generalized pustular PSO)
- Subject PsA assessments (HAQ-DI, Patient's Assessment of Arthritis Pain, and PGADA for subjects with PsA)
- Physician PsA assessments (swollen and tender joint counts and PhGADA for subjects with PsA)
- Pustular and erythrodermic PSO assessments (Global Improvement Score, JDA Severity Index, and CGI-I for subjects with generalized pustular PSO or CGI-I for subjects with erythrodermic PSO)
- Medical procedures

- Concomitant medication
- AEs
- IRT information
- Study drug administration (after all other visit assessments completed)

8.11 Visit 11 (Week 18)

Subjects will have the following procedures performed/recorded prior to administration of study drug:

- Medical procedures
- Concomitant medication
- AEs
- IRT information
- Study drug administration (after all other visit assessments completed)

8.12 Visit 12 (Week 20)

Subjects will have the following procedures performed/recorded prior to administration of study drug:

- Blood pressure
- Hematology and biochemistry for clinical laboratory values
- Urine pregnancy test for women of childbearing potential
- PASI (will not be performed in subjects with generalized pustular PSO)
- PGA (will not be performed in subjects with generalized pustular PSO)
- Itch Numeric Rating Scale
- Subject PsA assessments (HAQ-DI, Patient's Assessment of Arthritis Pain, and PGADA for subjects with PsA)
- Physician PsA assessments (swollen and tender joint counts and PhGADA for subjects with PsA)
- Pustular and erythrodermic PSO assessments (Global Improvement Score, JDA Severity Index, and CGI-I for subjects with generalized pustular PSO or CGI-I for subjects with erythrodermic PSO)
- Medical procedures
- Concomitant medication
- AEs
- IRT information
- Study drug administration (after all other visit assessments completed)

8.13 Visit 13 (Week 22)

Subjects will have the following procedures performed/recorded prior to administration of study drug:

- Medical procedures
- Concomitant medication
- AEs
- IRT information
- Study drug administration (after all other visit assessments completed)

8.14 Visit 14 (Week 24)

Subjects will have the following procedures performed/recorded prior to administration of study drug:

- Blood pressure
- 12-lead ECG
- Hematology, biochemistry, and urine (dipstick) for clinical laboratory values, including beta-D-glucan and sialylated carbohydrate antigen KL-6
- Urine pregnancy test for women of childbearing potential
- Chest x-ray
- IGRA
- Subject TB questionnaire
- Plasma for PK and immunogenicity samples
- Physical examination, including evaluation for signs and symptoms of TB
- PASI (will not be performed in subjects with generalized pustular PSO)
- PGA (will not be performed in subjects with generalized pustular PSO)
- Itch Numeric Rating Scale
- DLQI
- mNAPSI (for subjects with psoriatic nail disease)
- Subject PsA assessments (HAQ-DI, Patient's Assessment of Arthritis Pain, and PGADA for subjects with PsA)
- Physician PsA assessments (swollen and tender joint counts and PhGADA for subjects with PsA)
- Pustular and erythrodermic PSO assessments (Global Improvement Score, JDA Severity Index, and CGI-I for subjects with generalized pustular PSO or CGI-I for subjects with erythrodermic PSO)

- Medical procedures
- Concomitant medication
- AEs
- IRT information
- Study drug administration (after all other visit assessments completed)

8.15 Visit 15 (Week 26)

Subjects will have the following procedures performed/recorded prior to administration of study drug:

- Medical procedures
- Concomitant medication
- AEs
- IRT information
- Study drug administration (after all other visit assessments completed)

8.16 Visit 16 (Week 28)

Subjects will have the following procedures performed/recorded prior to administration of study drug:

- Blood pressure
- Hematology and biochemistry for clinical laboratory values
- Urine pregnancy test for women of childbearing potential
- PASI (will not be performed in subjects with generalized pustular PSO)
- PGA (will not be performed in subjects with generalized pustular PSO)
- Itch Numeric Rating Scale
- Subject PsA assessments (HAQ-DI, Patient's Assessment of Arthritis Pain, and PGADA for subjects with PsA)
- Physician PsA assessments (swollen and tender joint counts and PhGADA for subjects with PsA)
- Pustular and erythrodermic PSO assessments (Global Improvement Score, JDA Severity Index, and CGI-I for subjects with generalized pustular PSO or CGI-I for subjects with erythrodermic PSO)
- Medical procedures
- Concomitant medication
- AEs
- IRT information

- Study drug administration (after all other visit assessments completed)

8.17 Visit 17 (Week 30)

Subjects will have the following procedures performed/recorded prior to administration of study drug:

- Medical procedures
- Concomitant medication
- AEs
- IRT information
- Study drug administration (after all other visit assessments completed)

8.18 Visit 18 (Week 32)

Subjects will have the following procedures performed/recorded prior to administration of study drug:

- Blood pressure
- Hematology, biochemistry, and urine (dipstick) for clinical laboratory values
- Urine pregnancy test for women of childbearing potential
- Subject TB questionnaire
- Plasma for PK and immunogenicity samples
- PASI (will not be performed in subjects with generalized pustular PSO)
- PGA (will not be performed in subjects with generalized pustular PSO)
- Itch Numeric Rating Scale
- DLQI
- mNAPSI (for subjects with psoriatic nail disease)
- Subject PsA assessments (HAQ-DI, Patient's Assessment of Arthritis Pain, and PGADA for subjects with PsA)
- Physician PsA assessments (swollen and tender joint counts and PhGADA for subjects with PsA)
- Pustular and erythrodermic PSO assessments (Global Improvement Score, JDA Severity Index, and CGI-I for subjects with generalized pustular PSO or CGI-I for subjects with erythrodermic PSO)
- Medical procedures
- Concomitant medication
- AEs
- IRT information

- Study drug administration (after all other visit assessments completed)

8.19 Visit 19 (Week 34)

Subjects will have the following procedures performed/recorded prior to administration of study drug:

- Medical procedures
- Concomitant medication
- AEs
- IRT information
- Study drug administration (after all other visit assessments completed)

8.20 Visit 20 (Week 36)

Subjects will have the following procedures performed/recorded prior to administration of study drug:

- Hematology and biochemistry for clinical laboratory values
- Urine pregnancy test for women of childbearing potential
- PASI (will not be performed in subjects with generalized pustular PSO)
- PGA (will not be performed in subjects with generalized pustular PSO)
- Itch Numeric Rating Scale
- Subject PsA assessments (HAQ-DI, Patient's Assessment of Arthritis Pain and PGADA for subjects with PsA)
- Physician PsA assessments (swollen and tender joint counts and PhGADA for subjects with PsA)
- Pustular and erythrodermic PSO assessments (Global Improvement Score, JDA Severity Index, and CGI-I for subjects with generalized pustular PSO or CGI-I for subjects with erythrodermic PSO)
- Medical procedures
- Concomitant medication
- AEs
- IRT information
- Study drug administration (after all other visit assessments completed)

8.21 Visit 21 (Week 38)

Subjects will have the following procedures performed/recorded prior to administration of study drug:

- Medical procedures

- Concomitant medication
- AEs
- IRT information
- Study drug administration (after all other visit assessments completed)

8.22 Visit 22 (Week 40)

Subjects will have the following procedures performed/recorded prior to administration of study drug:

- Blood pressure
- Hematology, biochemistry, and urine (dipstick) for clinical laboratory values
- Urine pregnancy test for women of childbearing potential
- Plasma for PK and immunogenicity samples
- PASI (will not be performed in subjects with generalized pustular PSO)
- PGA (will not be performed in subjects with generalized pustular PSO)
- Itch Numeric Rating Scale
- DLQI
- mNAPSI (for subjects with psoriatic nail disease)
- Subject PsA assessments (HAQ-DI, Patient's Assessment of Arthritis Pain, and PGADA for subjects with PsA)
- Physician PsA assessments (swollen and tender joint counts and PhGADA for subjects with PsA)
- Pustular and erythrodermic PSO assessments(Global Improvement Score, JDA Severity Index, and CGI-I for subjects with generalized pustular PSO or CGI-I for subjects with erythrodermic PSO)
- Medical procedures
- Concomitant medication
- AEs
- IRT information
- Study drug administration (after all other visit assessments completed)

8.23 Visit 23 (Week 42)

Subjects will have the following procedures performed/recorded prior to administration of study drug:

- Medical procedures
- Concomitant medication

- AEs
- IRT information
- Study drug administration (after all other visit assessments completed)

8.24 Visit 24 (Week 44)

Subjects will have the following procedures performed/recorded prior to administration of study drug:

- Hematology and biochemistry for clinical laboratory values
- Urine pregnancy test for women of childbearing potential
- PASI (will not be performed in subjects with generalized pustular PSO)
- PGA (will not be performed in subjects with generalized pustular PSO)
- Itch Numeric Rating Scale
- Subject PsA assessments (HAQ-DI, Patient's Assessment of Arthritis Pain, and PGADA for subjects with PsA)
- Physician PsA assessments (swollen and tender joint counts, and PGADA for subjects with PsA)
- Pustular and erythrodermic PSO assessments (Global Improvement Score, JDA Severity Index, and CGI-I for subjects with generalized pustular PSO or CGI-I for subjects with erythrodermic PSO)
- Medical procedures
- Concomitant medication
- AEs
- IRT information
- Study drug administration (after all other visit assessments completed)

8.25 Visit 25 (Week 46)

Subjects will have the following procedures performed/recorded prior to administration of study drug:

- Medical procedures
- Concomitant medication
- AEs
- IRT information
- Study drug administration (after all other visit assessments completed)

8.26 Visit 26 (Week 48)

Subjects will have the following procedures performed/recorded prior to administration of study drug:

- Weight
- Hematology, biochemistry, and urine (dipstick) for clinical laboratory values
- Urine pregnancy test for women of childbearing potential
- PASI (will not be performed in subjects with generalized pustular PSO)
- PGA (will not be performed in subjects with generalized pustular PSO)
- Itch Numeric Rating Scale
- DLQI
- mNAPSI (for subjects with psoriatic nail disease)
- Subject PsA assessments (HAQ-DI, Patient's Assessment of Arthritis Pain, and PGADA for subjects with PsA)
- Physician PsA assessments (swollen and tender joint counts and PhGADA for subjects with PsA)
- Pustular and erythrodermic PSO assessments (Global Improvement Score, JDA Severity Index, and CGI-I for subjects with generalized pustular PSO or CGI-I for subjects with erythrodermic PSO)
- Medical procedures
- Concomitant medication
- AEs
- IRT information
- Study drug administration (after all other visit assessments completed)

8.27 Visit 27 (Week 50)

Subjects will have the following procedures performed/recorded prior to administration of study drug:

- Medical procedures
- Concomitant medication
- AEs
- IRT information
- Study drug administration (after all other visit assessments completed)

8.28 Visit 28 (Week 52)

Subjects will have the following procedures performed/recorded:

- Blood pressure
- 12-lead ECG
- Weight
- Hematology, biochemistry, and urine (dipstick) for clinical laboratory values, including beta-D-glucan and sialylated carbohydrate antigen KL-6
- Urine pregnancy test for women of childbearing potential
- Chest x-ray
- IGRA
- Subject TB questionnaire
- Plasma for PK and immunogenicity samples
- Physical examination, including evaluation for signs and symptoms of TB
- PASI (will not be performed in subjects with generalized pustular PSO)
- PGA (will not be performed in subjects with generalized pustular PSO)
- Itch Numeric Rating Scale
- BSA affected by PSO (will not be performed in subjects with generalized pustular PSO)
- DLQI
- mNAPSI (for subjects with psoriatic nail disease)
- Subject PsA assessments (HAQ-DI, Patient's Assessment of Arthritis Pain, and PGADA for subjects with PsA)
- Physician PsA assessments (swollen and tender joint counts and PhGADA for subjects with PsA)
- Pustular and erythrodermic PSO assessments(Global Improvement Score, JDA Severity Index, and CGI-I for subjects with generalized pustular PSO or CGI-I for subjects with erythrodermic PSO)
- Medical procedures
- Concomitant medication
- AEs
- IRT information

8.29 Safety Follow-Up Visit

Subjects will have the following procedures performed/recorded 10 weeks after the last dose of study drug:

- Blood pressure
- Physical examination

- Hematology, biochemistry, and urine (dipstick) for clinical laboratory values
- Urine pregnancy test for women of childbearing potential
- Plasma for PK and immunogenicity samples
- AEs
- Medical procedures
- Concomitant medications

8.30 Withdrawal Visit

Subjects will have the following procedures performed/recorded:

- Blood pressure
- 12-lead ECG
- Weight
- Hematology, biochemistry, and urine for clinical laboratory values, including beta-D-glucan and sialylated carbohydrate antigen KL-6
- Urine pregnancy test for women of childbearing potential
- Plasma for PK and immunogenicity samples
- Physical examination, including evaluation for signs and symptoms of TB
- Chest x-ray
- IGRA
- Subject TB questionnaire
- PASI (will not be performed in subjects with generalized pustular PSO)
- PGA (will not be performed in subjects with generalized pustular PSO)
- Itch Numeric Rating Scale
- DLQI
- BSA affected by PSO (will not be performed in subjects with generalized pustular PSO)
- mNAPSI (for subjects with psoriatic nail disease)
- Subject PsA assessments (HAQ-DI, Patient's Assessment of Arthritis Pain, and Patient's Global Assessment of Disease Activity for subjects with PsA)
- Physician PsA assessments (swollen and tender joint counts and Physician's Global Assessment of Disease Activity for subjects with PsA)
- Pustular and erythrodermic PSO assessments(Global Improvement Score, JDA Severity Index, and CGI-I for subjects with generalized pustular PSO or CGI-I for subjects with erythrodermic PSO)
- Medical procedures

- Concomitant medication
- AEs
- IRT information

8.31 Unscheduled Visit

Unscheduled visits will be permitted during the study to allow follow-up of abnormal laboratory results or physical findings. Assessments during unscheduled visits may include:

- Blood pressure
- Physical examination
- Hematology, biochemistry, and urine for clinical laboratory values
- Urine pregnancy test for women of childbearing potential
- AEs
- Medical procedures
- Concomitant medications

9 ASSESSMENT OF EFFICACY

All assessments will be completed as outlined in the Schedule of Study Assessments (Table 5–1).

