CLINICAL STUDY PROTOCOL

A Randomized, Active-Controlled, Double-Blind, Phase 3 Study to Compare the Efficacy and Safety of CT-P43 to Stelara in Patients with Moderate to Severe Plaque Psoriasis

Protocol Number CT-P43 3.1

EudraCT Number:	2020-001045-39
Sponsor:	[redacted]
Sponsor Contact:	[redacted]
SAE Reporting and Data Center:	[redacted]
Version of Protocol:	Protocol Version 2.0, including country specific B.0, 14 July 2021

CONFIDENTIAL

Protocol Approval – Sponsor Signatory

Study Title	A Randomized, Active-Controlled, Double-Blind, Phase 3 Study to Compare the Efficacy and Safety of CT-P43 to Stelara in Patients with Moderate to Severe Plaque Psoriasis
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Protocol accepted and approved by:

[redacted]

Declaration of Investigator

I have read and understood all sections of the protocol entitled "A Randomized, Active-Controlled, Double-Blind, Phase 3 Study to Compare the Efficacy and Safety of CT-P43 to Stelara in Patients with Moderate to Severe Plaque Psoriasis" and the accompanying Investigator's Brochure.

I agree to supervise all aspects of the protocol and to conduct the clinical investigation in accordance with the Protocol Version 2.0, including country specific B.0, dated 14 July 2021, the International Council for Harmonisation harmonised tripartite guideline E6 (R2): Good Clinical Practice and all applicable government regulations. I will not make changes to the protocol before consulting with CELLTRION, Inc. or implement protocol changes without Independent Ethics Committee approval except to eliminate an immediate risk to subjects. I agree that the study drug will only be administered to subjects under my personal supervision or the supervision of a sub-Investigator.

I will not supply the investigational drug to any person not authorized to receive it. Confidentiality will be protected. Subject identity will not be disclosed to third parties or appear in any study reports or publications.

I will not disclose information regarding this clinical investigation or publish results of the investigation without authorization from CELLTRION, Inc.

Signature of Principal Investigator	Date

Printed Name of Principal Investigator

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Protocol Synopsis

Protocol Number: CT-P43 3.1

Title: A Randomized, Active-Controlled, Double-Blind, Phase 3 Study to Compare the Efficacy and Safety of CT-P43 to Stelara in Patients with Moderate to Severe Plaque Psoriasis

Study Phase: Phase 3

Planned Number of Study Centers/Countries: This study will be conducted in 34 centers in 4 countries

Test Formulation, Dose, and Regimen:

- Patients who weigh ≤100 kg: CT-P43 45 mg (1 injection of 45 mg/0.5 mL) by subcutaneous (SC) injection via pre-filled syringe (PFS)
- Patients who weigh >100 kg: CT-P43 90 mg (2 injections of 45 mg/0.5 mL) by SC injection via PFS

Patients will receive an initial dose of CT-P43 45 or 90 mg administered subcutaneously, followed by another dose 4 weeks later, and then every 12 weeks thereafter up to Week 40.

Reference Drug, Dose, and Regimen:

- Patients who weigh ≤100 kg: Stelara 45 mg (1 injection of 45 mg/0.5 mL) by SC injection via PFS
- Patients who weigh >100 kg: Stelara 90 mg (2 injections of 45 mg/0.5 mL) by SC injection via PFS

Patients will receive an initial dose of Stelara 45 or 90 mg administered subcutaneously, followed by another dose 4 weeks later, and then every 12 weeks thereafter up to Week 40.

Objectives:

Primary objective:

- To demonstrate that CT-P43 is equivalent to Stelara, in terms of efficacy as determined by the mean percent improvement from baseline in Psoriasis Area and Severity Index (PASI) score at Week 12.

Secondary objectives:

- To evaluate efficacy, pharmacokinetics (PK), quality of life (QoL), and overall safety including immunogenicity up to Week 52.

Exploratory objectives:

- To evaluate additional efficacy up to Week 52 and to characterize biomarker.

Main Selection Criteria: Male or female patients with moderate to severe plaque psoriasis who are candidates for phototherapy or systemic therapy will be considered for enrollment in the study if they meet all of the inclusion criteria and none of the exclusion criteria.

Inclusion Criteria:

Each patient must meet all of the following criteria to be enrolled in this study:

1. Patient is male or female aged 18 to 80 years old, both inclusive.
2. Patient has had diagnosis of plaque-type psoriasis for at least 24 weeks before the first administration of the study drug (Day 1).
3. Patient has stable moderate to severe chronic plaque psoriasis with or without psoriatic arthritis (PsA) at both Screening and at the time of the first administration of the study drug (Day 1) as defined by the following:
   - a PASI score of ≥12 and
   - an involved body surface area (BSA) ≥10% and
   - a static Physician's Global Assessment (sPGA) score of ≥3
4. Patient is a candidate for phototherapy or systemic therapy.

5. Patient has adequate renal and hepatic function at Screening as defined by the following clinical chemistry results:
   - Serum creatinine ≤1.5 × upper limit of normal (ULN) or an estimated creatinine clearance level >50 mL/min (by Cockcroft-Gault formula) (SI [Système International d'Unités] units: 0.84 mL/s)
   - Serum alanine aminotransferase or aspartate aminotransferase ≤2.5 × ULN
   - Serum total bilirubin ≤1.5 × ULN
6. Patient has the following hematology laboratory test results at Screening:
   - Hemoglobin ≥10.0 g/dL (SI units: >100 g/L or 6.21 mmol/L)
   - Absolute neutrophil count ≥1.5 × 10^3 cells/μL (SI units: ≥1.5 × 10^9 cells/L)
   - Platelet count ≥100 × 10^3 cells/μL (SI units: ≥100 × 10^9 cells/L)
7. Patient (or legal guardian, if applicable) is informed of the full nature and purpose of the study, including possible risks and side effects, and given ample time and opportunity to read and understand this information, and signs and dates the written informed consent before participation in the study.
8. Female patient who is considered of childbearing potential (i.e., fertile, following menarche and until becoming post-menopausal unless permanently sterile) must agree to use highly effective methods of contraception consistent with local regulations during the course of the study and at least 15 weeks following discontinuation of study drug (excluding women who are not of childbearing potential). Examples include the following:
   - Combined (estrogen and progestogen containing) or progestogen-only hormonal contraceptives associated with inhibition of ovulation
   - Intrauterine device or intrauterine hormone-releasing system
   - True abstinence, when this is in line with the preferred and usual lifestyle of the patient. Periodic abstinence (e.g., calendar, ovulation, symptothermal, post-ovulation methods), declaration of abstinence for the duration of exposure to investigational drug, and withdrawal are not acceptable methods of contraception.

   Male patient who is sexually active with a woman of childbearing potential must agree to use the highly effective method described as above or medically acceptable methods of contraception (e.g., male or female condom AND additional hormonal or barrier method by female partner) consistent with local regulations during the study and for 15 weeks following discontinuation of study drug.

   If patient or their partner has been surgically sterilized for less than 24 weeks prior to the date of informed consent form (ICF), they also must agree to use method(s) of contraception as described above. Postmenopausal female patients must have experienced their last menses more than 1 year prior to the date of ICF without an alternative medical cause to be classified as not of childbearing potential.

Exclusion Criteria:

Patients meeting any of the following criteria will be excluded from the study:

1. Patient diagnosed with forms of psoriasis other than plaque-type such as erythrodermic psoriasis, pustular psoriasis, guttate psoriasis, medication-induced psoriasis, or other skin conditions (e.g., eczema) at the time of the Screening visit that would interfere with evaluations of the effect of investigational product on psoriasis.
2. Patient previously received ustekinumab or a biosimilar of ustekinumab or any drug that targets directly interleukin (IL)-12, or IL-23.
3. Patient who has prior exposure to 2 or more biologic agents approved for the treatment of psoriasis. Patient with 1 prior biologics can be enrolled after sufficient wash-out period of 12 weeks or 5 half-lives (whichever is longer) prior to the first administration of the study drug (Day 1) (see Exclusion criteria 11 for other prohibited medications or treatment).
4. Patient who has current or chronic inflammatory or autoimmune disease or symptoms other than psoriasis and psoriatic arthritis that might confound study evaluations.

5. Patient who has allergies to the active substance or any of the excipients of ustekinumab or study drug, or patients with a hypersensitivity to immunoglobulin products or natural rubber and latex.
6. Patient who has received a live or live-attenuated vaccination within 4 weeks prior to the first administration of the study drug (Day 1). Patient must agree not to receive a live or live-attenuated vaccines during the study and at least 15 weeks after the last dose of the study drug.
7. Patient who has had Bacillus Calmette-Guérin (BCG) vaccination within 1 year prior to the first administration of the study drug (Day 1). Patients must agree not to receive a BCG vaccination during the study and up to 1 year after the last dose of the study drug.
8. Patient who has a current or past history of any of the following infections:
   - Current or past history of infection with human immunodeficiency virus (HIV) or current infection with hepatitis B or hepatitis C. However, a patient with past hepatitis B or C virus infection is allowed if resolved (See Section 6.3.2.8).
   - Current or past history of serious infection requiring hospitalization or parenteral injection of antibiotics within 8 weeks prior to the first administration of the study drug (Day 1).
   - Herpes zoster infection within 8 weeks prior to the first administration of the study drug (Day 1).
   - Current or past granulomatous infections or other severe or chronic or recurrent infections (such as sepsis, abscess or opportunistic infections, or invasive fungal infections such as histoplasmosis or nontuberculous mycobacterial infection or infected skin wounds or ulcer). However, a patient who has a past diagnosis with sufficient documentation of complete resolution of the infection can be enrolled in the study.
9. Patient who has a current or past history of any of the following tuberculosis (TB) conditions:
   - Patient who has current or a history of active TB. Patient who has any evidence of history of active TB cannot be enrolled despite sufficient documentation of complete resolution of active TB.
   - Patient who has signs or symptoms suggestive of active TB.
   - Patient who has had exposure to a person with active TB such as first-degree family members or co-workers within 16 weeks prior to the first administration of the study drug (Day 1).
   - Patient who has a past diagnosis of latent TB unless they have documentation of completing TB prophylaxis, or have received at least the first 3 weeks of country-specific TB prophylaxis prior to the first administration of the study drug (Day 1) and intends to complete its entire course can be enrolled.
   - Patient who has a current diagnosis of latent TB (defined as a positive result of interferon-γ release assay [IGRA] with a negative examination of chest X-ray) at Screening without a history of active TB or latent TB. However, a patient who has received at least the first 3 weeks of country-specific TB prophylaxis prior to the first administration of the study drug (Day 1) and intends to complete its entire course can be enrolled.
   - Patient who is without a history of active TB or latent TB and has an indeterminate result of IGRA with a negative examination of chest X-ray at Screening. If the result of IGRA is indeterminate at Screening, 1 retest will be allowed during the Screening Period. Depending on the result of retest, the enrollment will be determined as follows:
     - If the repeated IGRA result is negative, the patient can be enrolled.
     - If the repeated IGRA result is positive, the patient who has received at least the first 3 weeks of country-specific TB prophylaxis prior to the first administration of the study drug (Day 1) and intends to complete its entire course can be enrolled.
     - If the repeated IGRA result is again indeterminate, the patient cannot be enrolled.
10. Patient who has a medical condition including 1 or more of the following:
    - Diabetes mellitus considered by the investigator to be clinically significant and uncontrolled.
    - Uncontrolled hypertension (as defined by systolic blood pressure [BP] ≥160 mmHg or diastolic BP ≥100 mmHg).

- Current or past history of any malignancy within the previous 5 years prior to the first administration of the study drug (Day 1) except adequately treated non-metastatic squamous carcinoma of the uterine cervix, cutaneous basal cell carcinoma, or cutaneous squamous cell carcinoma with no evidence of recurrence for at least 12 weeks prior to the first administration of the study drug (Day 1).
- Current or past history of severe uncontrolled cardiac disease (such as unstable angina or clinically significant electrocardiogram [ECG] abnormalities), or myocardial infarction within the 24 weeks prior to the first administration of the study drug (Day 1).
- History of organ transplantation, with exception of a corneal transplant within 12 weeks prior to the first administration of the study drug (Day 1).
- Any respiratory disease that can be judged as clinically significant at the investigator's discretion, including but not limited to chronic obstructive pulmonary disease, asthma, or pleural effusion.
- Any major surgical procedure within 12 weeks prior to the first administration of the study drug (Day 1) or planned during the study.
- History or evidence of any other clinically significant medical or psychiatric condition that, in the opinion of the investigator, would pose a risk to patient safety or interfere with the study evaluation, procedures, or completion.

11. Patient who has received or plans to receive any of the following prohibited medications or treatment that could affect psoriasis:
    - Topical therapies for the treatment of psoriasis (including, but not limited to, corticosteroids, vitamin D analogs, calcineurin inhibitors or retinoids) within 2 weeks prior to the first administration of the study drug (Day 1). However, low-potency topical corticosteroids (Class 6 or 7) applied to the face and intertriginous areas are permitted during study participation to reduce patient's burden with a restriction of use within 12 hours prior to study visits requiring PASI or sPGA measures. Shampoos with salicylic acids and bland moisturizers/emollients (without urea or beta or alpha hydroxy acids) are also allowed for treatment of psoriasis, but these should not be used in the mornings of study visits when efficacy assessments are going to be performed.
    - Ultraviolet A phototherapy (with or without oral psoralen) or ultraviolet B phototherapy for the treatment of psoriasis within 4 weeks prior to the first administration of the study drug (Day 1).
    - Any systemic steroids or nonbiologic systemic therapies that could affect psoriasis within 4 weeks prior to the first administration of the study drug (Day 1).
    - Any investigational drug within 4 weeks or 5 half-lives (whichever is longer) prior to the first administration of the study drug (Day 1).
    - Initiation or dose modification of drugs that may aggravate psoriasis (e.g., beta-blockers, lithium, antimalarials) within 4 weeks prior to the first administration of the study drug (Day 1). Patients who have been on stable dose without exacerbation of psoriasis for at least 4 weeks prior to the first administration of the study drug (Day 1) can be enrolled, however, the same dose should remain throughout the study.
    - Herbal treatment within 2 weeks prior to the first administration of the study drug (Day 1).
12. Female patient who is currently pregnant or breastfeeding, or is planning to become pregnant or breastfeed within 15 weeks of the last dose of study drug.
13. Male patient who is planning to donate sperm or father a child within 15 weeks of the last dose of study drug.
14. Patient who is not willing to limit ultraviolet light exposure (e.g., excessive sun exposure and/or the use of tanning devices) during the study.
15. Patient who has currently active alcohol or drug abuse or history of alcohol or drug abuse within the previous 1 year from Screening.

16. Patient is vulnerable (e.g., employees of the study center or any other individuals involved with the conduct of the study, or immediate family members of such individuals, persons kept in prison, or other institutionalized persons by law enforcement).
17. Patient who, in the opinion of the investigator, should not participate in the study.

Study Design:

This study is a randomized, active-controlled, double-blind, multicenter, Phase 3 study designed to evaluate efficacy, PK, QoL, and overall safety including immunogenicity and biomarker of CT-P43 compared with Stelara in patients with moderate to severe plaque psoriasis who are candidates for phototherapy or systemic therapy.

During Treatment Periods I and II, patients will receive either 45 or 90 mg of CT-P43 or Stelara by SC injection via PFS Weeks 0, 4, 16, 28, and 40 based on patient's baseline body weight. Patients who weigh ≤100 kg at baseline will receive an initial study drug dose of 45 mg, followed by another 45 mg dose 4 weeks later, and then every 12 weeks thereafter (up to Week 40). Patients who weigh >100 kg at baseline will receive a study drug dose of 90 mg as per the same schedule. However, in case significant body weight change occurs and results in over 10% outside from threshold weight (i.e., 100 kg) at Week 16 predose (e.g., ≤100 kg at baseline but increased to >110 kg at Week 16 OR >100 kg at baseline but decreased to ≤90 kg at Week 16), adjusted dose will be administered to all treatment groups in Treatment Period II.

Treatment Period I

A minimum of 446 patients with moderate to severe plaque psoriasis will be enrolled and randomly assigned to one of the 2 groups in a 1:1 ratio (a minimum of 223 patients in each treatment group of CT-P43 and Stelara).

The first randomization to treatment assignment will be stratified by;

- Country
- Body weight (≤100 kg vs. >100 kg)
- Prior biologic use approved for psoriasis treatment (Yes or No)

The second dosing schedule of the study drug is at Week 4. At Week 12, it is recommended that patients who achieve at least 50% improvement from baseline in PASI (PASI 50) continue study drug administration in the Treatment Period II in all groups.