9.1 Psoriasis Area Severity Index (PASI)

The PASI is the most commonly used and validated assessment for grading the severity of PSO in clinical studies (Feldman, 2004). The PASI quantifies the severity and extent of the disease and weighs these with the percentage of BSA involvement.

The percent area of involvement (BSA%) is estimated across 4 body areas; head, upper limbs, trunk, and lower limbs and then transferred into a grade (Table 9–1).

The Investigator assesses the average redness, thickness, and scaliness of lesions in each body area (each on a 5-point scale); 0=none, 1=slight, 2=moderate, 3=marked, and 4=very marked.

The PASI score ranges from 0 to 72 with a higher score indicating increased disease severity.

Table 9–1: Body areas for calculation of percent BSA for PASI

Body area	Details of area	BSA	Degree of involvement of body area[a]
Head	Face, back of head	10%	0 to 6
Upper limbs	Left, right, upper lower, flexor surface, extensor surface	20%	0 to 6
Trunk	Front, back, groin	30%	0 to 6
Lower limbs	Left, right, upper lower, flexor surface, extensor surface, including buttocks	40%	0 to 6
Total		100%	

BSA=body surface area; PASI=Psoriasis Area and Severity Index

[a] Where 0=none; 1=1% to <10% affected, 2=10% to <30% affected, 3=30% to <50% affected, 4=50% to <70% affected, 5=70% to <90% affected, 6=90% to 100% affected

The PASI50, PASI75, PASI90, and PASI100 responses are based on at least 50%, 75%, 90%, and 100% improvement in the PASI score.

9.2 BSA affected by psoriasis

The BSA palm method will be used for the evaluation of BSA as follows:

Body surface area estimation uses the palm (subject's flat hand and thumb together, fingers included) as representing around 1% of the total BSA.

- Subject's palm=1%
- Head and neck=10% (10 palms)
- Upper extremities=20 % (20 palms)
- Trunk=30% (30 palms)
- Lower extremities=40 % (40 palms)
- Total BSA=100%

9.3 Physician's Global Assessment of Psoriasis (PGA)

A static PGA for PSO will be used to assess disease severity in all subjects during the study. The Investigator will assess the overall severity of PSO using the following 5-point scale:

Physician's Global Assessment		
Score	**Short Descriptor**	**Definition**
0	Clear	No signs of psoriasis; post-inflammatory hyperpigmentation may be present
1	Almost clear	No thickening; normal to pink coloration; no to minimal focal scaling

2	Mild	Just detectable to mild thickening; pink to light red coloration; predominately fine scaling
3	Moderate	Clearly distinguishable to moderate thickening; dull to bright red, clearly distinguishable to moderate thickening; moderate scaling
4	Severe	Severe thickening with hard edges; bright to deep dark red coloration; severe/coarse scaling covering almost all or all lesions

The PGA score will be entered into the eCRF.

9.4 Dermatology Life Quality Index (DLQI)

The Dermatology Life Quality Index (DLQI) is a questionnaire designed for use in adult subjects with PSO. The DLQI is a skin disease-specific questionnaire aimed at the evaluation of how symptoms and treatment affect patients' HRQoL. This instrument asks subjects 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 change 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). Subjects will be asked to complete the DLQI as outlined in the Schedule of Study Assessments (Table 5–1).

Study site personnel should ensure that each subject completes the instrument prior to leaving the study site.

Responses to the DLQI will be obtained, and study staff should respond in the eCRF whether or not it was completed.

9.5 Modified Nail Psoriasis Severity Index (mNAPSI)

Subjects with psoriatic nail disease will have a target nail selected at the Baseline visit for evaluation using the mNAPSI. The nail selected should be the most affected nail observed at Baseline and should be the only one assessed throughout the study. The target nail will be scored (0 to 3) for onycholysis/oil drop dyschromia, nail plate crumbling, and pitting and will be scored (0 for "no" or 1 for "yes") for leukonychia, nail bed hyperkeratosis, splinter haemorrhages and red spots in the lunula.

Data will be entered into the eCRF.

9.6 Itch Numeric Rating Scale

The Itch Numeric Rating Scale has been developed as a simple, single item instrument to assess the patient-reported severity of itch at its most intense during the past 24h period. Subjects indicate itch severity by circling the integer that best describes the worst level of itching due to PSO in the past 24h period on an 11-point scale anchored at 0, representing "no itching" and 10, representing "worst itch imaginable" (Kimball et al, 2016).

9.7 Assessments for subjects with PsA

9.7.1 ACR20, ACR50, and ACR70 responses

For subjects with PsA, the ACR20, ACR50, and ACR70 response will be evaluated. The assessments are based on a 20%, 50%, 70% or greater improvement in the number of tender joints and swollen joints each and a 20%, 50%, 70% or greater improvement in at least 3 of the 5 remaining core set measures: Patient's and Physician's Global Assessments of Disease Activity (Section 9.7.8 and Section 9.7.7, respectively), Patient's Assessment of Arthritis Pain (Section 9.7.6), HAQ-DI (Section 9.7.5), and C-reactive protein (CRP).

9.7.2 Swollen and tender joint counts (66/68 joints evaluation)

The following 68 joints are to be examined for tenderness by the Principal Investigator, another delegated physician, or an appropriately qualified medical professional (based on local requirements) who has had documented training on how to perform these assessments correctly. Preferably the same assessor should evaluate the subject at each arthritis assessment.

- Upper body (6): bilateral temporomandibular, sternoclavicular, and acromioclavicular joints
- Upper extremity (34): bilateral shoulders, elbows, wrists (includes radiocarpal, and carpal and carpometacarpal bones considered as a single unit), MCP I, II, III, IV, and V, thumb interphalangeals (IP), PIP II, III, IV, and V and distal interphalangeals (DIP, II, III, IV, and V)
- Lower extremity (28): bilateral hips, knees, ankles, tarsi (includes subtalar, transverse tarsal, and tarsometatarsal considered as a single unit), metatarsophalangeals (MTP I, II, III, IV, and V), great toe interphalangeals, and proximal interphalangeals (PIP II, III, IV, and V)

The assessment for swelling is made on 66 joints from the above list. The hip joints are excluded. Artificial and ankylosed joints are excluded from both tenderness and swelling assessments.

These assessments are completed as outlined in the Schedule of Study Assessments (Table 5–1).

Table 9–2: Swelling and tenderness grading

Grade	Swelling response (66)	Tenderness response (68)
0	None	None (not tender)
1	Detectable	Positive (tenderness)

9.7.3 Swollen and tender joint counts (28 joints evaluation)

The following 28 joints will be used for calculation of the DAS28(CRP).

- Upper extremity (26): bilateral shoulders, elbows, wrists (includes radiocarpal, and carpal and carpometacarpal bones considered as a single unit), MCP I, II, III, IV, and V, thumb interphalangeals (IP), PIP II, III, IV, and V
- Lower extremity (2): knees

9.7.4 Disease Activity Score

The DAS28(CRP) will be calculated using CRP (mg/dL) (see Table 12–1) and the Patient's Global Assessment of Disease Activity (VAS) (see Section 9.7.8).

The joint assessment utilized for the DAS calculation will be based on 28 of the joints assessed for the 66/68-joint assessments (see Section 9.7.2, using the same 2-point scale for the assessment of swelling and tenderness of each joint.

DAS28(CRP) is calculated as follows:

$$DAS28(CRP) = 0.56 \cdot \sqrt{TJC} + 0.28 \cdot \sqrt{SJC} + 0.014 \cdot PGADA + 0.36 \cdot \ln(CRP + 1) + 0.96$$

9.7.5 Health Assessment Questionnaire Disability Index score

The HAQ-DI contains 20 items divided into 8 domains that measure: dressing and grooming, arising, eating, walking, hygiene, reach, grip, and common daily activities. Subjects are required to indicate the degree of difficulty they have experienced in each domain in the past week on a 4-point scale that ranges from 0 (without difficulty) to 3 (unable to do). Any individual score of less than 2 is adjusted to 2 if the activity requires assistance from another individual or the use of an assistive device. The highest score in each category is then summed (0 to 24) and divided by the number of categories scored to give a score that ranges from 0 to 3 (Matsuda et al, 2003).

The HAQ-DI will be completed outlined in the Schedule of Study Assessments (Table 5–1).

9.7.6 Patient's Global Assessment of Arthritis Pain (VAS)

The Patient's Assessment of Arthritis Pain VAS or "Pain VAS" is part of the ACR core set of measures in arthritis (Felson et al, 1993).

The Pain VAS consists of a horizontal line 100mm in length on which subjects are asked to indicate the level of their arthritis pain at the day of the visit between 0 ("no pain") and 100 ("most severe pain"), in response to the question: "Please mark a vertical line on the scale below to show how much pain you have from your arthritis today" (Dworkin et al, 2008).

The Pain VAS will be completed as outlined in the Schedule of Study Assessments (Table 5–1).

9.7.7 Physician's Global Assessment of Disease Activity (VAS)

The Investigator will assess the overall status of the subject with respect to their PsA signs and symptoms and functional capacity (considering both joint and skin components) using a VAS where 0 is "very good, asymptomatic and no limitation of normal activities" and 100 is "very poor, very severe symptoms which are intolerable and inability to carry out all normal activities."

This assessment by the Investigator should be made blind to the PGADA.

The Physician's Global Assessment of Disease Activity (VAS) will be completed as outlined in the Schedule of Study Assessments (Table 5–1).

9.7.8 Patient's Global Assessment of Disease Activity (VAS)

Subjects will score their Global Assessment of Disease Activity in response to the question, "Considering all the ways your arthritis affects you, please mark a vertical line on the scale below to show how you are feeling today", using a VAS where 0 is "very good, no symptoms" and 100 is "very poor, severe symptoms." The subject should be asked to consider both joint and skin components in their response to this question.

The PGADA will be completed as outlined in the Schedule of Study Assessments (Table 5–1).

9.8 Assessments for subjects with generalized pustular PSO or erythrodermic PSO

9.8.1 Clinical Global Impression of Improvement (CGI-I)

The CGI-I is evaluated by the Investigators on a 4-point scale (remission, improved, no change, worsened) based on changes from the Baseline findings of PSO. The CGI will be completed as outlined in the Schedule of Study Assessments (Table 5–1).

9.8.2 Global Improvement Score for Pustular PSO

The Global Improvement Score is evaluated by the Investigators as "very much improved," "much improved," "minimally improved," "no change," or "worsened" based on changes from the baseline JDA severity index scores and components, as presented in Table 9–3.

Table 9–3: Global Improvement Score

	Change in JDA Severity Classification Score		Other criteria
Very much improved	Reduction by ≥3 points	or	Clear or almost clear of signs of generalized pustular PSO
Much improved	Reduction of 1 or 2 points	or	At least 1 of the following: • Erythema area with pustules (%) reduced by ≤30% compared to Baseline[a] • Clinically meaningful improvement in at least 2 other components of the JDA Severity Index for generalized pustular PSO (erythema area, edema area, WBC, CRP, albumin)
Minimally improved	0 points (no change)	and	At least 1 of the following: • Erythema area with pustules (%) reduced by ≤20% compared to Baseline[a] • Clinically meaningful improvement in at least 1 other component of the JDA Severity Index for generalized pustular PSO (erythema area, edema area, WBC, CRP, albumin)
No change	0 points (no change)	and	Not meeting the other criteria of minimally improved
Worsened	≥+1 point	-	Not applicable

CRP=C-reactive protein; JDA=Japanese Dermatological Association; PSO=psoriasis; WBC=white blood cell
[a] Prior to first study drug administration at Baseline (Visit 2)

9.8.3 JDA severity index score for generalized pustular PSO

The JDA severity index score for generalized pustular PSO consists of area of erythema with pustules, area of erythema (total), area of edema, fever, WBC, CRP, and serum albumin.