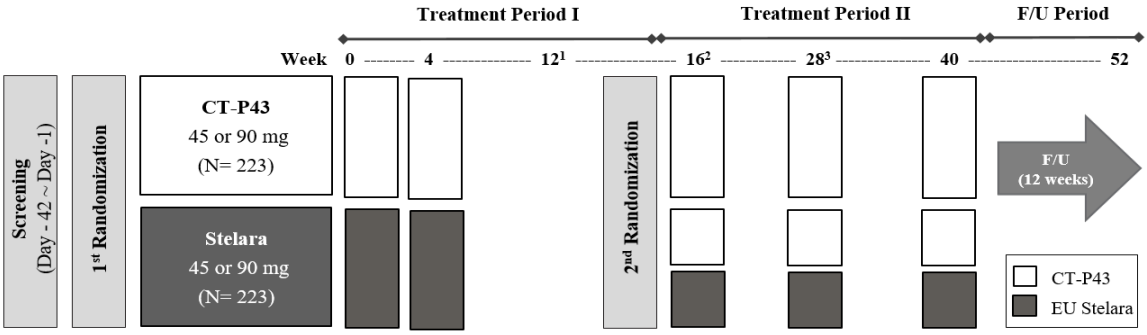
Treatment Period II

Prior to dosing at Week 16, patients in the Stelara group will be randomly assigned again in a ratio of 1:1 to either continue Stelara or undergo a transition to CT-P43 from Week 16. All patients who were initially randomized to the CT-P43 group on Day 1 (Week 0) will continue their treatment with CT-P43 until Week 40. The dose of study drug will be adjusted for further study drug dosing at Weeks 16, 28, and 40 if significant body weight occurs and results in over 10% outside from threshold weight (i.e., 100 kg) at Week 16 predose.

The second randomization for the Stelara group will be stratified by dose at Week 16 (45 mg vs. 90 mg). The second randomization process will also be conducted in the CT-P43 group prior to dosing at Week 16 to maintain the study blind. At Week 28, it is recommended that patients who achieve at least a 75% improvement from baseline in PASI (PASI 75) continue further study drug administration in all groups.

The study design and patient assessment overview are presented in **Figure S1**.

- **Figure S1 Study Design Overview**



Week	0	2	4	8	12[1]	16[2]	28[3]	40	52 (EOS)
Study drug administration	●		●			●	●	●	
Efficacy[4]	●	●	●	●	●	●	●	●	●
Pharmacokinetics	●		●		●	●	●	●	●
Immunogenicity	●		●		●	●	●	●	●
Safety	←	—	—	—	—	—	—	—	→

[1] At Week 12, it is recommended that patients who achieve at least PASI 50 continue study drug administration in the Treatment Period II in all groups.

[2] Prior to dosing at Week 16, all patients will undergo a second randomization process. Patients who were initially randomized to Stelara will be randomized again in a ratio of 1:1 to either continue Stelara or undergo transition to CT-P43. All patients who were initially randomized to the CT-P43 group on Day 1 (Week 0) will continue their treatment with CT-P43 until Week 40.

[3] At Week 28, it is recommended that patients who achieve at least PASI 75 continue further study drug administration in all groups.

[4] The investigator-reported outcomes assessments (i.e., PASI, sPGA) will be performed by a qualified efficacy assessor at the site. If possible, it is recommended that the same assessor perform the investigator-reported outcomes assessments throughout the entire study period.

After database lock for data up to Week 28 treatment, the study will be unblinded to predefined unblinded personnel from the sponsor and contract research organization (CRO) for reporting purposes and efficacy, PK, QoL, and overall safety including immunogenicity and biomarker will be evaluated. The unblinded personnel will be predefined before breaking the study blind. The study will remain blinded to the investigators, patients, and predefined blinded personnel from the sponsor and CRO until all patients have completed the study and the database has been finalized for study termination.

Study Schedule:

There will be 4 periods in the study; Screening Period, Treatment Period I, Treatment Period II, and EOS visit.

Screening Period (Day –42 [6 weeks] to Day –1):

Screening will take place between Day –42 and –1, prior to the first study drug administration.

Treatment Period (Week 0 to Week 40):

- Treatment Period I (16 weeks)
- Treatment Period II (24 weeks)

On Day 1, Week 0, patients who meet all of the inclusion criteria and none of the exclusion criteria will be enrolled in the study and randomly assigned to receive either CT-P43 or Stelara. The patients will receive either CT-P43 or Stelara, as per the first and second randomization, by SC injection at Weeks 0, 4, 16, 28 and 40. Study drug will be administered by a predefined unblinded staff at the site and the investigator and patients will remain blinded during the study. The unblinded staff will not be permitted to conduct any patient assessments during the study.

Patients will comply with all appropriate visits and assessments. Patients will return to the site at predefined time intervals for clinical assessments and blood sampling. At each visit, patients will be questioned about adverse events (AEs) and concomitant medications and will be monitored for the clinical signs and symptoms of TB.

End-of-Study (EOS) visit:

The EOS visit will be performed at Week 52 for patients who completed or discontinued study drugs. For all patients who discontinue study drug before Week 40, every effort should be made to complete regularly scheduled study visits for efficacy and safety assessments. If a patient cannot or is unwilling to attend any visit(s), a safety follow-up will be conducted by telephone according to the study visit schedule. If a patient discontinues study drug prior to Week 12, when the primary endpoint assessed, they should return to the site at Week 12 for the primary efficacy endpoint assessment, even if they initiated psoriasis medication changes (including those prohibited by the protocol).

Efficacy Assessments:

Primary endpoint:

The primary efficacy endpoint will be the mean percent improvement from baseline in PASI score at Week 12.

Secondary endpoints:

The secondary efficacy endpoints will be assessed during the study.

- The PASI scores at Weeks 0, 2, 4, 8, 12, 16, 28, 40, and 52
- The mean percent improvement from baseline in PASI score at Weeks 2, 4, 8, 16, 28, 40, and 52
- The proportion of patients who achieve at least 50/75/90/100% improvement from baseline in PASI (PASI 50/75/90/100) at Weeks 2, 4, 8, 12, 16, 28, 40, and 52
- The proportion of patients with sPGA score on a 5-point scale of clear (0) or almost clear (1) at Weeks 0, 2, 4, 8, 12, 16, 28, 40, and 52
- The change in Dermatology Life Quality Index (DLQI) score from baseline at Weeks 2, 4, 8, 12, 16, 28, 40, and 52

Exploratory endpoints:

- The change in patient pain VAS from baseline at Weeks 12, 16, 28, and 52 in patients with PsA
- The change in Patient Global Assessment VAS from baseline at Weeks 12, 16, 28, and 52 in patients with PsA

Pharmacokinetic Assessments:

Secondary endpoint:

The serum concentration will be assessed at Weeks 0, 4, 12, 16, 28, 40, and 52.

Safety Assessments:

Secondary endpoints:

Safety assessments will be performed on immunogenicity, hypersensitivity monitoring, vital sign measurements (including BP, pulse and respiratory rates, and body temperature), IGRA, chest X-ray, hepatitis B and C and HIV status, physical examination findings, clinical laboratory analyses, ECGs, AEs (including serious AEs), adverse events of special interest (AESIs; infections/serious infections, injection site reactions,

hypersensitivity reactions, and malignancies), pregnancy tests, prior and concomitant medications, local site pain using 100 mm VAS, and signs and symptoms of TB monitored throughout the study.

The serum samples for immunogenicity will be assessed at Weeks 0, 4, 12, 16, 28, 40, and 52.

Biomarker Assessments (Optional):

Exploratory endpoint:

Blood samples for analysis of evaluation of genotype (Human Leukocyte Antigen [HLA]-Cw6 [C*06:02] and/or any necessary genotypes) will be collected prior to dosing on Day 1 (Week 0) for patients who sign a separate ICF for this assessment.

Sample Size:

A total sample size is planned to be a minimum of 446 patients (a minimum of 223 patients in each treatment group of CT-P43 and Stelara). Considering that the drop-out rate has been hypothesized at 10%, a minimum sample size of 400 patients (a minimum of 200 patients in each treatment group of CT-P43 and Stelara) is estimated to provide at least 90% statistical power for the demonstration of similarity of the mean percent improvement from baseline in PASI score at Week 12 with an equivalence margin of ±10% using a 90% confidence interval (CI) approach corresponding to two one-sided test with significance level of 5%. In this sample size calculation, the standard deviation (SD) of the percent improvement in PASI score at Week 12 is assumed to be 29.0 and the expected difference to be 0. Sample size was derived using PASS (version 16.0.3, NCSS Statistical Software, LLC. Utah, United States of America [USA]).

Statistical Analyses:

[redacted] The statistical methods for this study will be described in a detailed statistical analysis plan (SAP), which will be finalized prior to database lock. Changes from analyses planned in this protocol will be documented in the SAP. Any deviations from the planned analysis as described in the SAP will be justified and recorded in the study report.

Continuous variables will be summarized by reporting the number of observations (n), mean, SD, median, minimum, and maximum. Categorical variables will be summarized using frequency tables showing the number and percentage of patients within a particular category.

Definition of Analysis Set:

- **Intent-to-Treat (ITT) Set:** The ITT Set is defined as all patients randomly assigned to receive study drug (CT-P43 or Stelara).
- **ITT–Treatment Period II subset:** The ITT–Treatment Period II subset is defined as all patients in ITT set who are randomly assigned to receive study drug (CT-P43 or Stelara) prior to dosing at Week 16.
- **Modified ITT (mITT) Set:** The mITT Set is defined as all patients who are randomly assigned and received at least 1 dose (full or partial) of study drug (CT-P43 or Stelara).
- **Modified ITT–Treatment Period II subset:** The mITT–Treatment Period II subset is defined as all patients in mITT Set who are randomly assigned at Week 16 prior to dosing and received at least 1 dose (full or partial) of study drug (CT-P43 or Stelara) at or after Week 16.
- **Per–Protocol Set (PPS):** The PPS is defined as all randomly assigned patients who receive the full dose of study drug (CT-P43 or Stelara) at Weeks 0 and 4, have a PASI assessment at baseline and Week 12, and do not have any major protocol deviation affecting primary endpoint. Final determinations of the PPS will be made at the blinded data review meeting (DRM) for the efficacy primary endpoint before unblinding.
- **Pharmacokinetic (PK) Set:** The PK Set is defined as all randomly assigned patients who receive at least 1 full dose of study drug (CT-P43 or Stelara) and who have at least 1 post-treatment PK result. If any patient is found to be non-compliant with respect to dosing, a determination of the PK Set will be made on a case-by-case basis at the blinded DRM.

- **PK–Treatment Period II subset:** The PK–Treatment Period II subset will consist of all patients in PK set who receive at least 1 full dose of either of study drug (CT-P43 or Stelara) and have at least 1 post-treatment PK result at or after Week 16.
- **Safety Set:** The Safety Set is defined as all randomly assigned patients who receive at least 1 dose (full or partial) of study drug (CT-P43 or Stelara).
- **Safety–Treatment Period II subset:** The Safety–Treatment Period II subset will consist of all patients in Safety set who receive at least 1 dose (full or partial) of study drug (CT-P43 or Stelara) at or after Week 16.

Efficacy Analysis:

- **Primary endpoint:** The mean percent improvement from baseline in PASI score at Week 12 will be analyzed using an analysis of covariance (ANCOVA) model with covariates of country, body weight, prior biologic use approved for psoriasis treatment, and baseline PASI score. Point estimate and 90% CI for the difference in the mean percent improvement in PASI between the 2 treatment groups will be produced. Therapeutic equivalence of clinical response according to mean percent improvement from baseline in PASI score at Week 12 will be concluded if the 90% CIs for the treatment difference is entirely within –10% to 10%.

  The primary efficacy analysis will be conducted on the mITT Set using an ANCOVA model coupled with Multiple imputation (MI) with the Missing at random (MAR) assumption for missing data handling. A supportive analysis for the primary efficacy endpoint will be conducted using the PPS. Definition of each analysis set is described in Section 7.2. To assess the robustness, sensitivity analysis using tipping point approach will be performed for the primary efficacy endpoint in the mITT Set. Tipping point analyses will be performed under Missing Not at Random (MNAR) scenario.
- **Secondary endpoints:** The secondary efficacy endpoints will be summarized using the mITT Set and PPS and data for Treatment Period II will be summarized on the mITT–Treatment Period II subset. Difference on mean (or proportion) between the 2 treatment groups and its 95% CIs will be provided as well.

Pharmacokinetic Analysis:

Serum concentration for Treatment Period I will be summarized on PK Set and data for Treatment Period II will be summarized on PK–Treatment Period II subset, unless otherwise specified. Serum concentrations will be summarized using quantitative descriptive statistics (including geometric mean and coefficient of variation, as appropriate).

Safety Analysis:

Adverse events will be coded to system organ class (SOC) and preferred term (PT) according to the Medical Dictionary for Regulatory Activities (MedDRA). Adverse events will be graded for intensity according to the Common Terminology Criteria for Adverse Events (CTCAE) v5.0. Prior and concomitant medication will be coded to drug class and PT using the World Health Organization (WHO) drug dictionary. All safety data including immunogenicity will be listed and summarized by treatment groups as appropriate for the Safety Set and data for Treatment Period II will be summarized on Safety–Treatment Period II subset, unless otherwise specified.

Biomarker Analysis:

Analyses will be performed on genotypes (HLA-C*06:02 and/or any necessary genotypes) in the ITT set.

List of Abbreviations

Abbreviation	Definition
ADA	anti-drug antibody
ADL	activities of daily living
AE	adverse event
AESI	adverse event of special interest
ANCOVA	analysis of covariance
BCG	Bacillus Calmette-Guérin
BP	blood pressure
BSA	body surface area
CFR	Code of Federal Regulations
CI	confidence interval
COVID-19	Coronavirus disease 2019
CRO	contract research organization
CSR	clinical study report
CTCAE	Common Terminology Criteria for Adverse Events
CV	curriculum vitae
DLQI	Dermatology Life Quality Index
DRM	data review meeting
DSMB	data safety monitoring board
ECG	electrocardiogram
eCRF	electronic case report form
EOS	End-of-study
EU	European Union
FDA	US Food and Drug Administration
GCP	Good Clinical Practice
HBcAb	hepatitis B core antibody
HBsAb	hepatitis B surface antibody
HBsAg	hepatitis B surface antigen
HBV	hepatitis B virus
HCV	hepatitis C virus

Abbreviation	Definition
HIV	human immunodeficiency virus
HLA	human leukocyte antigen
ICF	informed consent form
ICH	International Council for Harmonisation
IgG	immunoglobulin G
IGRA	interferon-γ release assay
IEC	independent ethics committee
IL	interleukin
IRB	institutional review board
ITT	intent to treat
IWRS	interactive web response system
MAR	Missing at random
MedDRA	Medical Dictionary for Regulatory Activities
MI	Multiple Imputation
mITT	Modified intent to treat
MNAR	Missing Not at Random
PASI	Psoriasis Area and Severity Index
PFS	pre-filled syringe
PK	pharmacokinetic(s)
PPS	Per-protocol Set
PsA	psoriatic arthritis
PT	preferred term
PVG	pharmacovigilance
QoL	quality of life
SAE	serious adverse event
SAP	statistical analysis plan
SC	subcutaneous
SD	standard deviation
SI	Système International d'Unités
SOC	system organ class
sPGA	static Physician Global Assessment
TB	tuberculosis

Abbreviation	Definition
TEAE	treatment-emergent adverse event
ULN	upper limit of normal
US	United States
USA	United States of America
VAS	visual analog scale
WHO	World Health Organization

1 Introduction

1.1 Background

Psoriasis is a chronic, immune-mediated, inflammatory condition that affects more than 8 million people in the United States (US) and approximately 125 million people (2% to 3% of the total population) worldwide (National Psoriasis Foundation, 2019a). In Europe, the prevalence of psoriasis among adults varies geographically. In Southern and North Eastern Europe, 3% to 5% of the population are affected, compared to just over 1% of the population in the United Kingdom (Parisi *et al.,* 2013). Psoriasis is characterized by scaly, erythematous papules, and plaques that are often pruritic and the most common form is plaque type psoriasis affecting 80% to 90% of patients. On Caucasian skin, plaque psoriasis typically appears as raised, red patches covered with a silvery white buildup of dead skin cells or scale. On skin of color, the discoloration is darker and thicker, more of a purple or grayish color or darker brown. These patches or plaques most often appear on the scalp, knees, elbows and lower back, and their size can range between 1 and more than 10 centimeters (cm) in diameter (Menter *et al.,* 2008; National Psoriasis Foundation, 2019b). Psoriasis causes as much disability as other major medical diseases, and affects psychosocial functions, and also significantly affects health-related quality of life (QoL) (Rapp *et al.,* 1999*;* Nguyen *et al.,* 2016*;* Duvetorp *et al.,* 2018).