The total score of JDA severity index for generalized pustular PSO is assigned a score of 0 to 17 (0=best, 17=worst).

Table 9–4: JDA severity index score for generalized pustular PSO

Severity classification	Mild	Moderate	Severe
A + B (combined scores)	0 to 6	7 to 10	11 to 17

A. Skin symptoms (total scores: 0 to 9)				
Scores	3	2	1	0
Erythematous area (BSA %)	≥75	≥25, <75	<25	0
Erythematous area with pustule (BSA %)	≥50	≥10, <50	<10	0
Edematous area (BSA %)	≥50	≥10, <50	<10	0

B. Systemic symptoms and laboratory findings (total scores: 0 to 8)			
Scores	2	1	0
Fever (˚C)	≥38.5	≥37.0, <38.5	<37.0
WBC count (/µL)	≥15,000	≥10,000, <15,000	<10,000
CRP (mg/dL)	≥7.0	≥0.3, <7.0	<0.3
Serum albumin (g/dL)	<3.0	≥3.0, <3.8	≥3.8

BSA=body surface area; CRP=C-reactive protein; JDA=Japanese Dermatological Association; PSO=psoriasis; WBC=white blood cell

10 ASSESSMENT OF PHARMACOKINETIC/ PHARMACODYNAMIC/PHARMACOGENOMIC VARIABLES

Plasma samples for the measurement of CZP concentrations will be taken as outlined in the Schedule of Study Assessments (Table 5-1). Study site staff will record the time and date of each sample collected. Plasma samples will be analyzed for CZP levels using a validated method.

For all PK samples, at each time point, collect at least 5mL blood into heparinized tube and centrifuged. Plasma will be aliquoted into 3 labeled transport tubes and stored frozen at -20˚C or colder and shipped on dry ice.

Supplies for PK will be provided by the central laboratory. Additional information will be outlined in the study Laboratory Manual.

11 ASSESSMENT OF IMMUNOLOGICAL VARIABLES

Plasma samples for the measurement of anti-CZP antibodies will be taken as outlined in the Schedule of Study Assessments (Table 5–1).

Additional information will be outlined in the study Laboratory Manual.

12 ASSESSMENT OF SAFETY

All assessments will be completed as outlined in the Schedule of Study Assessments (Table 5-1).

12.1 Adverse events

12.1.1 Definitions

12.1.1.1 Adverse event

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

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

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

12.1.1.2 Serious adverse event

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

- Death
- Life-threatening

  (Life-threatening does not include a reaction that might have caused death had it occurred in a more severe form.)
- Significant or persistent disability/incapacity
- Congenital anomaly/birth defect (including that occurring in a fetus)
- Important medical event that, based upon appropriate medical judgment, may jeopardize the patient or subject and may require medical or surgical intervention to prevent 1 of the other outcomes listed in the definition of serious

(Important medical events may include, but are not limited to, potential Hy's Law [see Section 12.1.1.3], allergic bronchospasm requiring intensive treatment in an emergency room or at home, blood dyscrasias that do not result in inpatient hospitalization, or the development of drug dependency or drug abuse.)

- Initial inpatient hospitalization or prolongation of hospitalization

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

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

12.1.1.3 Adverse events of interest

An AE of interest is any AE which is listed in the European 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." The following AEs of interest will be reported as SAEs, even if not meeting the definition as outlined in Section 12.1.1.2:

- 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 illness
- Serious skin reactions (eg, Stevens Johnson Syndrome, toxic epidermal necrosis, and erythema multiforme)
- Potential Hy's Law, defined as ≥3xULN ALT or AST with coexisting ≥2xULN total bilirubin in the absence of ≥2xULN ALP, with no alternative explanation for the biochemical abnormality, must ALWAYS be reported to UCB as an AE of special interest (ie, without waiting for any additional etiologic investigations to have been concluded). Follow-up

information should then be reported if an alternative etiology is identified during investigation and monitoring of the subject.

12.1.1.4 Malfunctions and Health Damage

Malfunction is condition of a device part in a study drug which does not broadly meet specific standards, such as a break and failure, concerning quality, safety, performance and other, whether or not it is confirmed on any phases of design, delivery, storage, or usage. Health damage is a suspected event being affected by a malfunction of a device part in a study drug.

Serious health damage is defined as health damage that meets any of the following criteria:

- Results in death
- Is life-threatening

  The term "life-threatening" refers to an event in which the subject 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.
- Requires inpatient hospitalization or prolongation of existing hospitalization,"Inpatient hospitalization for treatment" refers to admission of a subject to a medical institution overnight or more for the treatment of health damage. This includes hospitalization for the treatment of health damage without special treatment (resting). On the other hand, "inpatient hospitalization for treatment" does not include any hospitalization for tests or procedures for the underlying disease that has not exacerbated since study entry or a complication, social or expedient hospitalization not for the treatment of an adverse event, or hospitalization for a planned treatment or test before study entry.
- Results in persistent or significant disability/incapacity
- Is a congenital anomaly/birth defect
- Is some other occurrence, such as an important medical event that may not be immediately life-threatening or result in death or hospitalization, but may jeopardize the subject or may require measures to prevent one of the other outcomes listed in the criteria above. These should also be considered serious. Examples of such events are bronchospasm requiring intensive treatment in an emergency room, blood disorders or convulsions that do not result in hospitalization, or the development of drug dependency or drug abuse.

12.1.2 Procedures for reporting and recording adverse events

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

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

12.1.2.1 Description of adverse events

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

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

12.1.2.2 Rule for repetition of an adverse event

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

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

12.1.2.3 Additional procedures for reporting serious adverse events

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

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

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

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

The Investigator is specifically requested to collect and report to UCB (or its representative) any SAEs (even if the Investigator is certain that they are in no way associated with the IMP), up to 10 weeks from the end of the study treatment for each subject, and to also inform participating subjects of the need to inform the Investigator of any SAE within this period. Serious AEs that the Investigator thinks may be associated with the IMP must be reported to UCB regardless of the time between the event and the end of the study.

Upon receipt of the SAE report form, UCB will perform an assessment of expectedness of the reported SAE. The assessment of the expectedness of the SAE is based on the IB.

12.1.3 Follow up of adverse events

An AE should be followed until it has resolved, has a stable sequelae, the Investigator determines that it is no longer clinically significant, or the subject is lost to follow up. This follow-up requirement applies to AEs, SAEs, and AEs of special interest; further details regarding follow up of PDILI events is provided in Section 12.2.1.4.

If an AE is ongoing at the end of the study for a subject, follow up should be provided until resolution/stable level of sequelae is achieved, or until the Investigator no longer deems that it is clinically significant, or until the subject is lost to follow up. If no follow up is provided, the Investigator must provide a justification. The follow up will usually be continued for 10 weeks after the subject has discontinued his/her IMP.

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

12.1.4 Pregnancy

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

- The subject should return for an early discontinuation visit.
- The subject should immediately stop the intake of the IMP.
- A Safety Follow-Up Visit should be scheduled 10 weeks after the subject has discontinued her IMP.

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

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

In cases where the partner of a male subject enrolled in a clinical study becomes pregnant, the Investigator or designee is asked to contact the subject to request consent of the partner via the Partner Pregnancy Consent form that has been approved by the responsible IRB and should be available in the Investigator site file. In case of questions about the consent process, the Investigator may contact the UCB/contract research organization (CRO) contract monitor for the study. The Investigator will complete the Pregnancy Report and Outcome form and send it to UCB's PS department (for contact details see Serious Adverse Event reporting information at the beginning of this protocol) only after the partner has agreed that additional information can be captured and has provided the signed Partner Pregnancy Consent form. UCB's PS department is also the primary contact for any questions related to the data collection for the partner pregnancy, eventual birth, and follow up.

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

12.1.5 Procedures for reporting malfunctions/health damage

12.1.5.1 Response to subjects

The Investigator will take sufficient medical measures for all study-related clinically significant health damage during and after the participation of each subject in the clinical study. If a subject needs treatment for health damage, the Investigator will inform the subject of the need to receive treatment.

12.1.5.2 Expedited reporting of serious health damage

12.1.5.2.1 Serious adverse events requiring expedited reporting

1. All serious health damage that occurs during the study period must be reported.
2. All infections: Infections induced by suspected contamination by a pathogen in a biological preparation or study drug, etc., including hepatitis B virus (HBV), hepatitis C virus (HCV), HIV, etc. Common colds due to changes in the season are not included.

12.1.5.2.2 Procedure for expedited reporting

1. In the occurrence of any of the events that correspond to any of the criteria listed in Section 12.1.1.2, the Investigator will notify the Sponsor promptly after first knowledge of the event (within 24 hours, as a rule) either orally, by telephone, or by e-mail.
2. The Investigator will subsequently submit a detailed report on any serious health damage that occurs after initiation of administration of the study drug to the head of the study site and the Sponsor within 10 days of first knowledge using either the report form of the study site or that of the Sponsor.

   Additional information will also be notified promptly (within 24 hours, as a rule) to the Sponsor orally, by telephone, or by e-mail, and if necessary, an additional report will be made.
3. If requested, the Investigator will provide additional information (autopsy report, terminal medical records, and/or other necessary information) about any serious health damage reported to the Sponsor, the head of the study site, and the IRB.

12.1.5.3 Reporting of malfunctions or nonserious health damage

1. Malfunctions or nonserious health damage that require reporting:

   All malfunctions or nonserious health damage that occur during the study period.
2. Procedure for expedited reporting:

   In the occurrence of any malfunctions or health damage, the Investigator will notify the Sponsor promptly after first knowledge of the event (within 24 hours, as a rule) either orally, by telephone, or by e-mail.

12.1.6 Suspected transmission of an infectious agent via a medicinal product

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

12.1.7 Overdose of investigational medicinal product

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

12.1.8 Safety signal detection

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

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

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

12.2 Laboratory measurements

The following laboratory parameters will be measured as outlined in the Schedule of Study Assessments (Table 5–1):

Table 12–1: Laboratory measurements

Hematology	Chemistry	Urinalysis
Basophils	Calcium	Albumin
Eosinophils	Chloride	Bacteria
Lymphocytes	C-reactive protein	Crystals
Atypical lymphocytes	Magnesium	Glucose
Monocytes	Potassium	pH
Neutrophils	Sodium	RBC
Hematocrit	Glucose	WBC
Hemoglobin	BUN	Urine dipstick for pregnancy testing[a]
MCH	Creatinine	
MCHC	ALP	
MCV	AST	
Platelet count	ALT	
RBC count	GGT	
WBC count	Total bilirubin	
	LDH	
	Total cholesterol	
	Albumin	
	Beta-D-glucan	
	Sialylated carbohydrate antigen KL-6	
	Hepatitis B surface antigen[b]	
	Hepatitis B core antibody[b,c]	
	Hepatitis B surface antibody[b,c]	
	Hepatitis type B virus DNA[c]	
	Hepatitis type C virus antibody[b]	
	Human immunodeficiency virus antigen[b]	
	Human immunodeficiency virus antibody[b]	
	T-cell lymphotropic virus type-1 antibody[b]	
	Serum pregnancy testing[a]	

ALP=alkaline phosphatase; ALT=alanine aminotransferase; AST=aspartate aminotransferase; BUN=blood urea nitrogen; DNA=deoxyribonucleic acid; GGT=gamma-glutamyltransferase; HBc=hepatitis type C virus; HBs=hepatitis B surface; HBV=hepatitis type B virus; LDH=lactate dehydrogenase; MCH=mean corpuscular hemoglobin; MCHC=mean corpuscular hemoglobin concentration; MCV=mean corpuscular volume; RBC=red blood cell; SFU=Safety Follow-Up; WBC=white blood cell

[a] Pregnancy testing will consist of serum testing at Screening. The pregnancy test will be urine at all other visits.

[b] Performed at Screening only

[c] If the subject is either HBs antibody-positive or HBc antibody-positive at Screening, quantitative measurement of HBV-DNA should be performed every 4 weeks from Baseline to Week 52 and at SFU.

12.2.1 Evaluation of PDILI

The PDILI IMP discontinuation criteria for this study are provided in Section 6.3.1, with the accompanying required follow-up investigation and monitoring detailed below. All PDILI events must be reported as an AE and reported to the study site and Sponsor within 24 hours of learning of their occurrence. Any PDILI event that meets the criterion for potential Hy's Law must be reported as an AE of special interest (see Section 12.1.1.3), and, if applicable, also reported as an SAE (see Section 12.1.1.2).

Evaluation of PDILI consists of the diagnostic testing and continued monitoring included in Table 12–2 (specific tests dependent on laboratory results and corresponding symptoms) and consultation with a local hepatologist (if applicable; discussed in Section 12.2.1.1). The local hepatologist is the expert usually consulted by the treating physician for assessment and management of potential hepatic disease. This would usually be a hepatologist, but may be a gastroenterologist. Additional investigation and monitoring may be required and adapted based on the diagnosis after the cause of the liver injury/abnormality is confirmed (details in Section 12.2.1.4).