Ustekinumab, a biologic agent, is a human immunoglobulin G (IgG)1κ monoclonal antibody that binds with specificity to the p40 protein subunit used by both the Interleukin (IL)-12 and IL-23 cytokines. Interleukin-12 and IL-23 are naturally occurring cytokines that are involved in inflammatory and immune responses, such as natural killer cell activation and CD4+ T-cell differentiation and activation. Abnormal regulation of IL-12 and IL-23 has been associated with immune-mediated diseases including psoriasis. In in vitro models, ustekinumab was shown to disrupt IL-12 and IL-23 mediated signaling and cytokine cascades by disrupting the interaction of these cytokines with a shared cell-surface receptor chain, IL-12Rβ1. By binding the shared p40 subunit of IL-12 and IL-23, ustekinumab may exert its clinical effects in psoriasis through interruption of the Th1 and Th17 cytokine pathways, which are central to the pathology of immune-mediated diseases. (Stelara USPI 2020, Stelara SmPC 2020).

The availability of targeted biological therapies has revolutionised the treatment of psoriasis. Although this has improved patient outcomes, it has occurred at a much higher financial cost than that for traditional treatment options (Blackstone and Fuhr, 2012). Consequently,

widespread use of biologics has placed substantial financial burden on healthcare systems, in some cases restricting patient access to treatment (Nast *et al*., 2013). This has led to interest in developing biosimilar products, which are highly similar, but not identical and not 'bioidentical', to approved 'reference' agents.

1.2 CT-P43

CT-P43, containing the active ingredient ustekinumab, is a human IgG1κ monoclonal antibody that is being developed as a biosimilar medicinal product to the reference product, Stelara. The reference product was originally approved in the European Union (EU) in January 2009 and in the United States (US) in September 2009. Stelara is indicated for the following conditions: moderate to severe plaque psoriasis, active psoriatic arthritis (PsA), and moderately to severely active Crohn's disease and ulcerative colitis (Stelara USPI 2020, Stelara SmPC 2020).

The reference product, Stelara, is supplied as a sterile, preservative-free, colorless to slightly yellow solution of ustekinumab. The EU-approved Stelara is available in single-dose pre-filled syringes (PFS) or vials containing 45 or 90 mg of ustekinumab for subcutaneous (SC) use (Stelara SmPC 2020). US-licensed Stelara is available in single-dose PFS or vials containing 45 mg of ustekinumab for SC use (Stelara USPI 2020). Stelara is also available in single-dose vials containing 130 mg ustekinumab for intravenous use (Stelara USPI 2020, Stelara SmPC 2020).

CT-P43 will be supplied in a single PFS at a concentration of 45 mg/0.5 mL as a colorless to pale yellow solution for SC administration. The CT-P43 drug product will have the same pharmaceutical form and strength as the EU-approve Stelara (45 mg/0.5 mL) PFS for SC injection and is intended to have a highly similar quality profile as Stelara.

CELLTRION, Inc. plans to seek approval for all indications for which the innovator product has been approved by demonstrating similarity of CT-P43 to the reference product through an extensive array of quality, non-clinical, and clinical comparability assessments.

1.3 Preclinical Studies

Detailed information regarding the non-clinical pharmacology and toxicology of CT-P43 can be found in the investigator's brochure.

1.4 Clinical Studies

The safety and efficacy of ustekinumab was assessed in 1,996 patients in 2 randomized, double-blind, placebo-controlled studies in patients with moderate to severe plaque psoriasis and who were candidates for phototherapy or systemic therapy (PHOENIX 1 and PHOENIX 2). In addition, a randomized, blinded assessor, active-controlled study compared ustekinumab and etanercept in patients with moderate to severe plaque psoriasis who had had an inadequate response to, intolerance to, or contraindication to cyclosporin, methotrexate, or psoralen and ultraviolet A.

Psoriasis Study 1 (PHOENIX 1) evaluated 766 patients. Patients randomized to ustekinumab received 45 or 90 mg doses at Weeks 0 and 4 followed by the same dose every 12 weeks. Patients originally randomized to ustekinumab who achieved Psoriasis Area and Severity Index (PASI) 75 response (PASI improvement of at least 75% relative to baseline) at both Weeks 28 and 40 were re-randomized to receive ustekinumab every 12 weeks or to receive placebo (i.e., withdrawal of therapy).

One hundred seventy one (67.1%) patients receiving ustekinumab 45 mg, 170 (66.4%) receiving ustekinumab 90 mg, and 8 (3.1%) receiving placebo achieved PASI 75 at Week 12 (difference in response rate vs placebo 63.9%, 95% confidence interval (CI) 57.8-70.1, $p<0.0001$ for 45 mg and 63.3%, 57.1-69.4, $p<0.0001$ for 90 mg). At Week 40, long-term response had been achieved by 150 patients in the 45 mg group and 172 patients in the 90 mg group. Of these, 162 patients were randomly assigned to maintenance ustekinumab and 160 to withdrawal. Psoriasis Area and Severity Index 75 response was better maintained to at least 1 year in those receiving maintenance ustekinumab than in those withdrawn from treatment at Week 40 ($p<0.0001$ by log-rank test). (Leonardi *et al.,* 2008).

In long term study, initial clinical responses were generally maintained through Week 244 (PASI 75: 63.4% and 72.0%; PASI 90: 39.7% and 49.0%; PASI 100: 21.6% and 26.4%) for patients receiving 45 mg and 90 mg, respectively. Similarly, PASI 75 responses were generally maintained among initial responders (79.1% [45 mg] and 80.8% [90 mg]) and partial responders (57.6% [45 mg] and 55.1% [90 mg]). (Kimball *et al.,* 2013).

Psoriasis Study 2 (PHOENIX 2) evaluated 1,230 patients. Patients randomized to ustekinumab received 45 or 90 mg doses at Weeks 0 and 4 followed by an additional dose at

Week 16. All patients were followed for up to Week 52 following first administration of study drug.

Two hundred seventy three (66.7%) patients receiving ustekinumab 45 mg, 311 (75.7%) receiving ustekinumab 90 mg, and 15 (3.7%) receiving placebo achieved the primary endpoint (difference in response rate 63.1%, 95% CI 58.2–68.0, p<0.0001 for the 45 mg group vs placebo and 72.0%, 67.5–76.5, p<0.0001 for the 90 mg group vs placebo). More partial responders at Week 28 who received ustekinumab 90 mg every 8 weeks achieved PASI 75 at Week 52 than did those who continued to receive the same dose every 12 weeks (22 [68.8%] vs 11 [33.3%]; difference in response rate 35.4%, 95% CI 12.7–58.1, p=0.004). (Papp *et al.,* 2008).

Psoriasis Study 3 (ACCEPT) evaluated 903 patients with moderate to severe psoriasis who inadequately responded to, were intolerant to, or had a contraindication to other systemic therapy and compared the efficacy of ustekinumab to etanercept and evaluated the safety of ustekinumab and etanercept. During the 12-week active-controlled portion of the study, patients were randomized to receive etanercept (50 mg twice a week), or ustekinumab 45 mg, or ustekinumab 90 mg (at Weeks 0 and 4).

There was at least 75% improvement in the PASI at Week 12 in 67.5% of patients who received 45 mg of ustekinumab and 73.8% of patients who received 90 mg, as compared with 56.8% of those who received etanercept (P=0.01 and P<0.001, respectively). Similarly, 65.1% of patients who received 45 mg of ustekinumab and 70.6% of patients who received 90 mg of ustekinumab had cleared or minimal disease according to the physician's global assessment, as compared with 49.0% of those who received etanercept (P<0.001 for both comparisons) (Griffiths *et al.,* 2010).

1.5 Study Rationale

CT-P43 is currently being developed by CELLTRION, Inc., and is intended to be developed as a biosimilar to Stelara. For a biosimilar to be approved, it must be shown that there are no clinically meaningful differences between the 2 products. The stepwise "totality of evidence" approach adopted by regulatory authorities for biosimilars means that the type of clinical studies needed varies on a case-by-case basis. However, statistically proven equivalence between biosimilar and reference product in both pharmacokinetics (PK) and efficacy are usually required, as is a demonstration of acceptable safety and immunogenicity. Therefore,

the PK profile of CT-P43, the EU-approved Stelara, and the US-licensed Stelara will be compared to demonstrate PK equivalence in a Phase 1 study in healthy volunteers (Study CT-P43 1.1). An additional assessment of the similarity in efficacy, PK, safety, and immunogenicity will be carried out in this proposed comparative clinical study (Study CT-P43 3.1) in patients with moderate to severe plaque psoriasis. CELLTRION, Inc. considers that the proposed clinical development program will be sufficient to demonstrate PK equivalence of CT-P43 (Study CT-P43 1.1 PK similarity healthy volunteer study) and therapeutic equivalence and safety (Study CT-P43 3.1 comparative clinical similarity) to the reference product. In accordance with regulatory guidances (EMA/CHMP/BMWP/403543/2010; FDA 2015; WHO 2009), safety, including immunogenicity, should be investigated in the patient population that carries the highest risk of an immune response. Based on previous data summarized in Stelara product labeling (Stelara USPI 2020, Stelara SmPC 2020), approximately 6% to 12.4% of patients treated with Stelara in psoriasis and PsA clinical studies developed antibodies to ustekinumab, which were generally low titer. In Crohn's disease and ulcerative colitis clinical studies, 2.9% to 4.6% of patients treated with Stelara for approximately one year developed antibodies to ustekinumab.

As Stelara is given as monotherapy in psoriasis, it allows for a much clearer approach for a demonstration of biosimilarity compared to PsA and Crohn's disease, ulcerative colitis, where other immunosuppressive agents would be given concomitantly. Consequently, psoriasis has been selected as the indication for the Phase 3 clinical study, due to the relatively high magnitude of the treatment effect and immunogenicity rates observed in the Stelara clinical studies in this indication; thus, facilitating the detection of potential differences between CT-P43 and the Stelara.

1.6 Benefit and Risk Assessment

The CT-P43 drug product will have the same pharmaceutical form and strength as Stelara (45 mg/0.5 mL). The proposed dosing regimen is in line with the approving labeling for Stelara (Stelara USPI 2020, Stelara SmPC 2020).

The proposed safety monitoring is deemed to be sufficient to monitor potential risks of CT-P43 administration. In view of the structural, biological, and toxicological similarity to Stelara, CT-P43 is expected to display a similar safety profile. Stelara has been studied extensively and has been shown to be effective at reducing symptoms in patients with

inflammatory conditions including psoriasis, PsA, Crohn's disease and ulcerative colitis (EMA EPAR Stelara 2020).

Based upon the clinical evidence (Section 1.4) as well as the proven sufficient of safety profile of Stelara, the benefits of the conduct of the proposed clinical study outweigh the associated risks.

With the escalation of the pandemic, such as Coronavirus disease 2019 (COVID-19), and as being increased safety risk of involvement in this study, benefit and risk assessment of each study participants will be conducted by the sponsor through a sufficient discussion with the investigators and data safety monitoring board (DSMB). This assessment and further alternative actions will be documented and reported in line with the local regulatory guidelines. The sponsor will reassess risks as the pandemic situation develops and the safety of the study participant will be considered primary importance.

2 Study Objectives

2.1 Primary Objective

- To demonstrate that CT-P43 is equivalent to Stelara, in terms of efficacy as determined by the mean percent improvement from baseline in PASI score at Week 12.

2.2 Secondary Objectives

- To evaluate efficacy, PK, QoL, and overall safety including immunogenicity up to Week 52.

2.3 Exploratory Objectives

- To evaluate additional efficacy up to Week 52 and to characterize biomarker.

3 Investigational Plan

3.1 Study Design

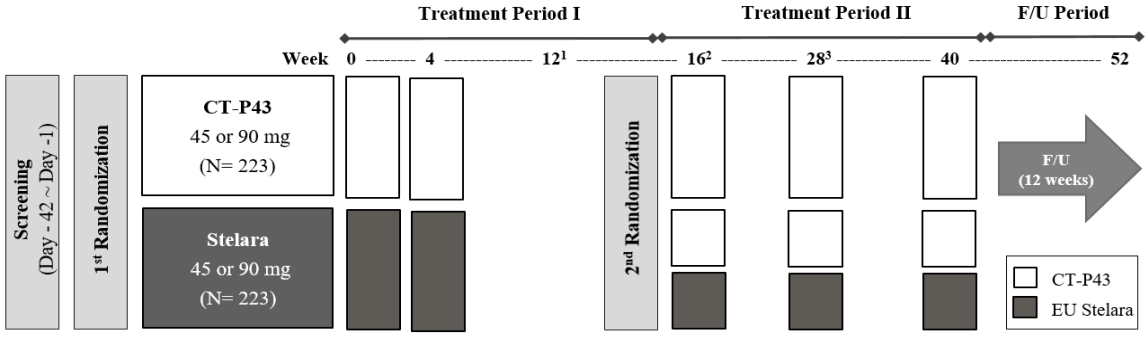
This study is a randomized, active-controlled, double-blind, multicenter, Phase 3 study designed to evaluate efficacy, PK, QoL, and overall safety including immunogenicity and biomarker of CT-P43 compared with Stelara in patients with moderate to severe plaque psoriasis who are candidates for phototherapy or systemic therapy.

A minimum of 446 patients with moderate to severe plaque psoriasis will be enrolled and randomly assigned to one of the 2 treatment groups in a 1:1 ratio (a minimum of 223 patients in each treatment group of CT-P43 and Stelara).

The duration of the study will be up to 58 weeks, which includes Screening (up to 6 weeks), Treatment Period (up to 40 weeks), and off-dose follow-up period (12 weeks) prior to the End-of-Study (EOS) visit.

The study design and patient assessment overview are presented in Figure 1.

Figure 1 Study Design Overview



Week	0	2	4	8	12[1]	16[2]	28[3]	40	52 (EOS)
Study drug administration	●		●			●	●	●	
Efficacy[4]	●	●	●	●	●	●	●	●	●
Pharmacokinetics	●		●		●	●	●	●	●
Immunogenicity	●		●		●	●	●	●	●
Safety	←	—	—	—	—	—	—	—	→

[1] At Week 12, it is recommended that patients who achieve at least 50% improvement from baseline in PASI (PASI 50) continue study drug administration in the Treatment Period II in all groups.

[2] Prior to dosing at Week 16, all patients will undergo a second randomization process. Patients who were initially randomized to Stelara will be randomized again in a ratio of 1:1 to either continue Stelara or undergo transition to CT-P43. All patients who were initially randomized to the CT-P43 group on Day 1 (Week 0) will continue their treatment with CT-P43 until Week 40.
[3] At Week 28, it is recommended that patients who achieve at least PASI 75 continue further study drug administration in all groups.
[4] The investigator-reported outcomes assessments (i.e., PASI, static Physician's Global Assessment [sPGA]) will be performed by a qualified efficacy assessor at the study center. If possible, it is recommended that the same assessor perform the investigator-reported outcomes assessments throughout the entire study period.

3.1.1 Screening Period

Screening will take place between Day –42 and Day –1, prior to the first study drug administration (Day 1). The Day 0 will not be used in the study day counting. The date immediately before will be counted as Day –1.

3.1.2 Treatment Periods

The study will comprise 2 treatment periods (I and II). During Treatment Periods I and II, patients will receive either 45 or 90 mg of CT-P43 or Stelara by SC injection via PFS at Weeks 0, 4, 16, 28, and 40 based on patient's baseline body weight.

Patients who weigh ≤100 kg at baseline will receive an initial study drug dose of 45 mg, followed by another 45 mg dose 4 weeks later, and then every 12 weeks thereafter (up to Week 40). Patients who weigh >100 kg at baseline will receive a study drug dose of 90 mg as per the same schedule. However, in case significant body weight change occurs and results in over 10% outside from threshold weight (i.e., 100 kg) at Week 16 predose (e.g., ≤100 kg at baseline but increased to >110 kg at Week 16 OR >100 kg at baseline but decreased to ≤90 kg at Week 16), adjusted dose will be administered to all treatment groups in Treatment Period II.