The results of all monitoring, including laboratory testing and other testing, should be made available to the study site and Sponsor.

All initial tests resulting in abnormal hepatic laboratory values need to be repeated, but appropriate medical action must not be delayed waiting for the repeat result.

If tests are done locally for more rapid results, a concurrent sample should also be sent to the central laboratory whenever possible. Medical care decisions are to be made initially using the most rapidly available results and a conservative approach must be taken if the results from the 2 laboratory tests are significantly different. Data from the local and central laboratory are to be recorded on the applicable eCRF pages.

When IMP is discontinued, all concomitant medications and herbal supplements that are not medically necessary should also be discontinued. In these cases, the Investigator should also consider dose reduction for medically necessary concomitant medication and consider changing any medically required concomitant medication known to be hepatotoxic to a suitable alternative.

Rechallenge with a substance potentially causing drug-induced liver injury is dangerous, may be fatal, and must not occur.

The table below summarizes the approach to investigate PDILI.

Table 12–2: Required investigations and follow up for PDILI

Laboratory value			Immediate		Follow up	
ALT or AST	**Total bilirubin**	**Symptoms[a] of hepatitis or hypersensitivity**	**Consultation requirements**	**Actions**	**Testing**	**Evaluation**
≥3xULN	≥2xULN[b]	NA	Hepatology consult.[c] Medical Monitor must be notified within 24 hours (eg, by laboratory alert) and subject discussed with Medical Monitor ASAP.	Immediate, permanent IMP discontinuation.	Essential: Must have repeat liver chemistry values and additional testing completed ASAP (see Section 12.2.1.3); recommended to occur at the site with HCP.	Monitoring of liver chemistry values at least twice per week until values normalize, stabilize, or return to within baseline values.[d]
≥8xULN	NA	NA				
≥3xULN	NA	Yes		Immediate, temporary or permanent, IMP discontinuation.		
≥3xULN (and ≥2x baseline) and <5xULN	<2xULN	No	Discussion with Medical Monitor required if the criterion that allows for IMP continuation is met.	Further investigation – immediate IMP discontinuation not required (see Section 12.2.1.2).	Not required unless otherwise medically indicated (at discretion of Investigator).	

Table 12–2: Required investigations and follow up for PDILI

≥5xULN (and ≥2x baseline) and <8xULN	<2xULN	No	Hepatology consult if there is no evidence of resolution (see Follow up requirements).[c] Discussion with Medical Monitor required.	IMP discontinuation required if any of the following occur: • Subject cannot comply with monitoring schedule. • Liver chemistry values continue to increase during 2 week monitoring period. • Liver chemistry values remain ≥5xULN (and ≥2x baseline) after 2 week monitoring period.	Essential: Every attempt must be made to have repeat liver chemistry values and additional testing completed within 48 hours at the site with HCP (see Section 12.2.1.3).	Monitoring of liver chemistry values at least twice per week for 2 weeks.[d] • Immediate IMP discontinuation required if liver chemistry values continue to increase. After 2 weeks of monitoring liver chemistry values: • Discontinue IMP if levels remain ≥5xULN (and ≥2x baseline); monitor until values normalize, stabilize, or return to within baseline values.[d] • Continue IMP if levels are no longer ≥5xULN (and ≥2x baseline); continue to monitor at least twice per week until values normalize, stabilize, or return to within baseline values.[d]

ALP=alkaline phosphatase; ALT=alanine aminotransferase; ASAP=as soon as possible; AST=aspartate aminotransferase; HCP=healthcare practitioner; IMP=investigational medicinal product; NA=not applicable; PDILI=potential drug-induced liver injury; ULN=upper limit of normal

[a] Hepatitis symptoms include fatigue, nausea, vomiting, and right upper quadrant pain or tenderness; hypersensitivity symptoms include eosinophilia (>5%), rash, and fever (without clear alternative cause).

[b] If the subject also has ≥2xULN ALP, the possibility of an indication of biliary obstruction should be discussed with the Medical Monitor.

[c] Details provided in Section 12.2.1.1. The local hepatologist is the expert usually consulted by the treating physician for assessment and management of potential hepatic disease. This would usually be a hepatologist, but may be a gastroenterologist.

[d] Unless an alternative monitoring schedule is agreed by the Investigator and UCB responsible physician. Determination of stabilization is at the discretion of the Investigator in consultation with the hepatologist (as applicable) and UCB responsible physician, as needed.

12.2.1.1 Consultation with Medical Monitor and local hepatologist

Potential drug-induced liver injury events require notification of the Medical Monitor within 24 hours (eg, by laboratory alert), and the subject must be discussed with the Medical Monitor as soon as possible. If required, the subject must also be discussed with the local hepatologist. The local hepatologist is the expert usually consulted by the treating physician for assessment and management of potential hepatic disease. This would usually be a hepatologist, but may be a gastroenterologist. If determined necessary, this discussion should be followed by a full hepatology assessment (see Section 12.2.1.3) and SAE report (if applicable).

12.2.1.2 Immediate action: determination of IMP discontinuation

All PDILI events require immediate action, testing, and monitoring.

The immediate action is dependent on the laboratory values and symptoms of hepatitis or hypersensitivity and ranges from continuation of IMP (followed by immediate investigation) to immediate and permanent discontinuation (see Section 6.3.1 and Table 12–2 for details).

When IMP is discontinued, all concomitant medications and herbal supplements that are not medically necessary should also be discontinued. The Investigator should also consider dose reduction for medically necessary concomitant medication and consider changing any medically required concomitant medication known to be hepatotoxic to a suitable alternative.

12.2.1.3 Testing: identification/exclusion of alternative etiology

The measurements and additional information required for the assessment of PDILI events when there is a reasonable possibility that they may have been caused by the IMP are detailed in Table 12–3 (laboratory measurements) and Table 12–4 (additional information). Results of the laboratory measurements and information collected are to be submitted to the Sponsor on the corresponding eCRF. If the medical history of the subject indicates a requirement for other assessments not included below, these additional assessments should be completed and submitted, as applicable.

All blood samples should be stored, if possible. If tests are done locally for more rapid results, a concurrent sample must also be sent to the central laboratory.

The following measurements are to be assessed:

Table 12–3: PDILI laboratory measurements

Virology-related	Hepatitis A IgM antibody
	HBsAg
	Hepatitis E IgM antibody
	HBcAb-IgM
	Hepatitis C RNA
	Cytomegalovirus IgM antibody
	Epstein-Barr viral capsid antigen IgM antibody (if unavailable, obtain heterophile antibody or monospot testing)
Immunology	Anti-nuclear antibody (qualitative and quantitative)
	Anti-smooth muscle antibody (qualitative and quantitative)
	Type 1 anti-liver kidney microsomal antibodies (qualitative and quantitative)
Hematology	Eosinophil count
Urinalysis	Toxicology screen
Chemistry	Amylase
	If total bilirubin ≥1.5xULN, obtain fractionated bilirubin to obtain % direct bilirubin
	Serum CPK and LDH to evaluate possible muscle injury causing transaminase elevation
Additional	Prothrombin time/INR[a]
	Serum pregnancy test
	PK sample

ALT=alanine aminotransferase; CPK=creatine phosphokinase; HBcAb-IgM=hepatitis B core antibody-IgM; HBsAg=hepatitis B surface antigen; IgM=immunoglobulin M; INR=international normalized ratio; LDH=lactate dehydrogenase; PDILI=potential drug-induced liver injury; PK=pharmacokinetic; RNA=ribonucleic acid; ULN=upper limit of normal

[a] Measured only for subjects with ALT >8xULN, elevations in total bilirubin, and symptoms of hepatitis or hypersensitivity. Hepatitis symptoms include fatigue, nausea, vomiting, and right upper quadrant pain or tenderness; hypersensitivity symptoms include eosinophilia (>5%), rash, and fever (without clear alternative cause).

The following additional information is to be collected:

Table 12–4: PDILI information to be collected

New or updated information
Concomitant prescription and over-the-counter medications (eg, acetaminophen, herbal remedies, vitamins); dosages and dates should be included.

Table 12–4: PDILI information to be collected

New or updated information
Pertinent medical history, including the following: • History of liver disease (eg, autoimmune hepatitis, nonalcoholic steatohepatitis or other "fatty liver disease") • Adverse reactions to drugs • Allergies • Relevant family history or inheritable disorders (eg, Gilbert's syndrome, alpha-1 antitrypsin deficiency) • Recent travel • Progression of malignancy involving the liver (Note: Metastatic disease to the liver, by itself, should not be used as an explanation for significant AST and/or ALT elevations.)
The appearance or worsening of clinical symptoms of hepatitis or hypersensitivity (eg, fatigue, nausea, vomiting, right upper quadrant pain or tenderness, decreased appetite, abdominal pain, jaundice, fever, or rash)
Recent clinically significant hypotension or hypoxemia with compromised cardiopulmonary function
Alcohol and illicit drug use
Results of liver imaging or liver biopsy, if done
Results of any specialist or hepatology consult, if done
Any postmortem/pathology reports

ALT=alanine aminotransferase; AST=aspartate aminotransferase; PDILI=potential drug-induced liver injury

12.2.1.4 Follow-up evaluation

Potential drug-induced liver injury events require follow-up monitoring as described in Table 12–2. Monitoring should continue until liver chemistry values normalize, stabilize, or return to baseline. Determination of stabilization is at the discretion of the Investigator in consultation with the hepatologist (as applicable) and UCB responsible physician, as needed.

12.3 Physical examination

The Investigator will conduct a complete physical examination in all subjects. The physical examination will cover the following general appearance, head, ears, eyes, nose, throat, hair, skin, respiratory, cardiovascular, gastrointestinal, musculoskeletal, hepatic, neurological, and mental status. Clinically relevant changes during the study will be recorded as AEs. In addition, TB signs and symptoms will be assessed.

Findings will be recorded in the eCRF.

12.4 Blood pressure

Blood pressure will be measured prior to dosing with study drug. Subjects should be sitting for 5 minutes prior and during the collection of blood pressure. Systolic and diastolic blood pressure should be recorded in mmHg.

Any abnormal findings which are clinically significant, in the opinion of the Investigator, will be recorded as an AE. Vital sign measurements will be recorded in the eCRF.

12.5 12-lead electrocardiogram

Twelve-lead standard ECGs will be recorded at the visits specified in Table 5–1.

12.6 Tuberculosis assessments and management

All subjects will be assessed for TB at Screening and at the timepoints noted in the schedule of assessments (Table 5–1) through the study through physical examination for signs and symptoms of TB, chest x-ray, laboratory testing, and patient questionnaire.

At Screening, all subjects will have an IGRA test (QuantiFERON TB GOLD is recommended. However, a T-SPOT test may be performed by a local laboratory), a chest x-ray (unless already performed within 3 months of screening), and examination for signs and symptoms of TB. In addition, each subject will complete a TB questionnaire with questions directed at symptoms of TB and potential exposure to TB. Chest x-rays must be read by a qualified radiologist/pulmonary physician to determine whether there is evidence of active or latent TB. Chest x-ray reports must be consistent with standard reporting practices.

At screening, subjects with latent TB must receive a full course of latent TB treatment (see Section 6.2.1, Exclusion Criterion 22) initiated at least 4 weeks prior to the first study drug injection.

One rescreening of subjects with latent TB who are unable to complete a minimum of 4 weeks of TB therapy within the Screening Period is permitted. In this event, all Screening assessments must be repeated.

In case of a TB test conversion defined as a positive result (IGRA) for the current test but previous test results were negative (IGRA), the subject is considered to have either a suspected new latent or an active TB infection. The study drug administration must be stopped immediately and an appropriate specialist (ie, pulmonologist, infectious disease specialist) must be consulted for further evaluation if test conversion indicates either a new latent or a new active TB. Additional assessments (eg, blood tests in case of a positive IGRA test, chest x-rays) should be performed.

In case the evaluation by the appropriate specialist indicates a new latent TB:

A prophylactic TB treatment (as described in this protocol) can be initiated and IMP can be continued no earlier than 4 weeks after start of prophylactic TB treatment, if it is deemed likely that the entire course of prophylactic TB treatment will be completed. In case no prophylactic treatment is initiated, the subject has to be withdrawn. Every action should be discussed with the Medical Monitor. Latent TB must be reported as an AE.

Subjects who develop active TB or NTMB (nontuberculosis mycobacterium) infection during the study (including, but not limited to, conversion demonstrated by IGRA or other diagnostic means during the course of the study) must be immediately discontinued from IMP and a Withdrawal Visit must be scheduled as soon as possible, but not later than the next regular visit.

Confirmed active TB is an SAE and must be captured on an SAE report form and provided to the Sponsor in accordance with SAE reporting requirements. As with all SAEs, periodic follow up reports should be completed as per protocol requirement until such time as the TB infection resolves.