3.1.2.1 Treatment Period I (16 weeks)

On Day 1, Week 0, patients who meet all of the inclusion criteria and none of the exclusion criteria will be enrolled in the study and randomly assigned (first randomization) in a ratio of 1:1 to receive either CT-P43 or Stelara by SC injection. Treatment assignment will be stratified by the following:

- Country
- Body Weight (≤100 kg vs. >100 kg)
- Prior biologic use approved for psoriasis treatment (Yes or No)

Study drug will be administered by a predefined unblinded staff at the study center and the investigator and patients will remain blinded during the study. The unblinded staff will not be permitted to conduct any patient assessments during the study and will be prohibited from telling blinded staff members which drug was given to which patient.

The second dosing schedule of the study drug is at Week 4.

At Week 12, it is recommended that patients who achieve at least 50% improvement from baseline in PASI (PASI 50) continue study drug administration in the Treatment Period II in all groups.

Patients will comply with all appropriate visits and assessments. Patients will return to the study center at predefined time intervals for clinical assessments and blood sampling. At each visit, patients will be questioned about adverse events (AEs) and concomitant medications and will be monitored for the clinical signs and symptoms of tuberculosis (TB).

3.1.2.2 Treatment Period II (24 weeks)

The third dosing schedule of the study is at Week 16. Prior to dosing at Week 16, patients in the Stelara group will be randomly assigned again (second randomization) in a ratio of 1:1 to either continue Stelara or undergo a transition to CT-P43 from Week 16. All patients who were initially randomly assigned to the CT-P43 group on Day 1 (Week 0) will continue their treatment with CT-P43 until Week 40. The dose of study drug will be adjusted for further study drug dosing at Weeks 16, 28, and 40 if significant body weight occurs and results in over 10% outside from threshold weight (i.e., 100 kg) at Week 16 predose.

The second randomization for the Stelara group will be stratified by dose at Week 16 (45 mg vs. 90 mg). The second randomization process will also be conducted in the CT-P43 group prior to dosing at Week 16 to maintain the study blind.

The fourth dosing schedule of the study drug is at Week 28. Prior to dosing at Week 28, all patients will be assessed for efficacy per schedule. At Week 28, in all groups, it is

recommended that patients who achieve at least a 75% improvement from baseline in PASI (PASI 75) receive the fifth dose at Week 40.

3.1.3 End-of-Study Visit (Week 52)

The EOS visit will be performed at Week 52 for patients who completed or discontinued study drugs. For all patients who discontinue study drug before Week 40, every effort should be made to complete regularly scheduled study visits for efficacy and safety assessments. If a patient cannot or is unwilling to attend any visit(s), a safety follow-up will be conducted by telephone according to the study visit schedule. If a patient discontinues study drug before Week 12, when the primary endpoint is assessed, they should return to the study center at Week 12 for the primary efficacy endpoint assessment, even if they initiated psoriasis medication changes (including those prohibited by the protocol).

4 Patient Selection and Withdrawal Criteria

4.1 Selection of Study Patients

It is expected that a minimum of 446 patients will be enrolled at 34 study centers in 4 countries. Male or female patients with moderate to severe plaque psoriasis will be considered for enrollment in the study if they meet all of the inclusion criteria and none of the exclusion criteria.

4.1.1 Inclusion Criteria

Each patient must meet all of the following criteria to be enrolled in this study:

1. Patient is male or female aged 18 to 80 years old, both inclusive.
2. Patient has had diagnosis of plaque-type psoriasis for at least 24 weeks before the first administration of the study drug (Day 1).
3. Patient has stable moderate to severe chronic plaque psoriasis with or without PsA at both Screening and at the time of the first administration of the study drug (Day 1) as defined by the following:
    - A PASI score of ≥12 and
    - An involved body surface area (BSA) ≥10% and
    - A static Physician's Global Assessment (sPGA) score of ≥3
4. Patient is a candidate for phototherapy or systemic therapy.
5. Patient has adequate renal and hepatic function at Screening as defined by the following clinical chemistry results:
    - Serum creatinine ≤1.5 × upper limit of normal (ULN) or an estimated creatinine clearance level >50 mL/min (by Cockcroft-Gault formula) (SI [Système International d'Unités] units: 0.84 mL/s)
    - Serum alanine aminotransferase or aspartate aminotransferase ≤2.5 × ULN
    - Serum total bilirubin ≤1.5 × ULN
6. Patient has the following hematology laboratory test results at Screening:
    - Hemoglobin ≥10.0 g/dL (SI units: >100 g/L or 6.21 mmol/L)

- Absolute neutrophil count $\geq 1.5 \times 10^3$ cells/μL (SI units: $\geq 1.5 \times 10^9$ cells/L)
- Platelet count $\geq 100 \times 10^3$ cells/μL (SI units: $\geq 100 \times 10^9$ cells/L)

7. Patient (or legal guardian, if applicable) is informed of the full nature and purpose of the study, including possible risks and side effects, and given ample time and opportunity to read and understand this information, and signs and dates the written informed consent before participation in the study.
8. Female patient who is considered of childbearing potential (i.e., fertile, following menarche and until becoming post-menopausal unless permanently sterile) must agree to use highly effective methods of contraception consistent with local regulations during the course of the study and at least 15 weeks following discontinuation of study drug (excluding women who are not of childbearing potential). Examples include the following:

    - Combined (estrogen and progestogen containing) or progestogen-only hormonal contraceptives associated with inhibition of ovulation
    - Intrauterine device or intrauterine hormone-releasing system
    - True abstinence, when this is in line with the preferred and usual lifestyle of the patient. Periodic abstinence (e.g., calendar, ovulation, symptothermal, post-ovulation methods), declaration of abstinence for the duration of exposure to investigational drug, and withdrawal are not acceptable methods of contraception.

    Male patient who is sexually active with a woman of childbearing potential must agree to use the highly effective method described as above or medically acceptable methods of contraception (e.g., male or female condom AND additional hormonal or barrier method by female partner) consistent with local regulations during the study and for 15 weeks following discontinuation of study drug.

    If patient or their partner has been surgically sterilized for less than 24 weeks prior to the date of informed consent form (ICF), they also must agree to use method(s) of contraception as described above. Postmenopausal female patients must have experienced their last menses more than 1 year prior to the date of ICF without an alternative medical cause to be classified as not of childbearing potential.

4.1.2 Exclusion Criteria

Patients meeting any of the following criteria will be excluded from the study:

1. Patient diagnosed with forms of psoriasis other than plaque-type such as erythrodermic psoriasis, pustular psoriasis, guttate psoriasis, medication-induced psoriasis, or other skin conditions (e.g., eczema) at the time of the Screening visit that would interfere with evaluations of the effect of the investigational product on psoriasis.
2. Patient previously received ustekinumab or a biosimilar of ustekinumab or any drug that targets directly interleukin (IL)-12, or IL-23.
3. Patient who has prior exposure to 2 or more biologic agents approved for the treatment of psoriasis. Patients with 1 prior biologics can be enrolled after sufficient wash-out period of 12 weeks or 5 half-lives (whichever is longer) prior to the first administration of the study drug (Day 1) (see Exclusion criteria 11 for other prohibited medications or treatment).
4. Patient who has current or chronic inflammatory or autoimmune disease or symptoms other than psoriasis and psoriatic arthritis that might confound study evaluations.
5. Patient who has allergies to the active substance or any of the excipients of ustekinumab or study drug, or patients with a hypersensitivity to immunoglobulin products or natural rubber and latex.
6. Patient who has received a live or live-attenuated vaccination within 4 weeks prior to the first administration of the study drug (Day 1). Patient must agree not to receive a live or live-attenuated vaccines during the study and up to 15 weeks after the last dose of the study drug.
7. Patient who has had Bacillus Calmette-Guérin (BCG) vaccination within 1 year prior to the first administration of the study drug (Day 1). Patients must agree not to receive a BCG vaccination during the study and at least 1 year after the last dose of the study drug.
8. Patient who has a current or past history of any of the following infections:

- Current or past history of infection with human immunodeficiency virus (HIV) or current infection with hepatitis B or hepatitis C. However, a patient with past hepatitis B or C virus infection is allowed if resolved (See Section 6.3.2.8).
- Current or past history of serious infection requiring hospitalization or parenteral injection of antibiotics within 8 weeks prior to the first administration of the study drug (Day 1).
- Herpes zoster infection within 8 weeks prior to the first administration of the study drug (Day 1).
- Current or past granulomatous infections or other severe or chronic or recurrent infections (such as sepsis, abscess or opportunistic infections, or invasive fungal infections such as histoplasmosis or nontuberculous mycobacterial infection or infected skin wounds or ulcer). However, a patient who has a past diagnosis with sufficient documentation of complete resolution of the infection can be enrolled in the study.

9. Patient who has a current or past history of any of the following TB conditions:
    - Patient who has current or a history of active TB. Patient who has any evidence of history of active TB cannot be enrolled despite sufficient documentation of complete resolution of active TB.
    - Patient who has signs or symptoms suggestive of active TB.
    - Patient who has had exposure to a person with active TB such as first-degree family members or co-workers within 16 weeks prior to the first administration of the study drug (Day 1).
    - Patient who has a past diagnosis of latent TB unless they have documentation of completing TB prophylaxis, or have received at least the first 3 weeks of country-specific TB prophylaxis prior to the first administration of the study drug (Day 1) and intends to complete its entire course can be enrolled.

- Patient who has a current diagnosis of latent TB (defined as a positive result of interferon-γ release assay [IGRA] with a negative examination of chest X-ray) at Screening without a history of active TB or latent TB. However, a patient who has received at least the first 3 weeks of country-specific TB prophylaxis prior to the first administration of the study drug (Day 1) and intends to complete its entire course can be enrolled.
- Patient who is without a history of active TB or latent TB and has an indeterminate result of IGRA with a negative examination of chest X-ray at Screening. If the result of IGRA is indeterminate at Screening, 1 retest will be allowed during the Screening Period. Depending on the result of retest, the enrollment will be determined as follows:
    - If the repeated IGRA result is negative, the patient can be enrolled.
    - If the repeated IGRA result is positive, the patient who has received at least the first 3 weeks of country-specific TB prophylaxis prior to the first administration of the study drug (day 1) and intends to complete its entire course can be enrolled.
    - If the repeated IGRA result is again indeterminate, the patient cannot be enrolled.

10. Patient who has a medical condition including 1 or more of the following:
    - Diabetes mellitus considered by the investigator to be clinically significant and uncontrolled
    - Uncontrolled hypertension (as defined by systolic blood pressure [BP] ≥160 mmHg or diastolic BP ≥100 mmHg)
    - Current or past history of any malignancy within the previous 5 years prior to the first administration of the study drug (Day 1) except adequately treated non-metastatic squamous carcinoma of the uterine cervix, cutaneous basal cell carcinoma, or cutaneous squamous cell carcinoma with no evidence of recurrence for at least 12 weeks prior to the first administration of the study drug (Day 1)

- Current or past history of severe uncontrolled cardiac disease (such as unstable angina or clinically significant electrocardiogram [ECG] abnormalities), or myocardial infarction within the 24 weeks prior to the first administration of the study drug (Day 1)
- History of organ transplantation, with exception of a corneal transplant within 12 weeks prior to the first administration of the study drug (Day 1)
- Any respiratory disease that can be judged as clinically significant at the investigator's discretion, including but not limited to chronic obstructive pulmonary disease, asthma, or pleural effusion
- Any major surgical procedure within 12 weeks prior to the first administration of the study drug (Day 1) or planned during the study
- History or evidence of any other clinically significant medical or psychiatric condition that, in the opinion of the investigator, would pose a risk to patient safety or interfere with the study evaluation, procedures, or completion

11. Patient who has received or plans to receive any of the following prohibited medications or treatment that could affect psoriasis:

- Topical therapies for the treatment of psoriasis (including, but not limited to, corticosteroids, vitamin D analogs, calcineurin inhibitors or retinoids) within 2 weeks prior to the first administration of the study drug (Day 1). However, low-potency topical corticosteroids (Class 6 or 7) applied to the face and intertriginous areas are permitted during study participation to reduce patient's burden with a restriction of use within 12 hours prior to study visits requiring PASI or sPGA measures. Shampoos with salicylic acids and bland moisturizers/emollients (without urea or beta or alpha hydroxy acids) are also allowed for treatment of psoriasis, but these should not be used in the mornings of study visits when efficacy assessments are going to be performed.
- Ultraviolet A phototherapy (with or without oral psoralen) or ultraviolet B phototherapy for the treatment of psoriasis within 4 weeks prior to the first administration of the study drug (Day 1)

- Any systemic steroids or nonbiologic systemic therapies that could affect psoriasis within 4 weeks prior to the first administration of the study drug (Day 1)
- Any investigational drug within 4 weeks or 5 half-lives (whichever is longer) prior to the first administration of the study drug (Day 1)
- Initiation or dose modification of drugs that may aggravate psoriasis (e.g., beta-blockers, lithium, antimalarials) within 4 weeks prior to the first administration of the study drug (Day 1). Patients who have been on stable dose without exacerbation of psoriasis for at least 4 weeks prior to the first administration of the study drug (Day 1) can be enrolled, however, the same dose should remain throughout the study.
- Herbal treatment within 2 weeks prior to the first administration of the study drug (Day 1)

12. Female patient who is currently pregnant or breastfeeding, or is planning to become pregnant or breastfeed within 15 weeks of the last dose of study drug.
13. Male patient who is planning to donate sperm or father a child within 15 weeks of the last dose of study drug.
14. Patient who is not willing to limit ultraviolet light exposure (e.g., excessive sun exposure and/or the use of tanning devices) during the study.
15. Patient who has currently active alcohol or drug abuse or history of alcohol or drug abuse within the previous 1 year from Screening.
16. Patient is vulnerable (e.g., employees of the study center or any other individuals involved with the conduct of the study, or immediate family members of such individuals, persons kept in prison, or other institutionalized persons by law enforcement).
17. Patient who, in the opinion of the investigator, should not participate in the study.

4.2 Study Drug Discontinuation and Study Termination

Patients are free to withdraw consent for treatment or participation in the study at any time for any reason. The investigator may also discontinue the study drug at any time in the interest of patient safety. Study drug discontinuation should not be considered study

termination. The primary reasons for the study drug discontinuation and study termination must be recorded in the patient's medical record and the electronic case report form (eCRF), with any comments (spontaneous or elicited) or complaints made by the patient.

Reasons for study drug discontinuation include the following:

- Patient has any AE that would compromise his or her safety if he or she continues the study drug
- Patient develops signs of disease flare, progression, or non-response which require treatment with prohibited medication in the judgment of the investigator
- Patient has a significant protocol deviation(s)
- Patient is pregnant
- Investigator's decision
- Patient withdraws consent for treatment
- Patient dies
- Patient is lost to follow-up

For all patients who discontinue study drug early, every effort should be made to complete regularly scheduled study visits for efficacy and safety assessments. If a patient cannot or is unwilling to attend any visit(s), a safety follow-up will be conducted by telephone according to the study visit schedule.

If a patient discontinues study drug prior to Week 12, when the primary endpoint is assessed, they should return to the study center at Week 12 for the primary efficacy endpoint assessment, even if they initiated psoriasis medication changes (including those prohibited by the protocol).

Reasons for study termination include the following:

- Patient withdraws consent or refuses to procedures/observations

- Patient is lost to follow-up
- Patient dies

If necessary, the investigator may discuss with CELLTRION, Inc or its designee any patient's reason for study termination or study drug discontinuation. The sponsor may be contacted if clarification is required on a case-by-case basis. All patients who terminate from the study will retain their patient number.

4.2.1 Recruitment of Additional Patients

Patients who receive study drug and terminate prior to study completion will not be replaced. Patients who are failed at Screening, for any reason, can be re-screened only once. If there is unusual situation that justifies consideration for additional rescreening, the investigator is recommended to discuss with the sponsor. Re-screened patient will be assigned with new patient identification number.

4.2.2 Premature Termination of the Study

The sponsor reserves the right to terminate the study at any time for reasonable medical and/or administrative reasons. If the study is terminated prematurely by the sponsor, all patients will be kept fully informed and an appropriate follow-up examination of the patients will be arranged. The investigator will inform the institutional review board (IRB) or independent ethics committee (IEC) of any premature termination or suspension of the study, where applicable.

5 Study Drugs

5.1 Method of Assigning Patients to Treatment Groups

An interactive web response system (IWRS) will be used for the randomization. Randomization statistician will generate the randomization schedule for IWRS, which will link sequential patient randomization numbers to treatment codes.