Subjects who prematurely discontinue treatment for latent TB, or, in the opinion of the Investigator or Sponsor, are noncompliant with anti-TB therapy must discontinue further use of study medication and be immediately withdrawn.

12.7 Chest x-ray for TB

A plain posteroanterior chest x-ray must be performed in the Screening Period unless one has been performed within 3 months prior to the Screening Visit. The chest x-ray must be clear of signs of TB infection (previous or current) before first study drug administration. Radiographic findings suggestive of inactive TB or active TB may include but are not limited to: apical fibrosis, pleural thickening, pulmonary nodules, fibrotic scars, calcified granulomas, upper lobe infiltrates, cavitations and pleural effusions, calcified lung nodules, calcified hilar lymph nodes, and pericardial calcification. The chest x-ray (or, if done, Computed Axial Tomography of the Chest) must be negative for TB infection as determined by a qualified radiologist/pulmonary physician. All chest imaging (particularly x-rays) should be available for review by the Investigator before randomization of the subject. Any new clinically significant findings during the physical examinations or on chest x-ray must be documented in the source documents and eCRF as an AE.

12.8 Interferon-gamma release assay (IGRA) testing for TB

All subjects will have IGRA testing conducted as part of the screening procedures and annually for those subjects with a previously negative chest x-ray. Interferon-gamma release assay test kits will be supplied by the central laboratory. Results from this test will be reported as positive, negative, or indeterminate.

Interferon-gamma release assay test kits and the test results will be provided to the site by the central laboratory and electronically transferred to the clinical database.

12.9 Subject questionnaire for TB

The questionnaire "Evaluation of signs and symptoms of tuberculosis" will be used as a source document. The questionnaire will assist with the identification of subjects who may require therapy for TB. A subject who answers "Yes" to the question [redacted] Screening, excludes the subject from study entry. A "Yes" response to any of the other questions within the questionnaire at Screening should trigger further careful assessment to determine if subject has latent or active TB. Subjects with a latent TB infection must receive prophylactic therapy prior to continuing study drug (if allowed by prophylactic therapy specific protocol). Subjects with active TB infection must be withdrawn from the study and will have further assessments.

12.10 Pregnancy testing

Pregnancy testing will consist of serum testing at Screening. Urine testing will be done at all other study visits as outlined in the Schedule of Study Assessments (Table 5–1).

Urine pregnancy testing supplies will be provided by the central laboratory. Testing will be conducted on site and results will be entered into the eCRF.

12.11 Height and weight

Height will be recorded in centimeters (cm) and weight will be recorded in kilogram (kg). Height and weight measurements will be recorded in the eCRF.

12.12 Other study measurements

12.12.1 Demographic information

Demographic information will be collected in all subjects and include age, gender, race, and ethnicity. Information on demographics will be collected according to local rules and regulations. Demographic information will be recorded in the eCRF.

12.12.2 Medical history

A complete medical history will be collected as part of the Screening assessment and include all clinically relevant past or coexisting medical conditions and surgeries. Findings will be recorded in the eCRF.

12.12.3 Psoriasis history

A detailed history of each subject's PSO history will be collected and include the date of onset and past treatments for PSO.

13 STUDY MANAGEMENT AND ADMINISTRATION

13.1 Adherence to protocol

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

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

13.2 Monitoring

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

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

The Investigator will allow UCB (or designee) to periodically review all eCRFs and corresponding source documents (eg, hospital and laboratory records for each study participant). Monitoring visits will provide UCB (or designee) with the opportunity to evaluate the progress

of the study, verify the accuracy and completeness of eCRFs, ensure that all protocol requirements, applicable authorities regulations, and Investigator's obligations are being fulfilled, and resolve any inconsistencies in the study records.

13.2.1 Definition of source data

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

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

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

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

13.2.2 Source data verification

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.

13.3 Data handling

13.3.1 Case Report form completion

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

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

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

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

Detailed instructions will be provided in the eCRF Completion Guidelines.

13.3.2 Database entry and reconciliation

Case Report forms/external electronic data will be entered/loaded into a validated electronic database using a clinical data management system (CDMS). Computerized data cleaning checks will be used in addition to manual review to check for discrepancies and to ensure consistency of the data. Case Report form data are entered into the clinical database using independent, double-data entry, with the exception of comment fields, which are verified by a second person. The data are entered into the eCRFs once and are subsequently verified if the study is performed using electronic data capture.

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.

13.3.3 Subject Screening and Enrollment log/Subject Identification Code list

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

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

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

13.4 Termination of the study

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

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

13.5 Archiving and data retention

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

All essential documents are to be retained by the Investigator until at least 2 years after the last approval of a marketing application in an ICH region and until there are no pending or contemplated marketing applications in an ICH region, or at least 2 years have elapsed since the formal discontinuation of clinical development of the IMP. These documents should be retained

for a longer period, however, if required by the applicable regulatory requirement(s) or by an agreement with UCB (CPMP/ICH/135/95, 2002 [Section 4.9.5]). The Investigator will contact UCB for authorization prior to the destruction of any study records or in the event of accidental loss or destruction of any study records. The Investigator will also notify UCB should he/she relocate or move the study-related files to a location other than that specified in the Sponsor's trial master file.

13.6 Audit and inspection

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

The main purposes of an audit or inspection are to confirm that the rights and well-being of the subjects enrolled have been protected, that enrolled subjects (ie, signing consent and undergoing study procedures) are appropriate for the study, and that all data relevant for the evaluation of the IMP have been processed and reported in compliance with the planned arrangements, the protocol, investigational site, and IRB SOPs, ICH GCP, and applicable regulatory requirements.

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

13.7 Good Clinical Practice

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

14 STATISTICS

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

14.1 Definition of analysis sets

The Enrolled Set (ES) will consist of all subjects who have given informed consent.

The Randomized Set (RS) will consist of all subjects randomized into the study.

The Safety Set (SS) will consist of all subjects in the RS who have received at least 1 dose of study medication.

The Full Analysis Set (FAS) will consist of all randomized subjects that received at least 1 dose of the study medication and have valid efficacy assessments for Baseline and for at least 1 post-Baseline visit.

The Per-Protocol Set (PPS) will consist of subjects in the FAS who have completed a minimal exposure of 16 weeks to the treatment regimen without any important protocol deviations that may influence the validity of the data for the primary efficacy variable. Important protocol deviations will be predefined and evaluated during a data evaluation meeting prior to unblinding of the data.

The PPS may exclude subjects who meet any of the following criteria:

- Have taken any prohibited concomitant medications
- Have not been compliant with the dosing regimen

The criteria for important protocol deviations leading to exclusion from the PPS will be discussed and appropriately documented (see Section 14.5).

The Pharmacokinetics Per-Protocol Set (PK-PPS) will consist of all randomized subjects who took at least 1 dose of the study medication and provided at least 1 quantifiable plasma concentration postdose.

The PsA Set (PsAS) will be consist of subjects in the FAS who with PsA disease at Baseline.

The NAPSI Set (NAPSIS) will be consist of subjects in the FAS who with nail disease at Baseline.

Subjects with generalized pustular PSO or erythrodermic PSO will be analyzed by cohort as follows:

The Cohort Enrolled Set (CES) will consist of subjects with generalized pustular PSO or erythrodermic PSO who have given informed consent.

The Cohort Randomized Set (CRS) will consist of subjects with generalized pustular PSO or erythrodermic PSO randomized into the cohort.

The Cohort Safety Set (CSS) will consist of subjects with generalized pustular PSO or erythrodermic PSO in the CRS who have received at least 1 dose of study medication.

The Cohort Full Analysis Set (CFAS) will consist of subjects with generalized pustular PSO or erythrodermic PSO in the CRS who received at least 1 dose of the study medication and have valid efficacy assessments for Baseline and for at least 1 post-Baseline visit.

The Cohort Pharmacokinetics Set (CPKS) will consist of subjects with generalized pustular PSO or erythrodermic PSO randomized into the cohort who took at least 1 dose of the study medication and provided at least 1 quantifiable plasma concentration postdose.

The Generalized Pustular PSO Set (GPPS) will consist of subjects in the CFAS with generalized pustular PSO disease at Baseline.

The Erythrodermic PSO Set (EPS) will consist of subjects in the CFAS with erythrodermic PSO disease at Baseline.

14.2 General statistical considerations

The primary efficacy variable will be analyzed for subjects with moderate to severe chronic plaque PSO in the FAS. In order to verify the robustness of the efficacy results, primary efficacy variables in the primary analysis will also be analyzed for the PPS as sensitivity analysis.

The statistical analysis of the primary and secondary efficacy variables will account for multiplicity by using a fixed sequence testing procedure. As these variables will be evaluated for both doses of CZP, the statistical analysis for each dose will be carried out in separation of one another. To account for the testing of multiple doses, the alpha level of 0.05 will be split evenly between CZP 400mg Q2W and CZP 200mg Q2W so that each dose is evaluated at an alpha level of 0.025.

Within each dose, the primary endpoints of PASI75 at Week 16 will be evaluated first. Statistical testing of PGA (clear or almost clear) response at Week 16 will be performed only if primary endpoint (PASI75) is significant at the 0.025 alpha level for a given dose.

Similarly, testing of PASI90 at Week 16 will be performed only if primary endpoint (PASI75) and PGA are significant at the 0.025 level, and similarly, testing of change from Baseline in DLQI at Week 16 will be performed only if PASI75, PGA, and PASI90 are significant at the 0.025 level.

Table 14–1 outlines the testing procedure.

Table 14–1: Statistical testing procedure

CZP 200mg Q2W vs Placebo	CZP 400mg Q2W vs Placebo
1. PASI75 response at Week 16	1. PASI75 response at Week 16
2. PGA response at Week 16	2. PGA response at Week 16
3. PASI90 response at Week 16	3. PASI90 response at Week 16
4. Change from Baseline in DLQI at Week 16	4. Change from Baseline in DLQI at Week 16

CZP=certolizumab pegol; DLQI=Dermatology Life Quality Index; PASI=Psoriasis Activity and Severity Index; PGA=Physician's Global Assessment; Q2W=every 2 weeks

Note: All significance tests are performed at an alpha level of 0.025.

14.3 Planned efficacy analyses

Because the majority of PBO subjects will be switched to CZP treatment at Week 16, all statistical comparisons between CZP and PBO will be limited to the time period through Week 16 for subjects with moderate to severe chronic plaque PSO. After Week 16, data will be summarized using descriptive statistics only. Tabular summaries of efficacy data will be based on treatment groups. Variables evaluated over time will be summarized using imputed and observed case values. Further details on data summarization will be provided in the SAP.

14.3.1 Analysis of the primary efficacy variable for subjects with moderate to severe chronic plaque PSO

The primary efficacy variable for this study is PASI75 response at Week 16. A subject will be classified as a PASI75 responder if the PASI score at the visit has improved at least 75% from Baseline. The primary analysis for this variable will be based on a logistic regression model which will include fixed effects for treatment group and prior biologic exposure (yes/no). Prior biologic exposure was selected as a fixed effect in the logistic regression model as it is a stratification variable for randomization and because it may have an impact on efficacy. The odds ratio and associated confidence interval will be presented.

The Markov Chain Monte Carlo (MCMC) method for multiple imputation will be used to account for missing values in the primary analysis of PASI75 at Week 16. The multiple imputation procedure for PASI 75 will be based on the actual PASI score.

Multiple imputation and subsequent analysis will involve 4 principal tasks as described below:

1. Calculate the number of missing values to be estimated by MCMC (nmiss) for the Week 16 value.

2. Create a data set, one for each treatment group, of subjects with observed values and those needing estimation by MCMC. The missing PASI75 values in each data set will be filled in using the MCMC method "5 x nmiss" times to generate "5 x nmiss" data sets. The resulting data sets for each treatment arm will be combined into one complete data set by imputation.
3. For each complete data set, the dichotomous responder rate will be computed. Each complete data set will be analyzed with a logistic regression model with factors of treatment group and prior biologic exposure (yes/no).
4. The results from these analyses will be combined into a single inference using SAS PROC MIANALYZE.

For derivation of PASI75 response, no rounding will be performed. That is, the imputed Week 16 PASI value will be compared directly to the observed Baseline PASI value to determine whether or not a reduction of at least 75% was achieved.

Each CZP dose will be compared against PBO to establish superiority over PBO and will be tested sequentially at an alpha of 0.025 as outlined in Table 14–1.

Analyses will be performed to evaluate the sensitivity of the efficacy results to the method for handling missing data and the statistical analysis method. The following sensitivity analyses will be performed on the primary variable.

1. Nonresponse imputation (NRI) will be used to impute missing values. Specifically, any subject with a missing PASI75 value at Week 16 will be treated as a nonresponder for analysis purposes.
2. A model-based multiple imputation method to impute missing data for the PASI75 responder data.
   a) Calculate the number of missing values (nmiss) for PASI75 responder at Week 16
   b) Intermittent missing values will be imputed first. Intermittent missing values are defined as values where data are missing at 1 time point but available at future time points for the same subject (ie, missing data not associated with study discontinuation). Multiple imputation for these missing values will be performed using the MCMC method to generate "5 x nmiss" times to generate "5 x nmiss" data sets.
   c) With intermittent missing values imputed, only monotone missing data will remain. That is, the only remaining missing data will be for subjects who discontinue study treatment and are missing data at every time point following discontinuation. The imputation model for these missing data will use logistic regression with factors of treatment group, and prior biologic exposure (yes/no) (ie, the imputation model will be the same as the analysis model). The data set used here is the output data set of the partial imputation using MCMC. Since this data set already has "5 x nmiss" imputed values at each visit, only one imputation will be performed.
      a. For each complete data set, the dichotomous responder rate will be computed. Each complete data set will be analyzed with a logistic regression with factors of treatment group and prior biologic exposure (yes/no).
      b. The results from these analyses will be combined into a single inference using SAS PROC MIANALYZE.

Subgroup analyses will be conducted for age, gender, duration of disease, BMI, weight, CRP, prior systemic chemotherapy/phototherapy, prior systemic therapy (nonbiologic), prior biologic exposure, prior anti-TNF exposure and overall anti-CZP antibody status. These subgroup analyses will be performed on the primary efficacy variable and will contain only descriptive statistics for Week 16.

14.3.2 Other efficacy analyses

14.3.2.1 Analysis of the secondary efficacy variables for subjects with moderate to severe chronic plaque PSO

The secondary efficacy variables will be analyzed for all subjects in the FAS.

Secondary efficacy variables are PASI90, PGA response, and change from Baseline in DLQI at Week 16.

A subject will be classified as a PGA responder if the PGA is Clear or Almost clear with at least a 2-category improvement relative to Baseline. The analysis of PASI90 and PGA response at Week 16 will be analyzed for treatment effects using pairwise comparisons based on the same method as that for the primary efficacy variable.

The MCMC algorithm is based on the multivariate normal model, imputed values for PGA will not generally be one of the discrete values actually used in PGA scoring (0, 1, 2, 3, or 4). Therefore, standard rounding rules will be applied to the imputed values in order to derive the binary PGA response variable. For example, if a subject has a PGA score imputed as 1.4 (and assuming a Baseline PGA score of 3), this imputed value would be rounded down to 1, and the minimum change from Baseline of 2 would have been met. Therefore, this subject would be considered a responder.

The significance testing of each CZP treatment group vs PBO will be part of the fixed sequential testing procedure described in Section 14.2.

The analysis of DLQI will be based on the change from Baseline at Week 16. Treatment group comparisons for each CZP treatment group vs PBO will be performed using an analysis of covariance (ANCOVA) model with treatment group and prior biologic exposure (yes/no) as factors and Baseline DLQI score as a covariate. The treatment differences and corresponding 97.5% confidence intervals will be calculated based on the adjusted means. Missing values will be imputed using last observation carried forward (LOCF). Each CZP dose will be compared against PBO to establish superiority over PBO and will be tested at an alpha of 0.025 as part of the fixed sequence testing procedure described in Section 14.2.

14.3.2.2 Analysis of the other efficacy variables for subjects with moderate to severe active plaque PSO

All other efficacy variables (eg, PASI50, PASI75, PASI90, PASI100, PGA, MCID) will be analyzed for all subjects in the FAS.

All categorical variables (eg, PASI score, PGA score, BSA score, DLQI) will be summarized using frequency tables by each visit.

All continuous variables (eg, number of available observations[n],mean, median, standard deviation, minimum, and maximum) will be summarized using descriptive statistics by each visit. In addition, absolute and percent change from baseline by each visit.

Additionally, PASI (eg, PASI50, PASI75, PASI90 and PASI100) and PGA response variables will be analyzed at scheduled time points prior to Week 16 using the same model described for the primary analysis. The p-values will not be adjusted for multiplicity and will be considered nominal.

The time to event variables (such as time to PASI50 and time to PASI75 response during the Initial Treatment Period) will be analyzed using Kaplan-Meier methods, and between group comparisons will be based on log-rank test statistic. For the response of PsA disease to treatment, the ACR20, 50, 70 and change from Baseline in all individual ACR core components will be investigated in the PsAS.

For the response of nail disease to treatment, the total mNAPSI score and change from Baseline in all individual nail severity index score components will be investigated in the NAPSIS.

Summary statistics will be provided for other efficacy variables.

14.3.2.3 Analysis of the other efficacy variables for subjects with generalized pustular PSO and erythrodermic PSO

All other efficacy variables will be analyzed for all subjects in the CFAS.

All categorical variables (eg, CGI-I) will be summarized using frequency tables by each visit.

All continuous variables will be summarized using descriptive statistics by each visit.

For the response of generalized pustular PSO to treatment, the Global Improvement Scores, change from Baseline in all individual JDA severity index score, and the clinical global impression will be investigated in the GPPS.

For the response of erythrodermic PSO to treatment, the clinical global impression will be investigated in the EPS.

14.4 Planned safety and other analyses

All safety summaries will be performed using the safety set (SS) or Cohort safety set (CSS).

14.4.1 Safety analyses

The frequency of all AEs during the study period will be presented for each treatment group separately by System Organ Class, high level term, and preferred term (MedDRA® version 18.1). The data will be displayed as number of subjects experiencing the AE, percentage of subjects, and number of AEs. Additional tables will summarize TEAEs by intensity and relationship to study drug, TEAEs leading to withdrawal from the study, treatment-emergent SAEs, and deaths. Data will also be corrected for exposure and reported by 100 patient-years.

Laboratory evaluations and vital signs will be analyzed over time in the SS (or CSS) for observed cases and end of observation.

14.4.2 Other analyses

Summaries of other analyses will be performed using the PK-PPS or the CPKS. Certolizumab pegol plasma concentration data will be tabulated and summarized by treatment group (overall and by anti-CZP antibody status within each treatment group) for each visit at which samples were taken using the geometric mean, arithmetic mean, minimum, maximum, SD, and %

coefficient of variation. For each treatment group, plasma concentration time curves will be plotted overall and by antibody status.

Frequency tables of anti-CZP antibody status by visit will be presented. In addition, safety and efficacy profiles by anti-CZP antibody status will be investigated.

Subjects will be classified as anti-CZP antibody positive if the anti-CZP antibody level is > cut point at any measurement during the treatment.

14.5 Handling of protocol deviations

Important protocol deviations are deviations from the protocol which potentially could have a meaningful impact on study conduct, or on the primary efficacy, key safety, or PK outcomes for an individual subject. The criteria for identifying important protocol deviations will be defined within the appropriate protocol-specific document. Important protocol deviations will be reviewed as part of the ongoing data cleaning process and all important deviations will be identified and documented prior to unblinding to confirm exclusion from analysis sets.

14.6 Handling of dropouts or missing data

Missing data for the primary endpoint will handled using the MCMC method for multiple imputation. Sensitivity analyses which apply different methods of handling missing data for the primary endpoint are planned. Further details are provided in Section 14.3.1.

Other binary efficacy variables evaluated during the initial Treatment Period which use a logistic regression model similar to the one described for the primary endpoint will handle missing data using the MCMC method for multiple imputation. Other binary efficacy variables evaluated during the initial treatment period that are summarized without statistical modeling will use NRI as the method for handling missing data.

Additionally, algorithms for imputing missing or partial dates for safety evaluations will be detailed in the SAP.

14.7 Planned interim analysis and data monitoring

After the Week 24 Visit of the final subject, the database will be locked and a first interim study report will be written.

14.8 Determination of sample size

14.8.1 Determination of sample size for double-blind for plaque PSO

A total of 125 subjects will be randomly assigned in a 2:2:1 ratio to the following treatment groups:

- CZP 200mg Q2W (with CZP 400mg loading dose at Weeks 0, 2, and 4) (n=50)
- CZP 400mg Q2W (n=50)
- Placebo (n=25)

Both CZP doses will be evaluated for superiority to PBO. The assumed response rates for PASI75 at Week 16 are 75%, 70%, and 15% for CZP 400mg Q2W, CZP 200mg Q2W, and PBO, respectively. Under these assumptions, 43 subjects for each CZP groups and 22 for PBO group were required to detect a difference between CZP (either dose) group and the PBO group with

the power of at least 98% and a 2-sided significance level of 0.025. To allow a margin for some subjects to be excluded from analysis and to consider ensuring the safety assessment cases, the target number of subjects is set to 50 subjects for each CZP groups and 25 for PBO group. The power to detect a statistically significant difference between CZP (either dose) and PBO based on PASI75 given the above assumptions and using a 2-sided test significance level of 0.025 is >99%.

14.8.2 Determination of sample size for generalized pustular PSO and erythrodermic PSO cohort

Expected number of subjects (n ≥10) will be randomly assigned in a 1:1 ratio to the following treatment groups:

- CZP 200mg Q2W (with CZP 400mg loading dose at Weeks 0, 2, and 4) (n ≥5)
- CZP 400mg Q2W (n ≥5).

Patients with plaque PSO account for 88.6% of all types of PSO, while generalized pustular PSO and erythrodermic PSO account for only 1.8% and 1.1%, respectively (Kawada et al, 2010). Thus, in view of subject enrollment, it is difficult to perform a clinical study in patients with generalized pustular PSO or erythrodermic PSO.

Therefore, sample size could not be calculated.

15 ETHICS AND REGULATORY REQUIREMENTS

15.1 Informed consent

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

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

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

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

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

15.2 Subject identification cards

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

15.3 Institutional Review Boards

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

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

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

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

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

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

15.4 Subject privacy

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

The Investigator agrees that representatives of UCB, its designee, representatives of the relevant IRB, or representatives of regulatory authorities will be allowed to review that portion of the

subject's primary medical records that directly concerns this study (including, but not limited to, laboratory test result reports, ECG reports, admission/discharge summaries for hospital admissions occurring during a subject's study participation, and autopsy reports for deaths occurring during the study).

15.5 Protocol amendments

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

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

16 FINANCE, INSURANCE, AND PUBLICATION

Insurance coverage will be handled according to local requirements.

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

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18 APPENDICES

18.1 Protocol Amendment 1

Rationale for the amendment

The purpose of this amendment is the following:

- Correct some inconsistencies between Table 5-1 and Section 8
- Clarify prohibited concomitant treatments
- Clarify that no down-titration is required upon early discontinuation

Modifications and changes

Global changes

The following changes were made throughout the protocol:

- Minor editorial revisions were made.

Specific changes

Change #1

Table 5-1 Schedule of assessments

[c] HBV DNA to be performed at Screening. If the subject is either hepatitis B surface antibody-positive or hepatitis type C virus antibody-positive at Screening, quantitative measurement of HBV-DNA should be performed every 4 weeks from Baseline to Week 52 and at SFU.

Has been changed to

[c] HBV DNA to be performed at Screening. If the subject is either hepatitis B surface antibody-positive or hepatitis **B core**~~**type C virus**~~ antibody-positive at Screening, quantitative measurement of HBV-DNA should be performed every 4 weeks from Baseline to Week 52 and at SFU.

Change #2

Section 7.8.3 Prohibited concomitant treatments (medications and therapies)

The following concomitant medications are prohibited during the double-blind study period:

- Systemic retinoids
- Systemic treatment for PSO (nonbiological)
  - Systemic immunosuppressants agents (eg, methotrexate, cyclosporine, azathioprine, thioguanine)
  - Systemic fumarate

– Systemic corticosteroids

Has been changed to

The following concomitant medications are prohibited during the double-blind study period:

- Systemic retinoids
- Systemic treatment for PSO (nonbiological)
  - Systemic immunosuppressants agents (eg, methotrexate, cyclosporine, azathioprine, thioguanine)
  - ~~**Systemic fumarate**~~
  - Systemic corticosteroids

Change #3

Section 8.2 Visit 2 (Baseline)

- Pustular and erythrodermic PSO assessments (Global Improvement Score, JDA Severity Index, and CGI-I for subjects with generalized pustular PSO or CGI-I for subjects with erythrodermic PSO)

Has been changed to

- Pustular and erythrodermic PSO assessments (~~**Global Improvement Score,**~~ JDA Severity Index~~**, and CGI-I**~~ for subjects with generalized pustular PSO~~**or CGI-I for subjects with erythrodermic PSO**~~)

Change #4

Section 8.5 Visit 5 (Week 6)

Subjects will have the following procedures performed/recorded prior to administration of study drug:

- Hematology, biochemistry, and urine for clinical laboratory values
- Urine pregnancy test for women of childbearing potential
- Plasma for PK and immunogenicity samples

Has been changed to

Subjects will have the following procedures performed/recorded prior to administration of study drug:

- Hematology, biochemistry, and urine for clinical laboratory values
- ~~**Urine pregnancy test for women of childbearing potential**~~
- Plasma for PK and immunogenicity samples

Change #5

Section 8.29 Safety Follow-Up Visit

Subjects will have the following procedures performed/recorded 10 weeks after the last dose of study drug:

- Blood pressure
- Physical examination
- Hematology, biochemistry, and urine (dipstick) for clinical laboratory values, including beta-D-glucan and sialylated carbohydrate antigen KL-6
- Urine pregnancy test for women of childbearing potential

Has been changed to

Subjects will have the following procedures performed/recorded 10 weeks after the last dose of study drug:

- Blood pressure
- Physical examination
- Hematology, biochemistry, and urine (dipstick) for clinical laboratory values~~, including beta-D-glucan and sialylated carbohydrate antigen KL-6~~
- Urine pregnancy test for women of childbearing potential

Change #6

Section 8.30 Withdrawal Visit

Subjects will have the following procedures performed/recorded:

- Blood pressure
- 12-lead ECG
- Weight
- Hematology, biochemistry, and urine for clinical laboratory values
- Urine pregnancy test for women of childbearing potential

Has been changed to

Subjects will have the following procedures performed/recorded:

- Blood pressure
- 12-lead ECG
- Weight
- Hematology, biochemistry, and urine for clinical laboratory values**, including beta-D-glucan and sialylated carbohydrate antigen KL-6**

- Urine pregnancy test for women of childbearing potential

Change #7

Section 8.31 Unscheduled Visit

- Urine pregnancy test for women of childbearing potential
- AEs
- Concomitant medications

Has been changed to

- Urine pregnancy test for women of childbearing potential
- AEs
- **Medical procedures**
- Concomitant medications

Change #8

Section 12.1.4 Pregnancy

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

- The subject should return for an early discontinuation visit.
- The subject should immediately stop the intake of the IMP or be down-titrated as instructed at the early discontinuation visit.
- A Safety Follow-Up Visit should be scheduled 10 weeks after the subject has discontinued her IMP.