A minimum of 446 patients will be enrolled and randomly assigned to one of the 2 treatment groups in a 1:1 ratio (a minimum of 223 patients in each treatment group of CT-P43 and Stelara).

The first randomization to treatment assignment will be stratified by the following;

- Country
- Body weight (≤100 kg vs. >100 kg)
- Prior biologic use approved for psoriasis treatment (Yes or No)

Prior to dosing at Week 16, patients in the Stelara group will be randomly assigned again in a ratio of 1:1 to either continue Stelara or undergo transition to CT-P43 from Week 16. All patients who were initially randomized to the CT-P43 group on Day 1 (Week 0) will continue their treatment with CT-P43 until Week 40.

The second randomization for Stelara group will be stratified by dose at Week 16 (45mg vs. 90mg). The second randomization process will also be conducted in the CT-P43 group prior to dosing at Week 16 to maintain the study blind.

5.2 Study Drugs Administered

Patients will receive either CT-P43 or Stelara 45 or 90 mg administered subcutaneously at Weeks 0, 4, 16, 28, and 40 based on patient's baseline body weight. However, in case significant body weight change occurs and results in over 10% outside from threshold weight (i.e., 100 kg) at Week 16 predose (e.g., ≤100 kg at baseline but increased to >110 kg at Week 16 OR >100 kg at baseline but decreased to ≤90 kg at Week 16), adjusted dose will be administered to all treatment groups in Treatment Period II.

Before study drug administration, the PFS will be taken out of the refrigerator and let the PFS stand outside the box for about half an hour, for letting the liquid come to a comfortable temperature for injection (i.e., room temperature). During this time, syringe's needle cover will not be removed.

Appropriate areas for the injection are the upper thigh or around the abdomen at least 5 cm away from the navel or upper arm or buttocks. If possible, areas of skin that show signs of psoriasis should be avoided. In the case of the 90 mg dose, 2 injections of 45 mg PFS of study drug should be given at 2 different sites for each injection, and give the second injection right after the first.

5.2.1 CT-P43

CT-P43 is the investigational product.

- Patients who weigh ≤100 kg: CT-P43 45 mg (1 injection of 45 mg/0.5 mL) by SC injection via PFS
- Patients who weigh >100 kg: CT-P43 90 mg (2 injections of 45 mg/0.5 mL) by SC injection via PFS

5.2.2 Stelara

EU-approved Stelara is the reference product.

- Patients who weigh ≤100 kg: Stelara 45 mg (1 injection of 45 mg/0.5 mL) by SC injection via PFS
- Patients who weigh >100 kg: Stelara 90 mg (2 injections of 45 mg/0.5 mL) by SC injection via PFS

5.3 Identity of Investigational Product

CT-P43 is a monoclonal antibody that is being developed by CELLTRION, Inc. as a potential biosimilar to Stelara.

The company code of the product is CT-P43. The International Non-proprietary Name of the commercially available reference material (Stelara) is ustekinumab and the Anatomical

Therapeutic Chemical Classification System code is L04AC05. CT-P43 is a human IgG1κ monoclonal antibody against the p40 subunit of the IL-12 and IL-23 cytokines. Ustekinumab is composed of 1,326 amino acids and has an estimated molecular mass that ranges from 148,079 to 149,690 Daltons.

The reference product, EU-approved Stelara, is supplied as a sterile, preservative-free solution of ustekinumab for SC administration. Stelara is a colorless to slightly yellow solution that may contain a few small translucent or white particles with a pH of 5.7 to 6.3 (Stelara SmPC 2020).

Each 0.5 mL PFS delivers 45 mg ustekinumab, L-histidine and L-histidine monohydrochloride monohydrate, Polysorbate 80, sucrose, and water for injections (Stelara SmPC 2020).

CT-P43 will be supplied in a single-use, PFS at a concentration of 45 mg/0.5 mL as a colorless to pale yellow solution.

Dosing instruction described in the Stelara prescribing information are to be followed (Stelara SmPC 2020).

CELLTRION, Inc. will provide adequate supplies of CT-P43 and Stelara for distribution to the study centers.

The following drug supplies will be used in the study:

Product	Supplied as:
CT-P43	PFS containing 45 mg/0.5 mL of CT-P43
EU-approved Stelara	PFS containing 45 mg/0.5 mL of ustekinumab

5.4 Management of Clinical Supplies

5.4.1 Study Drug Packaging, Labeling, and Storage

The sponsor will provide the investigator and study centers with adequate quantities of CT-P43, and EU-approved Stelara. A label will be attached to the safety guard of each PFS kit. CT-P43 will be manufactured and packaged in accordance with Good Manufacturing Practice

(GMP) for Medicinal Products for use in human clinical trials and provided with a certificate of analysis. All study drugs will be labeled in accordance with GMP and local regulatory requirements.

CT-P43 and EU-approved Stelara must be kept in a secured area at a controlled refrigerated temperature between 2°C and 8°C and must not be frozen. The study drug PFS must be kept in the original carton until use to protect it from light. The recommended storage conditions, and expiry date where required, are stated on the product label approved by each regulatory authority.

5.4.2 Study Drug Accountability

It is the responsibility of the clinical investigator to ensure that all study drug received at the study center will be inventoried and accounted for throughout the study and the result recorded in the drug accountability form maintained at the study center. The study drug accountability will be verified by the monitor during on-site monitoring visits. Study drug will be stored in a limited-access area or in a locked cabinet under appropriate environmental conditions.

The investigator agrees not to supply the study drug to any person other than the unblinded staff who will administer the study drug to the patients participating in the study. Study drug may not be relabeled or reassigned for use by other patients unless approved by CELLTRION, Inc.

Unused study drug syringes should be returned to sponsor. Study drug accountability must be completed at the study center level and discrepancies, if any, need to be resolved prior to return.

The used syringes can only be destroyed if it is written in local standard operating procedures (SOPs) and a specific authorization is given by CELLTRION, Inc. Permission will be granted by CELLTRION, Inc. on a study center-by-study center basis after reviewing the study center destruction policy. This authorization may also be granted to destroy used syringes immediately after administering to patients. The list of destroyed syringes must be recorded. The investigator agrees to neither dispense the study drug from, nor store it at, any study center other than the study centers agreed upon with CELLTRION, Inc. Details regarding

study drug supplies, handling, accountability, return and destruction will be followed according to the Pharmacy Manual.

5.5 Blinding

This study will be double-blind.

5.5.1 Unblinded Study Drug Administration

Study drug will be administered by a predefined unblinded staff at the study center, and the investigator and patients will remain blinded during the study. The unblinded staff will not be permitted to conduct any patient assessments during the study and will be prohibited from telling blinded staff members which drug was given to which patient.

5.5.2 Breaking the Blind

Under normal circumstances, the blind should not be broken. The blind should be broken only if specific emergency treatment would be dictated as knowing the study drug assignment is required for medical management. In such cases, the investigator may, in an emergency, determine the identity of the study drug by using the applicable procedure in the IWRS (see study manual, which is provided as a separate document).

The date, time, and reason for the unblinding must be documented in the appropriate field of the eCRF and source documents, and the medical monitor will be informed as soon as possible. All calls resulting in an unblinding event will be recorded and reported by the IWRS to the medical monitor and CELLTRION, Inc. Any patients for whom the blind is broken may continue in the study and receive the study drug at the investigator’s discretion.

The overall randomization code will be broken only for reporting purposes. This will occur after database lock for data up to Week 28 for all patients. The unblinded team will be predefined and documented prior to performing the analyses. The study will remain blinded to the investigators, patients, and predefined CELLTRION, Inc. and contract research organization (CRO) blinded teams until all patients have completed the study and the database has been finalized for study termination.

5.6 Treatment Compliance

CT-P43 and Stelara will be administered by the unblinded staff while the patient is at the study center. The time of injection as well as any deviations from the planned injection will be recorded in both the source documents and the eCRF.

Every effort will be made to encourage patients' compliance with the study visits. A dose visit window of ±3 days is recommended up to and including Week 12 and a visit window of ±7 days is recommended thereafter, including the EOS visit. If any study visit has to be rescheduled, subsequent visits should follow the original visit date scheduled.

5.7 Prior and Concomitant Therapies

Use of all prior and concomitant medications and/or therapies for the treatment of psoriasis, and the systemic agents that could affect psoriasis, from the diagnosis of disease until the EOS visit, will be recorded in both the source documents and the eCRF and used for analysis of safety.

Use of all medications for other purposes, taken from 42 days prior to the first administration of study drug will be recorded until the EOS visit in both the source documents and the eCRF.

However, in order to check eligibility, prior medications will be reviewed for the times specified in the related exclusion criteria. This will include all prescription drugs, herbal products, vitamins, minerals, and over-the-counter medications. Any changes in concomitant medications also will be recorded in the patient's eCRF.

Any concomitant medication deemed necessary for the welfare of the patient during the study may be given at the discretion of the investigator. However, it is the responsibility of the investigator to ensure that details regarding the medication are recorded in both the source documents and the eCRF. If the patients are receiving concomitant cytochrome P450 (CYP450) substrates, it is recommended to monitor for therapeutic effect or drug concentration and adjust the individual co-administered drug dose as needed. Prior and concomitant medications will be coded to drug class and preferred term (PT) according to the World Health Organization (WHO) Drug Dictionary Mar 2020 or later.

5.8 Prohibited Therapies

The following medications and treatments are prohibited during the study period. Patients who have received or plan to receive these prohibited medications or treatments will not be enrolled in the study (see Section 4.1.2 for complete list). Patient who is permanently discontinued from study drug can be treated with alternative therapy at the investigator's discretion. Inactivated vaccines are acceptable during the study:

- Any biosimilar of ustekinumab or any drug that targets directly IL-12, or IL-23
- Any biologic agents approved for the treatment of psoriasis
- Any conventional systemic therapy that could affect psoriasis (including, but not limited to, methotrexate, cyclosporine)
- Any systemic steroids that could affect psoriasis
- Topical therapies for the treatment of psoriasis (including, but not limited to, corticosteroids, vitamin D analogs, calcineurin inhibitors, or retinoids)
  [Note. Low-potency topical corticosteroids (Class 6 or 7) applied to the face and intertriginous areas are permitted during study participation to reduce patient's burden with a restriction of use within 12 hours prior to study visit requiring PASI or sPGA measures. Shampoos with salicylic acids and bland moisturizers/emollients (without urea or beta or alpha hydroxy acids) are also allowed for treatment of psoriasis, but these should not be used in the mornings of study visits when efficacy assessments are going to be performed.]
- Topical corticosteroids for the treatment of indications other than psoriasis will be allowed during the study with the limited situations for topical effect (otic, nasal or inhaled) within recommended dose and for 14 consecutive days or less.
- Ultraviolet A phototherapy (with or without oral psoralen) or ultraviolet B phototherapy for the treatment of psoriasis
- Any investigational drug

- Initiation or dose modification of drugs that may aggravate psoriasis (e.g., beta-blockers, lithium, antimalarials)
- Herbal treatment that could affect psoriasis
- Live or live-attenuated vaccination during the study and at least 15 weeks after the last dosing of study drug
- BCG vaccination during the study and 1 year after the last dosing of study drug

6 Study Assessments and Procedures

Prior to performing any study procedures, all potential patients will sign an ICF. Patients will have the opportunity to have any questions answered prior to signing the ICF. The investigator must address all questions raised by the patient. The investigator or designee will also sign the ICF.

All patients will return to the study center by regular scheduled time intervals for clinical assessments and blood sampling. Patients will undergo the procedures at the time points specified in the schedule of events (Table 11-1).

6.1 Efficacy Assessments

Efficacy will be assessed by the evaluation of the PASI, sPGA, Dermatology Life Quality Index (DLQI), patient pain visual analog scale (VAS) for PsA, and Patient Global Assessment for PsA at the time points specified in the schedule of events (Table 11-1).

6.1.1 Psoriasis Area Severity Index

The PASI is a quantitative rating score for measuring the severity of psoriatic lesions based on area coverage and plaque appearance and their response to therapy (Fredriksson and Pettersson, 1978). For the PASI assessment, the body is divided into 4 regions: the head, upper limbs, trunk, and lower limbs (Appendix 11.2). Each of these areas is assessed separately for erythema, induration/thickness, and scaling, which are each rated on a scale of 0 to 4 based on severity of the lesion. The sum of all lesion scores can range from 0 to 72, with the higher score indicating more severe disease. PASI scores are treated as a continuous score with 0.1 increments and if any individual score is missing, the PASI score will not be calculated.

The investigator-reported PASI evaluations will be performed by a qualified efficacy assessor at the study center. If possible, it is recommended that the same assessor perform the investigator-reported outcomes assessments throughout the entire study period.

6.1.2 Static Physician's Global Assessment

The sPGA is a quantitative rating score of the patient's psoriasis based on physician's assessment at a given time point according to the following categories: induration, erythema,

and scaling (Appendix 11.3). The sPGA is a 5-point scale and patient's psoriasis is graded as clear (0), almost clear (1), mild (2), moderate (3), severe (4).

The investigator-reported sPGA evaluations will be performed by a qualified efficacy assessor at the study center. If possible, it is recommended that the same assessor perform the investigator-reported outcomes assessments throughout the entire study period.

6.1.3 Dermatology Life Quality Index

The DLQI is a dermatology-specific QoL instrument designed to assess the impact of the disease on a patient's QoL (Finlay and Khan, 1994) (Appendix 11.4). It is a 10-item patient-reported outcome questionnaire that, in addition to evaluating overall QoL, can be used to assess 6 different aspects that may affect QoL: symptoms and feelings, daily activities, leisure, work or school performance, personal relationships, and treatment. Response categories include "not relevant" (score of 0), "not at all" (score of 0), "a little" (score of 1), "a lot" (score of 2) and "very much" (score of 3). Question 7 is a "yes"/ "no" question where "yes" is scored as 3. Total scores range from 0 to 30 (less to more impairment) and a 5-point change from baseline is considered a clinically important difference. If the answer to one question in a domain is missing, that domain is treated as missing. If two or more questions are left unanswered (missing), DLQI total score is treated as missing.

6.1.4 Patient Pain Visual Analog Scale for Psoriatic Arthritis

Patients with concomitant PsA will assess psoriatic pain using VAS (Appendix 11.5) at the time points specified in the schedule of events (Table 11-1). Patient assessment of psoriatic pain is measured by the patient indicating the extent of their pain by marking one line (|) through the 100-mm line, ranging from 0 (no pain) to 100 (severe pain) after the following question:

"How much pain have you had because of your psoriatic arthritis in the past week? Place a vertical (|) mark on the line to indicate the severity of the pain."

6.1.5 Patient Global Assessment for Psoriatic Arthritis

Patients with concomitant PsA will assess disease activity using VAS (Appendix 11.6) at the time points specified in the schedule of events (Table 11-1). The patient's global assessment of disease activity is measured by the patient indicating the extent of their condition by

marking one line (|) through the 100-mm line, ranging from 0 (very well) to 100 (very poor) after the following question:

"Considering all the ways your psoriatic arthritis affects you, how would you rate the way you felt over the past week? Place a vertical (|) mark on the line to indicate how you felt."

6.2 Pharmacokinetic Assessments

For all patients, PK blood samples for the determination of serum concentration of study drug will be collected prior to dosing at the time points specified in the schedule of events (Table 11-1). The PK of CT-P43 and Stelara will be assessed using a validated method for serum concentration. It will be specified in a separate validation document.

Sample analysis will be performed at the bioanalytical laboratory.

6.3 Safety Assessments

Safety assessments will be performed on immunogenicity, hypersensitivity monitoring, vital sign measurements (including BP, pulse and respiratory rates, and body temperature), IGRA, chest X-ray, hepatitis B and C, physical examination findings, clinical laboratory analyses, ECGs, AEs (including serious adverse events [SAEs]), adverse events of special interest (AESIs; infections/serious infections, injection site reactions, hypersensitivity reactions, and malignancies), pregnancy tests, prior and concomitant medications, local site pain using 100 mm VAS, and signs and symptoms of TB monitored throughout the study. HIV status will be tested to determine subject's eligibility.

Serum samples for immunogenicity testing will be collected at the same time as the clinical laboratory tests before dosing specified in the schedule of events (Table 11-1).

6.3.1 Adverse Events

6.3.1.1 Definitions of Adverse Events

The investigator is responsible for reporting all AEs that are observed or reported during the study, regardless of their relationship to study drug or their clinical significance.