Has been changed to

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

- The subject should return for an early discontinuation visit.
- The subject should immediately stop the intake of the IMP ~~**or be down-titrated as instructed at the early discontinuation visit**~~.

- A Safety Follow-Up Visit should be scheduled 10 weeks after the subject has discontinued her IMP.

18.2 Protocol Amendment 2

Rationale for the amendment

The purpose of this amendment is the following:

- Update administrative information
- Clarify withdrawal criteria for PDILI
- Clarify that the CGI-I and Global Improvement Scale will not be performed at Screening or Baseline for subjects with generalized pustular PSO or erythrodermic PSO
- Clarify actions and follow up required for PDILI

Modifications and changes

Global changes

The following changes were made throughout the protocol:

- Minor editorial revisions were made.

Specific changes

Change #1

Study contact information

Clinical Monitoring Contract Research Organization

Name:	PAREXEL International
Address:	6F Kayabacho First Building 1-17-21 Shinkawa Chuo-ku Tokyo 104-0033 JAPAN
Phone:	+81 3 3537 5460
Fax:	+81 3 3552 0451

Has been changed to

Name:	PAREXEL International
Address:	6F Kayabacho First Building 1-17-21 Shinkawa Chuo-ku Tokyo 104-0033 JAPAN
Phone:	+81 3 3537 5~~899460~~
Fax:	+81 3 3552 0451

Change #2

Table 5-1 Footnote g

[g] PASI, PGA, and BSA will not be performed for subjects with generalized pustular PSO. The Global Improvement Score, JDA Severity Index, and CGI-I will be performed for subjects with generalized pustular PSO. For subjects with erythrodermic PSO, the CGI-I will be performed. Note: The CGI-I will not be performed at Screening.

Has been changed to

[g] PASI, PGA, and BSA will not be performed for subjects with generalized pustular PSO. The Global Improvement Score, JDA Severity Index, and CGI-I will be performed for subjects with generalized pustular PSO. For subjects with erythrodermic PSO, the CGI-I will be performed. Note: The CGI-I **and Global Improvement Score** will not be performed at Screening **or Baseline**.

Change #3

Exclusion criteria #18 and #19

18. Subject has any of the following clinically significant laboratory abnormalities at the Screening:
    a. AST >3 x upper limit of normal (ULN)
    b. ALT >3 x ULN
    c. Total bilirubin >1.5 x ULN
    d. Creatinine >ULN
    e. White blood cell (WBC) <3.0 x10^9/L
    f. Hepatitis B surface (HBs) antigen, hepatitis B core (HBc) antibody, hepatitis B surface (HBs) antibody, Hepatitis type B virus (HBV) DNA assay: Positive to any of these (However, patients with negative HBs antigen and HBV-DNA and positive HBc antibody and/or HBs antibody may be included provided that they undergo a HBV-DNA assay every 4 weeks (from Baseline to Week 52) and then at SFU.

g. Hepatitis type C virus (HCV) antibody: Positive

h. Human immunodeficiency virus (HIV) antigen or antibody: Positive to either test

i. T-cell lymphotropic virus type-1 (HTLV-1) antibody: Positive

19. Subject has ≥3x upper limit of normal (ULN) of any of the following: alanine aminotransferase (ALT), aspartate aminotransferase (AST), alkaline phosphatase (ALP), or >ULN total bilirubin (≥1.5xULN total bilirubin if known Gilbert's syndrome). If subject has elevations only in total bilirubin that are >ULN and <1.5xULN, fractionate bilirubin to identify possible undiagnosed Gilbert's syndrome (ie, direct bilirubin <35%).

Has been changed to

18. Subject has any of the following clinically significant laboratory abnormalities at the Screening:

a. **Aspartate aminotransferase** (AST) ~~>~~≥3 x upper limit of normal (ULN)

b. **Alanine aminotransferase** (ALT) ~~>~~≥3 x ULN

c. ~~**Total bilirubin >1.5 x ULN**~~

c. Alkaline phosphatase (ALP) ≥3 x ULN

d. Creatinine >ULN

e. White blood cell (WBC) <3.0 x10^9/L

f. Hepatitis B surface (HBs) antigen, hepatitis B core (HBc) antibody, hepatitis B surface (HBs) antibody, Hepatitis type B virus (HBV) DNA assay: Positive to any of these (However, patients with negative HBs antigen and HBV-DNA and positive HBc antibody and/or HBs antibody may be included provided that they undergo a HBV-DNA assay every 4 weeks (from Baseline to Week 52) and then at SFU.

g. Hepatitis type C virus (HCV) antibody: Positive

h. Human immunodeficiency virus (HIV) antigen or antibody: Positive to either test

i. T-cell lymphotropic virus type-1 (HTLV-1) antibody: Positive

19. Subject has ~~**≥3x upper limit of normal (ULN) of any of the following: alanine aminotransferase (ALT), aspartate aminotransferase (AST), alkaline phosphatase (ALP), or**~~ >ULN total bilirubin (≥1.5xULN total bilirubin if known Gilbert's syndrome). If subject has elevations only in total bilirubin that are >ULN and <1.5xULN, fractionate bilirubin to identify possible undiagnosed Gilbert's syndrome (ie, direct bilirubin <35%).

Change #4

Section 6.3.1 Potential drug-induced liver injury IMP discontinuation criteria

The PDILI criteria below require immediate and permanent discontinuation of IMP:

- Subjects with either of the following:
  - ALT or AST ≥5xULN

– ALT or AST ≥3xULN and coexisting total bilirubin ≥2xULN

The PDILI criterion below requires immediate discontinuation of IMP:

- Subjects with ALT or AST ≥3xULN who exhibit temporally associated symptoms of hepatitis or hypersensitivity. Hepatitis symptoms include fatigue, nausea, vomiting, right upper quadrant pain or tenderness. Hypersensitivity symptoms include fever (without clear alternative cause), rash, or eosinophilia (ie, >5%).

If a nondrug-related cause for the symptoms can be confirmed, these subjects may resume IMP administration after discussion with the responsible UCB physician, but only when the requirements for rechallenge with IMP as provided in Section 12.2.1.2.1 are followed.

The PDILI criterion below allows for subjects to continue on IMP at the discretion of the Investigator.

- Subjects with ALT or AST ≥3xULN (and ≥2x baseline) and {8xULN or 5xULN}, total bilirubin <2xULN, and no eosinophilia (ie, ≤5%), with no fever, rash, or symptoms of hepatitis (eg, fatigue, nausea, vomiting, right upper quadrant pain or tenderness).

Has been changed to

The PDILI criteria below require immediate and permanent discontinuation of IMP:

- Subjects with either of the following:
  - ALT or AST ≥~~8~~5xULN
  - ALT or AST ≥3xULN and coexisting total bilirubin ≥2xULN

The PDILI criterion below requires immediate discontinuation of IMP:

- Subjects with ALT or AST ≥3xULN who exhibit temporally associated symptoms of hepatitis or hypersensitivity. Hepatitis symptoms include fatigue, nausea, vomiting, right upper quadrant pain or tenderness. Hypersensitivity symptoms include fever (without clear alternative cause), rash, or eosinophilia (ie, >5%).

~~**If a nondrug-related cause for the symptoms can be confirmed, these subjects may resume IMP administration after discussion with the responsible UCB physician, but only when the requirements for rechallenge with IMP as provided in Section 12.2.1.2.1 are followed.**~~

The PDILI criterion below allows for subjects to continue on IMP at the discretion of the Investigator.

- Subjects with ALT or AST ≥3xULN (and ≥2x baseline) and <~~(~~8xULN~~ or 5xULN)~~, total bilirubin <2xULN, and no eosinophilia (ie, ≤5%), with no fever, rash, or symptoms of hepatitis (eg, fatigue, nausea, vomiting, right upper quadrant pain or tenderness).

Change #5

Section 7.8.3.1 Prohibited concomitant treatments (medications and therapies) for subjects with generalized pustular PSO or erythrodermic PSO

The following concomitant medications are prohibited for subjects with generalized pustular PSO or erythrodermic PSO:

- Systemic treatment for PSO (nonbiological)
  - Phototherapy or chemophototherapy
  - Granulocyte and monocyte adsorption apheresis
  - Anti-TNFs: infliximab, adalimumab, golimumab, etanercept

Has been changed to

The following concomitant medications are prohibited for subjects with generalized pustular PSO or erythrodermic PSO:

- Systemic treatment for PSO (nonbiological)
  - Phototherapy or chemophototherapy
  - Granulocyte and monocyte adsorption apheresis
  - Anti-TNFs: infliximab **(including biosimilar)**, adalimumab, golimumab, etanercept

Change #6

Section 10 Assessment of pharmacokinetic/pharmacodynamic/pharmacogenomic variables

For all PK samples, at each time point, collect at least 5mL blood into heparinized tube and centrifuged. Plasma will be aliquoted into 2 labeled transport tubes and stored frozen at -20°C or colder and shipped on dry ice.

Has been changed to

For all PK samples, at each time point, collect at least 5mL blood into heparinized tube and centrifuged. Plasma will be aliquoted into ~~2~~**3** labeled transport tubes and stored frozen at -20°C or colder and shipped on dry ice.

Change #7

Section 14.3.1 Analysis of the primary efficacy variable for subjects with moderate to severe chronic plaque PSO

The following paragraph has been deleted

The primary efficacy variable will be analyzed for subjects with moderate to severe chronic plaque PSO in the FAS. In order to verify the robustness of the efficacy results, primary efficacy variables in the primary analysis will also be analyzed for the PPS as sensitivity analysis.

18.3 Protocol Amendment 3

Rationale for the amendment

The purpose of this amendment is the following:

- Clarify prohibited concomitant treatments
- Clarify that study medication will not be administered at Visit 28 (Week 52)
- Clarify that subject treatment assignment will be stratified by prior biologic exposure and psoriatic arthritis
- Allow the T-SPOT test for TB if the QuantiFERON TB GOLD test is not available

Modifications and changes

Specific changes

Change #1

Section 7.8.2.1 Prohibited concomitant treatments (medications and therapies) for subjects with generalized pustular PSO or erythrodermic PSO

The following concomitant medications are prohibited for subjects with generalized pustular PSO or erythrodermic PSO:

- Systemic treatment for PSO (nonbiological)
  - Phototherapy or chemophototherapy
  - Granulocyte and monocyte adsorption apheresis
  - Anti-TNFs: infliximab (including biosimilar), adalimumab, golimumab, etanercept
  - Other biologics and systemic therapies: ustekimumab, secukinumab, ixekizumab, and brodalumab
  - Any other antipsoriatic agent (systemic) under investigation (or approved after the protocol is approved)
  - Antipsoriatic agent (topical) under investigation

Has been changed to

The following concomitant medications are prohibited for subjects with generalized pustular PSO or erythrodermic PSO:

- Systemic treatment for PSO (nonbiological)
  - Phototherapy or chemophototherapy
  - Granulocyte and monocyte adsorption apheresis
  - Anti-TNFs: infliximab (including biosimilar), adalimumab, golimumab, etanercept
  - Other biologics and systemic therapies: ustekimumab, secukinumab, ixekizumab, and brodalumab

- Any other antipsoriatic agent (systemic) under investigation (or approved after the protocol is approved)
- Antipsoriatic agent (topical) under investigation
- **Rituximab**

Change #2

Section 7.10 Randomization and numbering of subjects

An IRT will be used for assigning eligible subjects to a treatment regimen (as applicable) based on a predetermined production randomization and/or packaging schedule provided by UCB (or designee). The randomization schedule will be produced by the IRT vendor. The IRT will generate individual assignments for subject kits of IMP, as appropriate, according to the visit schedule.

Has been changed to

An IRT will be used for assigning eligible subjects to a treatment regimen (as applicable) based on a predetermined production randomization and/or packaging schedule provided by UCB (or designee). The randomization schedule will be produced by the IRT vendor. **Subject treatment assignment will be stratified by prior biologic exposure (yes/no) and psoriatic arthritis (yes/no).** The IRT will generate individual assignments for subject kits of IMP, as appropriate, according to the visit schedule.

Change #3

Section 8.28 Visit 28 (Week 52)

Subjects will have the following procedures performed/recorded prior to administration of study drug:

- Blood pressure
- 12-lead ECG

Has been changed to

Subjects will have the following procedures performed/recorded ~~**prior to administration of study drug**~~:

- Blood pressure
- 12-lead ECG

Change #4

Section 12.6 Tuberculosis assessments and management

At Screening, all subjects will have an IGRA test (QuantiFERON TB GOLD), a chest x-ray (unless already performed within 3 months of screening), and examination for signs and

symptoms of TB. In addition, each subject will complete a TB questionnaire with questions directed at symptoms of TB and potential exposure to TB. Chest x-rays must be read by a qualified radiologist/pulmonary physician to determine whether there is evidence of active or latent TB. Chest x-ray reports must be consistent with standard reporting practices.

Has been changed to

At Screening, all subjects will have an IGRA test (QuantiFERON TB GOLD **is recommended. However, a T-SPOT test may be performed by a local laboratory**), a chest x-ray (unless already performed within 3 months of screening), and examination for signs and symptoms of TB. In addition, each subject will complete a TB questionnaire with questions directed at symptoms of TB and potential exposure to TB. Chest x-rays must be read by a qualified radiologist/pulmonary physician to determine whether there is evidence of active or latent TB. Chest x-ray reports must be consistent with standard reporting practices.

18.4 Protocol Amendment 4

Rationale for the amendment

The purpose of this amendment is the following:

- Clarify prohibited concomitant treatments and that they are prohibited throughout the study
- Clarify that antipsoriatic agents (topical) under investigation or approved after the protocol is approved are prohibited
- Add time to onset of action, defined as the time to PASI90 and time to onset of action, defined as time to PASI100 as other efficacy variables for subjects in the Double-Blind Overall population for subjects with moderate to severe chronic plaque PSO
- Change the Sponsor Study Physician to [redacted] MD, PhD

Modifications and changes

Specific changes

Change #1

Sponsor Study Physician

Name:	[redacted], MD, PhD
Address:	UCB Japan Co. Ltd. Shinjuku Grand Tower 8-17-1 Nishi-shinjuku Shinjuku-ku Tokyo 160-0023 JAPAN
Phone:	[redacted]

Fax:	[redacted]

Has been changed to

Name:	[redacted] MD, PhD
Address:	UCB Japan Co. Ltd. Shinjuku Grand Tower 8-17-1 Nishi-shinjuku Shinjuku-ku Tokyo 160-0023 JAPAN
Phone:	[redacted]
Fax:	

Change #2

Section 4.1.3.1.1 Double-Blind Overall population

The following bullets were added:

- Time to onset of action, defined as the time to PASI90
- Time to onset of action, defined as the time to PASI100

Change #3

Section 5.2 Schedule of study assesssments

Table 5-1 Footnotes i and j

[i] For subjects with PsA: HAQ-DI, Patient's Assessment of Arthritis Pain (VAS), and PGADA (VAS)

[j] For subjects with PsA: swollen and tender joint counts and PhGADA (VAS)

Has been changed to

[i] **Only F~~f~~or chronic plaque PSO** subjects with PsA: HAQ-DI, Patient's Assessment of Arthritis Pain (VAS), and PGADA (VAS)

[j] **Only F~~f~~or chronic plaque PSO** subjects with PsA: swollen and tender joint counts and PhGADA (VAS)

Change #4

Section 6.2.1 Exclusion criterion #25, Table 6-1

Topical agents Any other antipsoriatic agent (topical) under investigation	Any dose	4 weeks

Has been changed to

Topical agents Any other antipsoriatic agent (topical) under investigation **(or approved after the protocol is approved)**	Any dose	4 weeks

Change #5

Section 6.2.3 Exclusion criterion #30, Table 6-2

Topical agents Antipsoriatic agent (topical) under investigation	Any dose	4 weeks

Has been changed to

Topical agents Antipsoriatic agent (topical) under investigation **(or approved after the protocol is approved)**	Any dose	4 weeks

Change #6

The heading for Section 7.8.1.1

Permitted concomitant treatments (medications and therapies) for subjects who escape

Has been changed to

Permitted concomitant treatments (medications and therapies) for subjects **with moderate to severe chronic plaque PSO** who escape **from double-blind treatment**

Change #7

Section 7.8.2 Prohibited concomitant treatments (medications and therapies)

The following text was added:

Prohibited concomitant treatments (medications and therapies) differ based on whether the subject is in the moderate to severe chronic plaque PSO, generalized pustular PSO, or erythrodermic PSO treatment group.

Change #8

The following heading was added, subsequent headings renumbered as appropriate, and text revised.

Section 7.8.2.1 Prohibited concomitant treatments (medications and therapies) for subjects with moderate to severe chronic plaque PSO

The following concomitant medications are prohibited during the double-blind study period:

- Systemic retinoids
- Systemic treatment for PSO (nonbiological)
  - Systemic immunosuppressants agents (eg, methotrexate, cyclosporine, azathioprine, thioguanine)
  - Systemic corticosteroids
  - Phototherapy or chemophototherapy
  - Anti-TNFs: infliximab (including biosimilar), adalimumab, golimumab, etanercept
  - Other biologics and systemic therapies: ustekimumab, secukinumab, ixekizumab, and brodalumab
  - Any other antipsoriatic agent (systemic) under investigation
  - Rituximab
- Topical agents for dermatologic use:
  - High potency topical corticosteroids (class I and II)
  - Any other antipsoriatic agent (topical) under investigation
  - Moderate potency (class III to V) topical corticosteroids during the double-blind study period
  - Vitamin D analogues and topical retinoids during the double-blind study period
  - Keratolitic and coal tar

Has been changed to

The following concomitant medications are prohibited for subjects with moderate to severe chronic plaque PSO:

- Systemic retinoids
- Systemic treatments for PSO ~~**(nonbiological)**~~
  - Systemic immunosuppressants agents (eg, methotrexate, cyclosporine, azathioprine, thioguanine)
  - Systemic corticosteroids
  - Phototherapy or chemophototherapy
  - Anti-TNFs: infliximab (including biosimilar), adalimumab, golimumab, etanercept

- Other biologics and systemic therapies: ustekimumab, secukinumab, ixekizumab, and brodalumab
- Any other antipsoriatic agent (systemic) under investigation (or approved after the protocol is approved)
- Rituximab

- Topical agents for dermatologic use:
  - High potency topical corticosteroids (class I and II)
  - Any other antipsoriatic agent (topical) under investigation **(or approved after the protocol is approved)**
  - Moderate potency (class III to V) topical corticosteroids ~~**during the double-blind study**~~
  - Vitamin D analogues and topical retinoids ~~**during the double-blind study**~~
  - Keratolitic and coal tar ~~**during the double-blind study**~~

Change #9

Section 7.8.2.2 Prohibited concomitant treatments (medications and therapies) for subjects with generalized pustular PSO or erythrodermic PSO

The following concomitant medications are prohibited for subjects with generalized pustular PSO or erythrodermic PSO:

- Systemic treatment for PSO (nonbiological)
  - Phototherapy or chemophototherapy
  - Granulocyte and monocyte adsorption apheresis
  - Anti-TNFs: infliximab (including biosimilar), adalimumab, golimumab, etanercept)
  - Other biologics and systemic therapies: ustekimumab, secukinumab, ixekizumab, and brodalumab
  - Any other antipsoriatic agent (systemic) under investigation (or approved after the protocol is approved)
  - Antipsoriatic agent (topical) under investigation
  - Rituximab

Has been changed to

The following concomitant medications are prohibited for subjects with generalized pustular PSO or erythrodermic PSO:

- Systemic treatments for PSO ~~**(nonbiological)**~~
  - Phototherapy or chemophototherapy
  - Granulocyte and monocyte adsorption apheresis

- Anti-TNFs: infliximab (including biosimilar), adalimumab, golimumab, etanercept)
- Other biologics and systemic therapies: ustekimumab, secukinumab, ixekizumab, and brodalumab
- Any other antipsoriatic agent (systemic) under investigation (or approved after the protocol is approved)
- Antipsoriatic agent (topical) under investigation **(or approved after the protocol is approved)**
- Rituximab

Change #10

Section 11 Assessment of immunological variables

Anti-CZP antibody supplies will be provided by the central laboratory. Additional information will be outlined in the study Laboratory Manual.

Has been changed to

~~**Anti-CZP antibody supplies will be provided by the central laboratory.**~~ Additional information will be outlined in the study Laboratory Manual.

Change #11

Section 14.1 Definition of analysis sets

The Full Analysis Set (FAS) will consist of all randomized subjects that received at least 1 dose of the study medication and have valid measurement of the primary efficacy variable at Baseline.

Has been changed to

The Full Analysis Set (FAS) will consist of all randomized subjects that received at least 1 dose of the study medication **and have valid efficacy assessments for Baseline and for at least 1 post-Baseline visit**~~**measurement of the primary efficacy variable at Baseline**~~.

Change #12

Section 14.1 Definition of analysis sets

The NAPSI Set (NAPSIS) will be consist of subjects in the FAS who with nail disease at Baseline.

The Cohort Enrolled Set (CES) will consist of subjects with generalized pustular PSO or erythrodermic PSO who have given informed consent.

Has been changed to

The NAPSI Set (NAPSIS) will be consist of subjects in the FAS who with nail disease at Baseline.

Subjects with generalized pustular PSO or erythrodermic PSO will be analyzed by cohort as follows:

The Cohort Enrolled Set (CES) will consist of subjects with generalized pustular PSO or erythrodermic PSO who have given informed consent.

Change #13

Section 14.1 Definition of analysis sets

The Cohort Full Analysis Set (CFAS) will consist of subjects with generalized pustular PSO or erythrodermic PSO in the CRS who received at least 1 dose of the study medication and have a valid measurement of the primary efficacy variable at Baseline.

Has been changed to

The Cohort Full Analysis Set (CFAS) will consist of subjects with generalized pustular PSO or erythrodermic PSO in the CRS who received at least 1 dose of the study medication **and have valid efficacy assessments for Baseline and for at least 1 post-Baseline visit~~a valid measurement of the primary efficacy variable at Baseline~~**.

Change #14

Section 14.3.2.3 Analysis of the other efficacy variables for subjects with generalized pustular PSO and erythrodermic PSO

All other efficacy variables will be analyzed for all subjects in the CFAS.

All categorical variables (eg, CGI-I) will be summarized using frequency tables by each visit.

All continuous variables (eg, CGI-I) will be summarized using descriptive statistics by each visit.

Has been changed to

All other efficacy variables will be analyzed for all subjects in the CFAS.

All categorical variables (eg, CGI-I) will be summarized using frequency tables by each visit.

All continuous variables ~~**(eg, CGI-I)**~~ will be summarized using descriptive statistics by each visit.

Change #15

14.8.2 Determination of sample size for generalized pustular PSO and erythrodermic PSO cohort

Patients with plaque PSO account for 88.6% of all types of PSO, while generalized pustular PSO and erythrodermic PSO account for only 1.8% and 1.1%, respectively (Kawata et al, 2010). Thus, in view of subject enrollment, it is difficult to perform a clinical study in patients with generalized pustular PSO or erythrodermic PSO.

Has been changed to

Patients with plaque PSO account for 88.6% of all types of PSO, while generalized pustular PSO and erythrodermic PSO account for only 1.8% and 1.1%, respectively (Kawadta et al, 2010). Thus, in view of subject enrollment, it is difficult to perform a clinical study in patients with generalized pustular PSO or erythrodermic PSO.

Change #16

Section 17 References

The following reference was added:

Kawada A, Nakamura K, Kaneko F, Ito H, Nakagawa H. National survey of psoriasis (commentary). Practical Dermatology. 2010;11:1238-42.

19 DECLARATION AND SIGNATURE OF INVESTIGATOR

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

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

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

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

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

Investigator:

Printed name	Date/Signature

20 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.

PS0017 Protocol Amendment 4

ELECTRONIC SIGNATURES

Signed by	Meaning of Signature	Server Approval Date (dd-mon-yyyy (HH:mm))
[redacted]	Clinical Approval	29-Jan-2018 02:15 GMT+01
	Clinical Approval	29-Jan-2018 06:12 GMT+01
	Clinical Approval	30-Jan-2018 01:06 GMT+01