An AE is defined as any untoward medical occurrence in a patient enrolled into this study regardless of its causal relationship to study drug. Patients will be instructed to contact the investigator at any time after the ICF was signed if any symptoms develop.

A TEAE is defined as any untoward medical occurrence in a subject after administration of a drug, whether or not considered drug related. This includes any occurrence that is new in onset or aggravated in intensity or frequency from the baseline condition; abnormal results of diagnostic procedures including laboratory test abnormalities are considered AEs if they fulfill the following:

- Result in discontinuation from the study
- Require treatment or any other therapeutic intervention
- Require further diagnostic evaluation (excluding a repetition of the same procedure to confirm the abnormality)
- Are associated with clinical signs or symptoms judged by the investigator to have a significant clinical impact

Disease progression of psoriasis and psoriatic arthritis will not be recorded as an AE or SAE.

Medical intervention such as surgery, diagnostic procedures, and therapeutic procedures are not AEs, but the action taken to treat the medical condition. They should be recorded as treatment(s) of the AEs. The event term of primary cause should be recorded as an AE instead of the term of surgery, diagnostic procedure, or therapeutic procedure.

6.3.1.1.1 Adverse Events of Special Interest

The following AEs of special interest; infections/serious infections, injection site reactions, hypersensitivity reactions, and malignancies will be reported using the same process as for AEs:

Infections/serious infections

All TEAEs related to infection including TB, sepsis, and other opportunistic infections will be reported.

Injection site reactions

Injection site reactions will be observed after study drug administration and assessed based on Common Terminology Criteria for Adverse Events (CTCAE) v5.0. All TEAEs related to injection site reaction including erythema, itching, hemorrhage, pain, and swelling will be reported.

Hypersensitivity reactions

All TEAEs related to hypersensitivity reactions occurring after the study drug administration will be reported.

Anaphylactic reactions

Anaphylaxis will be identified according to Sampson criteria (Sampson *et al.,* 2006). Anaphylaxis is likely when any 1 of the 3 criteria are fulfilled.

1. *Acute onset of an illness (minutes to several hours) with involvement of the skin, mucosal tissue, or both (e.g., generalized hives, pruritus or flushing, swollen lips-tongue-uvula) and at least one of the following:*
    a. Respiratory compromise (e.g., dyspnea, wheeze or bronchospasm, stridor, reduced peak expiratory flow, hypoxemia)
    b. Reduced BP or associated symptoms of end-organ dysfunction (e.g., hypotonia [collapse], syncope, incontinence)
2. *Two or more of the following that occur rapidly after exposure to a likely allergen for that patient (minutes to several hours):*
    a. Involvement of the skin-mucosal tissue (e.g., generalized hives, itch-flush, swollen lips-tongue-uvula)
    b. Respiratory compromise (e.g., dyspnea, wheeze-bronchospasm, stridor, reduced peak expiratory flow, hypoxemia)
    c. Reduced BP or associated symptoms (e.g., hypotonia [collapse], syncope, incontinence)
    d. Persistent gastrointestinal symptoms (e.g., crampy abdominal pain, vomiting)
3. *Reduced BP after exposure to known allergen for that patient (minutes to several hours):*
    Adults: Systolic BP of less than 90 mmHg or greater than 30% decrease from that person's baseline.

Malignancies

All TEAEs related to malignancy including but not limited to the following: hepatosplenic T cell lymphoma, leukemia, lymphoma, melanoma, and Merkel cell carcinoma.

6.3.1.1.2 Serious Adverse Events

An SAE is defined as any untoward medical occurrence that at any dose:

- Results in death
- Is immediately life threatening
- Requires inpatient hospitalization or prolongation of existing hospitalization
- Results in persistent or significant disability/incapacity
- Is a congenital anomaly/birth defect
- Important medical events that may not result in death, be life threatening, or require hospitalization may be considered SAEs when, based upon appropriate medical judgment, they may jeopardize the patient or may require medical or surgical intervention to prevent one of the outcomes listed in this definition. Examples of such medical events include allergic bronchospasm requiring intensive treatment in an emergency room or at home, blood dyscrasias or convulsions that do not result in inpatient hospitalization, or the development of drug dependency or drug abuse.

Adverse events associated with hospitalization or prolongations of hospitalization are considered as SAEs. Any initial admission (even if less than 24 hours) to a healthcare facility meets these criteria. Admission also includes transfer within the hospital to an acute/intensive care unit (e.g., from the psychiatric wing to a medical floor, from medical floor to a coronary care unit, from neurological floor to a TB unit).

Hospitalization or prolongation of hospitalization in the absence of a precipitating clinical AE is not in itself an SAE. Examples include the following:

- Admission for treatment of a pre-existing condition not associated with the development of a new AE or worsening of the pre-existing condition (e.g., for work-up of persistent pre-treatment laboratory abnormality)
- Social admission (e.g., patient has no place to sleep)
- Administrative admission (e.g., for yearly physical examination)

- Protocol-specified admission during a study (e.g., for a procedure required by the study protocol)
- Optional admission not associated with a precipitating clinical AE (e.g., for elective cosmetic surgery)
- Hospitalization for observation without a medical AE
- Pre-planned treatments or surgical procedures; these should be noted in the baseline documentation for the entire protocol and/or for the individual patient
- Hospitalization purely for convenience (e.g., for easier performance of study assessments)
- Hospitalization solely due to disease progression without any other AEs as decided by the Investigator

6.3.1.1.3 Unlisted (Unexpected) Serious Adverse Events

An unlisted or unexpected SAE is defined as an event of which the nature or intensity is not consistent with the applicable reference documents (e.g., study drug investigator's brochure).

6.3.1.2 Eliciting and Documenting Adverse Events

Adverse events will be assessed from the date the patient signs the ICF until the EOS visit.

All AEs will be followed until resolution or improvement to baseline, death, confirmed by the investigator that no further improvement could be expected, no more collection of clinical or safety data, or final database closure. Adverse events of special interest (i.e., infections/serious infections, injection site reactions, hypersensitivity reactions, and malignancies) will be closely monitored.

At every study visit, patients will be asked a standard non-leading question to elicit any medically related changes in their well-being. They will also be asked if they have been hospitalized, had any accidents, used any new medications, or changed concomitant medication regimens (both prescription and over-the-counter medications).

In addition to patient observations, AEs identified from any study data (e.g., laboratory values, physical examination findings, ECG changes) or identified from review of other documents (e.g., patient diaries) that are relevant to patient safety will be documented on the AE page in the eCRF.

6.3.1.3 Reporting Adverse Events

All AEs reported or observed during the study will be recorded on the AE page in the eCRF. Information to be collected includes drug treatment, dose, event term, time of onset, investigator-specified assessment of intensity and relationship to study drug, time of resolution of the event, seriousness, action taken with study drug, any required treatment or evaluations, and outcome.

Adverse events resulting from concurrent illnesses, reactions to concurrent illnesses, reactions to concurrent medications, or progression of disease states must also be reported. Adverse events will be recorded according to the CTCAE v5.0. The Medical Dictionary for Regulatory Activities (MedDRA) will be used to code all AEs.

Any medical condition that is present at the time that the patient is screened but does not deteriorate should not be reported as an AE. However, if it deteriorates at any time during the study, it should be recorded as an AE.

The investigator's assessment of an AE's relationship to study drug is part of the documentation process, but it is not a factor in determining what is or is not reported in the study. If there is any doubt as to whether a clinical observation is an AE, the event will be reported.

The severity and the relationship or association of the study drug in causing or contributing to the AE will be characterized as defined in Sections 6.3.1.5 and 6.3.1.6, respectively.

Adverse events (and SAEs) should be reported until the EOS visit regardless of the relationship to the study drug. After the EOS visit, serious adverse drug reactions will be reported to CELLTRION, Inc. or its designee.

6.3.1.4 Reporting Serious Adverse Events

Any AE considered serious by the investigator or which meets SAE criteria (Section 6.3.1.1.2) must be reported to CRO PVG within 24 hours from the time study center staff first learn about the event. The following contact information is to be used for SAE reporting:

Data entry should be completed in the remote data capture system by the investigator within 24 hours of awareness of an SAE. In the event that this is not possible (e.g., system failure or access problems), the study center should complete an SAE report form and fax it to CRO PVG within 24 hours of awareness of the event. The remote data capture system should be updated as soon as it is available. If the patient is hospitalized during an SAE or because of an SAE, a copy of the hospital discharge summary will be faxed to CRO PVG as soon as it becomes available. Withdrawal from the study and all therapeutic measures will be at the discretion of the principal investigator or sub-investigator. All SAEs (regardless of relationship with the study drug) will be followed up until satisfactory resolution or until the principal investigator or sub-investigator deems the event to be chronic or not clinically significant or the patient to be stable.

CELLTRION, Inc. or its designee is responsible for reporting relevant SAEs to the competent authority, other applicable regulatory authorities, and participating investigators, in accordance with European Clinical Trials Directive (Directive 2001/20/EC), International Council for Harmonisation (ICH) guidelines, and/or local regulatory requirements.

CELLTRION, Inc. or its designee is responsible for reporting fatal or life-threatening suspected unexpected serious adverse reactions (expedited reports) to the regulatory agencies and competent authorities within 7 calendar days after being notified of the event. CELLTRION, Inc. or its designee should report other relevant SAEs associated with the use of the study drug to the appropriate competent authorities (according to local guidelines),

investigators, and central ethics committees by a written safety report within 15 calendar days of notification.

6.3.1.5 Assessment of Intensity

The intensity of an AE refers to the extent to which an AE affects the patient's daily activities. The intensity of the AE will be graded based on the CTCAE v5.0, based on the following general guidelines (a semicolon indicates "or" within each description):

Grade 1:	Mild: asymptomatic or mild symptoms; clinical or diagnostic observations only; intervention not indicated
Grade 2:	Moderate: minimal, local, or non-invasive intervention indicated; limiting age appropriate instrumental activities of daily living (ADL)*
Grade 3:	Severe or medically significant but not immediately life-threatening: hospitalization or prolongation of hospitalization indicated; disabling; limiting self-care ADL**
Grade 4:	Life-threatening consequences: urgent intervention indicated
Grade 5:	Death related to AE

* Instrumental ADL refer to preparing meals, shopping for groceries or clothes, using the telephone, managing money, etc.

** Self-care ADL refer to bathing, dressing and undressing, feeding self, using the toilet, taking medications, and not bedridden.

The investigator will assess of the maximum intensity that occurred over the duration of the event. However, if an AE changes from a non-serious to a serious event, a new SAE needs to be reported separately. Adverse events characterized as intermittent do not require documentation of onset and duration of each episode.

6.3.1.6 Assessment of Causality

As discussed in Section 6.3.1.3, the investigator's assessment of an AE's relationship to study drug is part of the documentation process, but it is not a factor in determining what is or is not reported in the study. If there is any doubt as to whether a clinical observation is an AE, the event will be reported.

The relationship or association of CT-P43 or Stelara in causing or contributing to the AE will be characterized using the following classification and criteria:

Unrelated: This relationship suggests that there is no association between the study drug and the reported event.

Possible: This relationship suggests that treatment with the study drug caused or contributed to the AE, e.g., the event follows a reasonable temporal sequence from the time of drug administration or follows a known response pattern to the study drug, but could also have been produced by other factors.

Probable: This relationship suggests that a reasonable temporal sequence of the event with drug administration exists and, based upon the known pharmacological action of the drug, known or previously reported adverse reactions to the drug or class of drugs, or judgment based on the investigator's clinical experience, the association of the event with the study drug seems likely. The event disappears or decreases on cessation or reduction of the dose of study drug.

Definite: This relationship suggests that a definite causal relationship exists between drug administration and the AE, and other conditions (concurrent illness, progression/expression of disease state, or concurrent medication reaction) do not appear to explain the event. The event reappears or worsens if the study drug is re-administered.

6.3.1.7 Follow-up of Patients Reporting Adverse Events

All AEs must be reported in detail on the appropriate page in the eCRF and followed to satisfactory resolution, until the investigator deems the event to be chronic or not clinically significant, or until the patient is stable.

6.3.2 Other Safety Assessment

6.3.2.1 Immunogenicity Testing

The immunogenicity of CT-P43 and Stelara will be assessed by anti-drug antibody (ADA) and neutralizing antibody test in validated immunoassay. It will be specified in a separate validation document.

Serum samples for immunogenicity testing will be collected prior to dosing of study drug at the time points specified in the schedule of events (Table 11-1). Additional immunogenicity will be assessed when immune-related AEs (e.g., hypersensitivity) occur.

A blood sample for immunogenicity for patients with immune-related AEs will be obtained on the onset date of immune-related AEs, if possible, or a blood sample can be used if it was obtained on the same date of study drug administration.

Sample analysis will be performed at the bioanalytical laboratory.

6.3.2.2 Injection Site Reaction Monitoring

Injection site reactions will be assessed 30 minutes (±10 minutes) after the end of the study drug administration, as specified in the schedule of events (Table 11-1).

Details will be recorded in both the source documents and the eCRF.

6.3.2.3 Hypersensitivity Monitoring

Hypersensitivity reactions will be assessed prior to the study drug administration and 1 hour (±10 minutes) after the end of the study drug administration, as specified in the schedule of events (Table 11-1), by additional vital sign measurements including BP, pulse and respiratory rates, and body temperature. If patients have signs and symptoms of hypersensitivity/allergic reactions at home (hives, difficulty breathing, or swelling of face, eyes, lips, or mouth or any symptoms of cardiac origin), patients or caregivers should be advised to call the study center or get immediate help.

In addition, hypersensitivity will be monitored by routine continuous clinical monitoring including patient-reported signs and symptoms. In case of hypersensitivity, emergency medication and equipment, such as adrenaline, antihistamines, corticosteroids, and respiratory support including inhalational therapy, oxygen, and artificial ventilation must be available and any types of ECG can be performed.

For patients who experience or develop life-threatening treatment-related anaphylactic reactions, study drug must be stopped immediately and succeeding doses need to be discontinued.

Details will be recorded in both the source documents and the eCRF.

6.3.2.4 Vital Signs and Weight, and Height

Vital signs and weight measurements will be performed at the time points specified in the schedule of events (Table 11-1). Vital signs (including BP, pulse and respiratory rates, and body temperature; while sitting) and weight will be measured by the investigator or his or her designee after 5 minutes of rest. In addition, measurement of height will be documented at Screening. All measurements will be documented at each study center visit. Details will be recorded in both the source documents and the eCRF.

Vital sign measurements will also be monitored prior to and after study drug injection as part of the hypersensitivity monitoring (Section 6.3.2.3).

6.3.2.5 Electrocardiograms

All scheduled 12-lead ECGs will be performed at the study center after the patient has rested quietly for at least 5 minutes in a supine position. A 12-lead ECG will be performed at the time points specified in the schedule of events (Table 11-1) and if the patient experienced cardiac symptoms during study drug administration. If following the ECG review by the investigator there are any ECG findings that would indicate cardiac insufficiency or QT prolongation, the patient will be referred to a cardiologist to confirm the abnormality. The investigator will then report the event in the source documents and the eCRF. Regardless of the 12-lead ECG result, further evaluation with a cardiologist can be done depending on the investigator's discretion. In case of hypersensitivity, any type of ECG can be performed (Section 6.3.2.3).

6.3.2.6 Physical Examinations

Physical examinations with particular attention to AESIs (i.e., infections/serious infections, injection site reactions, hypersensitivity reactions, and malignancies) will be performed prior to study drug administration at the time points specified in the schedule of events (Table 11-1).

Investigators should carefully evaluate patients for any indication of infections and injection site reactions and pursue further investigation and treatment indicated in accordance with the investigator's medical judgment.

Physical examinations will be performed when patients visit the study center by regular scheduled time intervals for clinical assessments.

Information about the physical examinations will be recorded by the investigator or designee in both the source documents and the eCRF. Any abnormalities will be recorded in the source documents. Clinically significant findings and illnesses reported after the start of the study that meet the definition of an AE will be recorded in both the source documents and eCRF.

6.3.2.7 Tuberculosis Assessment

At Screening, current or a history of active TB will result in patient exclusion from the study. A patient who has a previous diagnosis of active TB cannot be enrolled in the study even if there is sufficient documentation of complete resolution of active TB.

Patients who have had exposure to a person with active TB such as first-degree family members or co-workers within 16 weeks prior to first administration of the study drug will not be included in the study.

Latent TB is defined as the presence of a positive IGRA (Section 6.3.2.7.2) with a negative examination of chest X-ray (Section 6.3.2.7.1).

A patient who has a past or current diagnosis of latent TB cannot be enrolled. However, a patient who has sufficient documentation of completing TB prophylaxis, or has received at least the first 3 weeks of country-specific TB prophylaxis prior to the first administration of the study drug (Day 1) and intends to complete its entire course can be enrolled. If there is a need to extend the Screening Period due to country-specific TB prophylaxis more than 3 weeks, it will be discussed with CELLTRION Inc. in advance.

A patient who is without a history of active TB or latent TB and has an indeterminate result of IGRA with a negative examination of chest X-ray at Screening cannot be enrolled. If the result of the IGRA is indeterminate at Screening, 1 retest will be allowed during the Screening Period. If the repeated IGRA result is negative, the patient can be enrolled in the study. If the repeated IGRA result is positive, the patient who has received at least the first 3 weeks of country-specific TB prophylaxis prior to the first administration of the study drug (Day 1) and intends to complete its entire course can be enrolled. If the IGRA result is again indeterminate, the patient should be excluded from the study.

Throughout the study, patients will be monitored for the clinical signs and symptoms of TB. An additional IGRA or chest X-ray can be performed at the investigator's discretion based on the judgment per the signs and symptoms of TB monitoring. The investigator will confirm the absence of active TB prior to the subsequent dose administration. Patients with active TB based on the chest X-ray result and/or the clinical signs and symptoms must be withdrawn from the study.

If the result of the IGRA is positive during the study, patients will be referred to the clinician immediately to investigate the presence of active TB based on medical history and any clinical signs and symptoms including chest X-ray result. Even in the absence of clinical suspicion for active TB, study drug administration will be temporarily stopped. It is recommended that study drug administration is resumed in patients who have received at least 3 weeks of country-specific TB therapy and who intend to complete the entire course of TB therapy. However, study drug administration can be resumed simultaneously with the start of country-specific TB therapy after discussion with the medical monitors of CELLTRION, Inc. or its designee in advance.

If the patient is exposed to a person with active TB during the study period, an IGRA test will be conducted immediately and country-specific TB therapy will be initiated immediately regardless of the IGRA test result being negative or positive. The IGRA test will be repeated 8 weeks after the initial IGRA test and country-specific TB therapy can be discontinued if the repeated result is negative.

No further IGRA testing is required during the treatment period for the following patients:

- Patient who has a history of latent TB with sufficient documentation of complete TB prophylaxis.
- Patient who has confirmed latent TB at Screening and enrolled after at least 3 weeks of latent TB prophylaxis. This patient should have sufficient documentation of complete TB prophylaxis.
- Patient with a positive result of IGRA during the study.

6.3.2.7.1 Chest X-Ray

A chest X-ray (both posterior–anterior and lateral views) should be taken during Screening and read by a qualified radiologist or pulmonary physician to specifically look for evidence of current or previous active or latent TB. If a chest X-ray within 12 weeks prior to the first administration of the study drug (Day 1) is available, a chest X-ray is not required at Screening, and the result will be recorded in both the source documents and the eCRF.

Radiographic findings suggestive of healed TB or active TB may include but are not limited to pulmonary nodules, fibrotic scars, calcified granulomas, upper lobe infiltrates, cavitations, and pleural effusions. Any abnormal X-ray changes should be discussed with the medical monitor prior to the first administration of the study drug (Day 1). The chest X-ray should be available to the investigator for review prior to the first administration of the study drug (Day 1) of the patient.

6.3.2.7.2 Interferon- γ Release Assay

Given the seriousness of TB in this patient population, an IGRA will be used to identify positive conversion of negative results for patients. Samples for this analysis will be obtained at the time points specified in the schedule of events (Table 11-1). The IGRA will be performed at the central laboratory.

Specifically, these assays detect cell-mediated immune responses to TB infections by quantifying interferon-γ in the presence of specific antimicrobial agents.

6.3.2.8 Viral Serology Tests

At Screening, hepatitis B surface antigen (HBsAg), hepatitis B surface antibody (HBsAb), and hepatitis B core antibody (HBcAb) will be assessed in all patients as specified in Table 1.

Table 1 Eligibility Based on Serologic Markers for Hepatitis B Infection

Test Results				Eligibility
HBsAg	**HBsAb**	**HBcAb**	**HBV DNA**	
+	+/–	+/–	Not applicable	Not eligible
–	+/–	+	+	Not eligible
			–	Eligible[1]
–	+/–	–	Not applicable	Eligible

Abbreviations: HBcAb, hepatitis B core antibody; HBsAb, hepatitis B surface antibody; HBsAg, hepatitis B surface antigen; HBV, hepatitis B virus.

1. Testing of HBsAg, HBsAb, HBV DNA, aspartate aminotransferase, alanine aminotransferase, and total bilirubin will be performed at Week 16 and EOS visit.

If the HBsAg test result is positive, the patient will be excluded from the study. If a patient has HBsAg negative, HBsAb negative or positive, and HBcAb positive, a hepatitis B virus (HBV) DNA test will be performed at Screening. If the HBV DNA test result is positive, the patient will be excluded from the study; if the HBV DNA test result is negative, the patient can be included in the study. For patients who are enrolled with a negative HBV DNA test, testing of HBsAg, HBsAb, HBV DNA, aspartate aminotransferase, alanine aminotransferase, and total bilirubin will be performed at the Week 16 and EOS visits. If the patient develops hepatitis B reactivation, a study drug should be discontinued. Hepatitis B analysis will be performed at the central laboratory.

At Screening, hepatitis C antibody and HIV will be assessed in all patients. If the hepatitis C virus (HCV) test results is positive, HCV RNA will be performed at Screening. If the HCV RNA test result is negative, the patient can be included in the study at the investigator's discretion. Further evaluation for the patients who are enrolled based on HCV RNA test can be done depending on the investigator's discretion during the study. If the HIV test result is positive, the patient must be excluded from the study. Hepatitis C and HIV analysis will be performed at the central laboratory.

6.3.2.9 Pregnancy

For women of childbearing potential who have not been surgically sterilized, a serum pregnancy test will be conducted at Screening and at the EOS visit by central laboratory and a urine pregnancy test will be used to confirm patients are not pregnant prior to dosing on

each scheduled visit specified in the schedule of events (Table 11-1) or more frequently if required by country-specific legislation. Only patients with a negative serum pregnancy test result can be enrolled in the study. A urine pregnancy test will be performed locally. If a urine pregnancy test result is positive, a confirmatory serum pregnancy test will be performed at the central laboratory.

In an event of unexpected pregnancy during study participation and for 6 months after the last dose of study drug, patients will be counselled to inform the investigator. If a female patient or the partner of a male patient becomes pregnant, the pregnancy must be reported to CELLTRION, Inc. and [redacted] Safety Department within 24 hours of the study center's knowledge of the pregnancy while confirmation is pending. Once the pregnancy is confirmed with a serum pregnancy test, female patients must permanently discontinue the study drug immediately. The study center must complete the supplied pregnancy form (female patient or partner of a male patient) and return it to CELLTRION, Inc. and [redacted] Safety Department within 24 hours after acquisition of the consent for the pregnancy form.

Pregnant patients or the pregnant partners of male patients will be followed until the end of the pregnancy (e.g., delivery, stillbirth, miscarriage) and the mother and the baby will be followed for 1 year after the birth, provided consent is obtained. Any SAE that occurs during pregnancy (e.g., maternal serious complications, ectopic pregnancy, stillbirth, neonatal death, congenital anomaly, birth defect) must be reported within 24 hours in accordance with the procedure for reporting SAEs (Section 6.3.1.4).

6.3.2.10 Laboratory Analyses

Blood and urine samples for clinical laboratory assessments will be collected at the time points specified in the schedule of events (Table 11-1). Blood samples do not need to be collected in a fasting state unless in the opinion of the investigator fasting blood samples are required.

The following clinical laboratory analyses will be performed:

Clinical chemistry	total protein, serum bilirubin (total, direct), alanine aminotransferase, aspartate aminotransferase, alkaline phosphatase, γ-glutamyltransferase, blood urea nitrogen, creatinine, albumin, sodium, potassium, calcium, chloride, inorganic phosphorus, glucose, lactate dehydrogenase, total cholesterol, triglyceride, high-density lipoprotein cholesterol, C-reactive protein, and uric acid
Hematology	red blood cells, total and differential white blood cell count, absolute neutrophil count, platelet count, hemoglobin, and hematocrit
Urinalysis	bilirubin, blood, glucose, ketones, leukocytes, nitrite, pH, protein, specific gravity, and urobilinogen

Creatinine clearance (by Cockcroft-Gault formula) will be calculated using serum creatinine level only at Screening for inclusion. Clinical laboratory (clinical chemistry, hematology, and urinalysis) test samples will be analyzed at the central laboratory.

6.3.2.11 Patient's Assessment of Local Site Pain

All patients will assess local site pain using 100 mm VAS immediately (within 15 minutes) after the administration of study drug at the time points specified in the schedule of events (Table 11-1). Patient assessment of pain is measured by the patient indicating the extent of their pain by marking one line (|) through the 100-mm line (Appendix 11.7).

6.4 Biomarker Assessments (Optional)

Blood samples for analysis of evaluation of genotype (Human Leukocyte Antigen [HLA]-Cw6 [C*06:02] and/or any necessary genotypes) will be collected prior to dosing on Day 1 (Week 0) (Table 11-1) for patients who sign a separate ICF for this assessment.

Details of the biomarker analysis are presented in Section 7.5.

6.5 Sample Collections

The total volume of blood collected for each assessment is discussed in each specific laboratory manual. The sample collection tube may be changed during the study and details will be provided in the laboratory manual.

6.5.1 Pharmacokinetic Blood Sampling

Blood samples for PK assessments will be obtained accordance with the laboratory manual from each patient at the time points specified in the schedule of events (Table 11-1). All samples should be collected as close as possible to the scheduled time point.

Samples should be stored and shipped as detailed in Section 6.6.2.

6.5.2 Biomarker Blood Sampling (Optional)

For patients who sign a separate ICF for the biomarker assessments, blood samples for evaluation of genotype (HLA-C*06:02, and/or any necessary genotypes) will be collected in accordance with the laboratory manual at the time points specified in the schedule of events (Table 11-1). These samples will be used for research purposes to identify dynamic biomarkers that may be predictive of response to CT-P43 treatment (in terms of dose, efficacy, safety, and tolerability).

Samples should be stored and shipped as detailed in Section 6.6.2.

6.5.3 Immunogenicity Blood Sampling

Blood samples for immunogenicity assessments will be obtained prior to study drug administration at the time points specified in the schedule of events (Table 11-1), or when immune-related AEs occur.

Samples should be stored and shipped as detailed in Section 6.6.2.

6.5.4 Interferon-γ Release Assay Blood Sampling

Blood samples for IGRA will be obtained at the time points specified in the schedule of events (Table 11-1). All samples should be collected at the scheduled time point.

Samples should be stored and shipped as detailed in Section 6.6.2.

6.5.5 Routine Safety Blood Sampling

Blood samples for routine safety (clinical laboratory testing) will be collected for analysis throughout the study at the time points specified in the schedule of events (Table 11-1).

An additional blood sample for hepatitis B and hepatitis C and HIV testing will be required at Screening. A serum pregnancy test sample will be required at Screening and at the EOS visit for women of childbearing potential who have not been surgically sterilized.

Samples should be stored and shipped as detailed in Section 6.6.2.

6.6 Labeling, Storage, and Transportation of Samples

6.6.1 Sample Labeling

Each sample tube will be clearly labeled with the following information: study number, patient number, tube identification, and scheduled sampling time point.

6.6.2 Sample Storage and Shipment

During the study, blood samples will be collected for PK, immunogenicity, safety and/or biomarker analyses.

Where appropriate, the serum should be transferred into a sufficient number of transfer tubes for transport to assigned testing facilities. Primary and back-up samples will be shipped to the central laboratory according to the laboratory manual, and primary samples should be shipped separately from the back-up samples.

Additionally, back-up samples for PK, immunogenicity, and/or biomarkers should be retained at the central laboratory as a back-up for up to 5 years after the end of the study in case additional analysis is required. If additional analysis for PK, immunogenicity, and/or biomarkers is not required, the sample will be stored at CELLTRION, Inc. or a designated biobank for a further 5 years (from the date the sample is transferred to the biobank) unless a specific authorization is given by CELLTRION, Inc. to destroy the sample. Additional tests can be conducted at CELLTRION, Inc. or the biobank if it is required from a regulatory or medical perspective. Details in storage and shipment will be followed according to the laboratory manual.

7 Statistical Considerations

[redacted] The statistical methods for this study will be described in a detailed statistical analysis plan (SAP), which will be finalized prior to database lock. Changes from analyses planned in this protocol will be documented in the SAP. Any deviations from the planned analysis as described in the SAP will be justified and recorded in the study report.

Continuous variables will be summarized by reporting the number of observations (n), mean, standard deviation (SD), median, minimum, and maximum. Categorical variables will be summarized using frequency tables showing the number and percentage of patients within a particular category.

7.1 Sample Size Calculation

A total sample size is planned to be a minimum of 446 patients (a minimum of 223 patients in each treatment group of CT-P43 and Stelara). Considering that the drop-out rate has been hypothesized at 10%, a minimum sample size of 400 patients (a minimum of 200 patients in each treatment group of CT-P43 and Stelara) is estimated to provide at least 90% statistical power for the demonstration of similarity of the mean percent improvement from baseline in the PASI score at Week 12 with an equivalence margin of ±10% using a 90% CI approach corresponding to two one-sided test with significance level of 5%. In this sample size calculation, the SD of the percent improvement in PASI score at Week 12 is assumed to be 29.0 and the expected difference to be 0. Sample size was derived using PASS (version 16.0.3, NCSS Statistical Software, LLC. Utah, USA).

7.2 Analysis Sets

The following analysis sets will be used in the statistical analyses.

Intent-to-Treat (ITT) Set: The ITT Set is defined as all patients randomly assigned to receive study drug (CT-P43 or Stelara).

ITT–Treatment Period II subset: The ITT–Treatment Period II subset is defined as all patients in ITT set who are randomly assigned to receive study drug (CT-P43 or Stelara) prior to dosing at Week 16.

Modified ITT (mITT) Set: The mITT Set is defined as all patients who are randomly assigned and received at least 1 dose (full or partial) of study drug (CT-P43 or Stelara).

Modified ITT (mITT) –Treatment Period II subset: The mITT–Treatment Period II subset is defined as all patients in mITT Set who are randomly assigned at Week 16 prior to dosing and received at least 1 dose (full or partial) of study drug (CT-P43 or Stelara) at or after Week 16.

Per-Protocol Set (PPS): The PPS is defined as all randomly assigned patients who receive the full dose of study drug (CT-P43 or Stelara) at Weeks 0 and 4, have a PASI assessment at baseline and Week 12, and do not have any major protocol deviation affecting primary endpoint interpretation. Final determinations of the PPS will be made at the blinded data review meeting (DRM) for the efficacy primary endpoint before unblinding.

Pharmacokinetic (PK) Set: The PK Set is defined as all randomly assigned patients who receive at least 1 full dose of study drug (CT-P43 or Stelara) and who have at least 1 post-treatment PK result. If any patient is found to be non-compliant with respect to dosing, a determination of the PK Set will be made on a case-by-case basis at the blinded DRM.

PK–Treatment Period II subset: The PK–Treatment Period II subset will consist of all patients in PK set who receive at least 1 full dose of either of study drug (CT-P43 or Stelara) and have at least 1post treatment PK result at or after Week 16.

Safety Set: The Safety Set is defined as all randomly assigned patients who receive at least 1 dose (full or partial) of study drug (CT-P43 or Stelara).

Safety–Treatment Period II subset: The Safety–Treatment Period II subset will consist of all patients in Safety set who receive at least 1 dose (full or partial) of study drug (CT-P43 or Stelara) at or after Week 16.

7.3 Efficacy Analyses

7.3.1 Primary Efficacy Analysis

The mean percent improvement from baseline in PASI score at Week 12 will be analyzed using an analysis of covariance (ANCOVA) model with covariates of country, body weight, prior biologic use approved for psoriasis treatment and baseline PASI score. Point estimate

and 90% CI for the difference in the mean percent improvement in PASI between the 2 treatment groups will be produced. Therapeutic equivalence of clinical response according to mean percent improvement from baseline in PASI score at Week 12 will be concluded if the 90% CIs for the treatment difference is entirely within –10% to 10%.

The primary efficacy analysis will be conducted on the mITT Set using an ANCOVA model coupled with Multiple imputation (MI) with the Missing at random (MAR) assumption for missing data handling. A supportive analysis for the primary efficacy endpoint will be conducted using the PPS. Definition of each analysis set is described in Section 7.2.

Multiple imputation (MI) with the MAR assumption will be applied. The multiple imputed datasets will be generated based on regression model with country, baseline body weight, prior biologic use approved for psoriasis treatment, baseline PASI score and treatment group as covariates. All patients with baseline PASI score in mITT Set will be included in the analysis. Ten imputed datasets will be created by multiple imputation and ANCOVA for the mean percent improvement from baseline in PASI at Week 12 will be applied to each of the imputed datasets. The results from imputed datasets will be computed using Rubin's rules for a final statistical inference.

In addition, descriptive statistics for the percent PASI improvement at Week 12 by ADA status at Week 12 and treatment group will be summarized for the mITT Set.

7.3.1.1 Sensitivity Analysis for Primary Efficacy Endpoint

To assess the robustness, sensitivity analysis using tipping point approach will be conducted for the primary efficacy endpoint in the mITT Set. Tipping point analysis will be performed under Missing Not at Random (MNAR) scenario.

Imputed values will be shifted gradually from the imputed values by MI under MAR, by treatment groups (CT-P43 vs. Stelara) to make MNAR scenarios. A point estimate and 90% CI for treatment difference will also be provided using an ANCOVA considering the treatment as a fixed effect and country, baseline body weight, prior biologic use approved for psoriasis treatment and baseline PASI score as covariates under the scenarios. The scenario where confidence interval no longer rules out differences in the percent PASI improvement from baseline at Week 12 for the therapeutic equivalence margin ±10% will be displayed. All the MNAR scenarios and corresponding CIs will be provided.

7.3.2 Secondary Efficacy Analysis

All secondary efficacy endpoints will be summarized using descriptive statics or frequency tables for the mITT Set, PPS and mITT–Treatment Period II subset. Difference on mean (or proportion) between the 2 treatment groups and its 95% CIs will be provided as well. These will be summarized by treatment group as appropriate and listed. The following secondary efficacy endpoints will be assessed at the time points specified in the schedule of events (Table 11-1).

- The PASI scores
- The mean percent improvement from baseline in PASI
- The proportion of patients who achieve at least 50/75/90/100% improvement from baseline in PASI (PASI 50/75/90/100)
- The proportion of patients with sPGA score on a 5-point scale of clear (0) or almost clear (1)
- The change in DLQI score from baseline

7.3.3 Exploratory Efficacy Analysis

All exploratory efficacy endpoints will be descriptively summarized for the mITT Set, PPS and mITT–Treatment Period II subset. These will be summarized by treatment group as appropriate and listed. The following exploratory efficacy endpoints will be assessed at the time points specified in the schedule of events (Table 11-1).

- The change in patient pain VAS from baseline in patients with PsA
- The change in Patient Global Assessment VAS from baseline in patients with PsA

7.4 Pharmacokinetic Analyses

Serum concentration for Treatment Period I will be summarized on PK Set and data for Treatment Period II will be summarized on PK–Treatment Period II subset, unless otherwise specified. Serum concentrations of study drug will be summarized using quantitative descriptive statistics (including geometric mean and coefficient of variation, as appropriate)

by treatment group and study visit at the time points specified in the schedule of events (Table 11-1). The PK Set will be the population for the summary of PK data.

An additional summary of descriptive statistics for the serum concentration will be produced by ADA status and treatment group for Treatment Period I. Listing will be provided by treatment group showing the serum concentrations.

7.5 Biomarker Analyses

Analyses will be performed on genotypes (HLA-C*06:02, and/or any necessary genotypes) in the ITT set. Genotypes will be summarized and listed using frequency tables.

7.6 Safety Analyses

Safety analyses will be performed on the Safety Set at the time points specified in the schedule of events (Table 11-1) with the exception of the summary of demographic and baseline and background Characteristics, which will be performed on the ITT set.

7.6.1 Demographic and Baseline and Background Characteristics

Demographics (including gender, age, ethnicity, and race) and baseline and background characteristics (including psoriasis history) will be presented in summary tables in ITT set. Qualitative data (e.g., medical history) will be summarized in frequency tables, and quantitative data (e.g., age) will be summarized using quantitative descriptive statistics.

Listings will be provided by treatment group showing the demographic, baseline, and background characteristics in ITT set. In addition, a listing of subjects whose trial participation is impacted by COVID-19 with details of the impact, will be prepared, if applicable.

7.6.2 Adverse Events

Adverse events will be coded to system organ class (SOC) and PT according to the MedDRA, and AEs will be graded for intensity according to the CTCAE v5.0. A TEAE is defined as described in Section 6.3.1.1. The following TEAE summaries will be reported by SOC, PT, and treatment group:

- Number and percentage of patients reporting at least 1 TEAE

- Number and percentage of patients reporting at least 1 treatment-emergent SAE
- Number and percentage of patients discontinuing the study drug due to a TEAE
- Number and percentage of patients with TEAEs of special interest (infections/serious infections, injection site reactions, hypersensitivity reactions, and malignancies)

An additional summary will be produced by ADA status and treatment group for Treatment Period I. Listings will be provided by treatment group showing the details of AEs.

7.6.3 Immunogenicity

All data will be listed and summarized by treatment group, where appropriate.

7.6.4 Clinical Laboratory Analyses

Clinical laboratory results (hematology, clinical chemistry, urinalysis) will be summarized and listed by treatment at each scheduled collection time and graded according to the CTCAE v5.0.

7.6.5 Patient's Assessment of Local Site Pain

Local site pain measurements by VAS (Appendix 11.7) will only be assessed immediately after the administration of study drug at each scheduled collection time and will be summarized and listed by treatment group.

7.6.6 Prior and Concomitant Medications

Prior and concomitant medications will be coded using the WHO Drug Dictionary. All prior and concomitant medications data will be listed and summarized by treatment group as appropriate.

7.6.7 Other Safety Analyses

The IGRA, and pregnancy testing will be summarized and listed by treatment group at each scheduled collection time.

Electrocardiograms, physical examination, vital signs (systolic and diastolic BP, pulse rate, respiratory rate, and body temperature) and weight will be summarized and listed by

treatment group at each scheduled collection time. Change from baseline will also be summarized for all scheduled collection times after the first administration of study drug.

All other safety data will be listed and summarized by treatment group as appropriate.

7.7 Interim Analyses

No interim analyses are planned for this study.

7.8 Data Quality Assurance

This study will be conducted according to the ICH E6(R2) risk and quality processes described in the applicable procedural documents. The quality management approach to be implemented in this study will be documented and will comply with the current ICH Good Clinical Practice (GCP) guidelines on quality and risk management.

Steps to be taken to ensure the accuracy and reliability of data include the selection of qualified investigators and appropriate study centers, review of protocol procedures with the investigator and associated staff prior to the study, periodic monitoring visits by CELLTRION, Inc. or its designee, and direct transmission of clinical laboratory data from a central laboratory into the clinical database. The eCRF will be reviewed for accuracy and completeness by the monitor during on-site or remote monitoring visits and after their return to CELLTRION, Inc. or its designee; any discrepancies will be resolved with the investigator or designees, as appropriate. The data will be entered into the clinical study database and verified for accuracy.

Quality assurance staff from CELLTRION, Inc. or its designee may visit the study center to carry out an audit of the study in compliance with regulatory guidelines and company policy. Such audits will require access to all study records, including source documents, for inspection and comparison with the eCRF. Patient privacy must, however, be respected. Sufficient prior notice will be provided to allow the investigator to prepare properly for the audit.

Similar auditing procedures may also be conducted by agents of any regulatory body reviewing the results of this study in support of a licensing application. The investigator should immediately notify CELLTRION, Inc. or its designee if he or she has been contacted by a regulatory agency concerning an upcoming inspection.

8 Investigator's Obligations

The following administrative items are meant to guide the investigator in the conduct of the study but may be subject to change based on industry and government SOPs, working practice documents, or guidelines. Changes will be reported to the IRB/IEC but will not result in protocol amendments.

8.1 Confidentiality

All laboratory specimens, evaluation forms, reports, and other records will be identified in a manner designed to maintain patient confidentiality. All records will be kept in a secure storage area with limited access. Clinical information will not be released without the written permission of the patient (or the patient's legal guardian), except as necessary for monitoring and auditing by the sponsor, its designee, the regulatory authorities, or the IRB/IEC.

The investigator, all employees, and co-workers involved with this study may not disclose or use for any purpose other than performance of the study any data, record, or other unpublished, confidential information disclosed to those individuals for the purpose of the study. Prior written agreement from the sponsor or its designee must be obtained for the disclosure of any said confidential information to other parties.

8.2 Independent Ethics Committee or Institutional Review Board

Regulations and the ICH guidelines require that approval be obtained from an IRB/IEC prior to participation of human patients in research studies. Prior to study onset, the protocol, informed consent, advertisements to be used for the recruitment of study patients, and any other written information regarding this study to be provided to the patient or the patient's legal guardian must be approved by the IRB/IEC. Documentation of all IRB/IEC approvals and of the IRB/IEC compliance with ICH harmonised tripartite guideline E6(R2): GCP will be maintained by the study center and will be available for review by the sponsor or its designee.

All IRB/IEC approvals should be signed by the IRB/IEC chairman or designee and must identify the IRB/IEC name and address, the clinical protocol by title or protocol number or both, and the date approval or a favorable opinion was granted.

The investigator is responsible for providing written summaries of the progress and status of the study at intervals not exceeding 1 year or otherwise specified by the IRB/IEC. The investigator must promptly supply the sponsor or its designee, the IRB/IEC, and, where applicable, the institution, with written reports on any changes significantly affecting the conduct of the study or increasing the risk to patients.

8.3 Patient Information and Consent

A written informed consent in compliance with the ICH E6(R2) guidelines shall be obtained from each patient prior to entering the study or performing any unusual or non-routine procedure that involves risk to the patient. An informed consent template may be provided by the sponsor to the study centers. If any institution-specific modifications to study-related procedures are proposed or made by the study center, the consent should be reviewed by the sponsor or its designee or both prior to IRB/IEC submission. Once reviewed, the consent will be submitted by the investigator to his or her IRB/IEC for review and approval prior to the start of the study. If the ICF is revised during the course of the study, all active participating patients must sign the revised form.

Prior to recruitment and enrollment, each prospective patient or his or her legal guardian will be given a full explanation of the study and be allowed to read the approved ICF. Once the investigator is assured that the patient/legal guardian understands the implications of participating in the study, the patient/legal guardian will be asked to give consent to participate in the study by signing the ICF.

In addition to the standard requirements that physicians are currently obliged to observe when providing information, the following points must also be covered:

- A description of the objectives of the study and how it will be organized
- The type of treatment
- Any potential negative effects attributable to the study drug
- The freedom to ask for further information at any time
- The patient’s right to withdraw from the clinical study at any time without giving reasons and without jeopardizing the patient’s further course of medical treatment

- The existence of patient insurance coverage and a summary of what is included in this coverage

- Adequate time and opportunity to satisfy questions will be given to the patients.

The investigator will be supplied with an adequate number of ICFs to be used. The forms will be signed and dated by both the investigator or sub-investigator and the patient's legal representatives (according to the local regulations) prior to the beginning of the study. The investigator shall retain the signed original ICF(s) and give a copy of the signed original form to the patient or legal guardian.

To ensure medical confidentiality and data protection, the signed ICFs will be stored in the investigator's study file. The investigator will allow inspection of the forms by authorized representatives of the sponsor, IRB/IEC members, and regulatory authorities. The investigator will confirm, by signing and dating the eCRF, that informed consent has been obtained.

8.4 Study Reporting Requirements

By participating in this study, the principal investigator or sub-investigator agrees to submit reports of SAEs according to the timeline and method outlined in Section 6.3.1.4. In addition, the principal investigator or sub-investigator agrees to submit annual reports to his or her IRB/IEC as appropriate.

8.5 Financial Disclosure and Obligations

Investigators are required to provide financial disclosure information to allow the sponsor to submit the complete and accurate certification or disclosure statements per regional requirements. In addition, the investigator must provide to the sponsor a commitment to promptly update this information if any relevant changes occur during the course of the investigation and for 1 year following the completion of the study.

Neither the sponsor nor CRO is financially responsible for further testing or treatment of any medical condition that may be detected during the Screening process. In addition, in the absence of specific arrangements, neither the sponsor nor CRO is financially responsible for further treatment of the patient's disease.

8.6 Investigator Documentation

Prior to beginning the study, the investigator will be asked to comply with ICH E6(R2) 8.2 and Title 21 of the Code of Federal Regulations (CFR) by providing the following essential documents, including but not limited to:

- IRB/IEC approval
- Original investigator-signed investigator agreement page of the protocol
- Curriculum vitae (CV) for the principal investigator and each sub-investigator listed on Form FDA 1572 or equivalent. Current licensure must be noted on the CV. The CV will be signed and dated by the principal investigators and sub-investigators at study start-up, indicating that they are accurate and current.
- Financial disclosure information to allow the sponsor to submit complete and accurate certification or disclosure statements required under 21 CFR 54. In addition, the investigators must provide to the sponsor a commitment to promptly update this information if any relevant changes occur during the course of the investigation and for 1 year after the completion of the study.
- IRB/IEC-approved informed consent, samples of study center advertisements for recruitment for this study, and any other written information regarding this study that is to be provided to the patient or legal guardian, and
- Laboratory certifications and normal ranges for any local laboratories used by the study center, in accordance with 42 CFR 493

8.7 Study Conduct

The investigator agrees that the study will be conducted according to the principles of ICH E6(R2). The investigator will conduct all aspects of this study in accordance with all national, state, and local laws or regulations. The analytical assays will be conducted according to the general principles of the Organization for Economic Cooperation and Development Principles of Good Laboratory Practices (GLP).

Prior to the study onset, the protocol, informed consent, advertisements to be used for patient recruitment and any other written information regarding this study to be provided to the patient or the patient’s legal guardian must be approved by the IRB/IEC. Documentation of

all IRB/IEC approvals and of the IRB/IEC compliance with the ICH E6(R2) guidelines will be maintained by the study center and will be available for review by the sponsor or its designee.

All IRB/IEC approvals will be signed by the IRB/IEC chairman or designee and must identify the IRB/IEC name and address, the clinical protocol by title and/or protocol number, and the date approval and/or favorable opinion was granted.

The principal investigator or designated sub-investigator is responsible for obtaining continued review of the clinical research at intervals not exceeding 1 year or otherwise specified by the IRB/IEC. The principal investigator or designated sub-investigator must supply the sponsor or its designee with written documentation of continued review of the clinical research.

8.8 Data Collection

8.8.1 Electronic Case Report Forms and Source Documents

It is the intent of this study to acquire study data via electronic format. As part of the responsibilities assumed by participating in the study, the principal investigator or sub-investigator agrees to maintain adequate case histories for the patients treated as part of the research under this protocol. The principal investigator or sub-investigator agrees to maintain source documentation (e.g., laboratory reports), enter patient data into the eCRF as accurately as possible, and respond to any reported discrepancies rapidly. These source documents may include laboratory reports, ECG strips, etc.

The analysis data sets will be a combination of these data and data from other sources (e.g., laboratory data).

An eCRF is accessed through the appropriate system, which allows for on-site data entry and data management. Study center users can read from and write to the sponsor’s database where the clinical data are collected. This provides immediate, direct data transfer to the database, as well as immediate detection of discrepancies, enabling study center coordinators to resolve and manage discrepancies in a timely manner.

Each study center staff involved with the study at each study center will have an individual logon and password that allow for record traceability. Thus, the system, and subsequently any

investigative reviews, can identify coordinators, investigators, and individuals who have entered or modified records.

8.9 Adherence to Protocol

The investigator agrees to conduct the study as outlined in this protocol in accordance with ICH E6(R2) and all applicable guidelines and regulations.

8.10 Adverse Events and Study Report Requirements

By participating in this study, the investigator agrees to submit reports of SAEs to the sponsor and/or IRB/IEC according to the timeline and method outlined in Section 6.3.1.4. In addition, the investigator agrees to submit annual reports to the study center IRB/IEC as appropriate.

8.11 Investigator's Final Report

Upon completion of the study, the investigator, where applicable, should inform the institution; the investigator/institution should provide the IRB/IEC with a summary of the study's outcome and the sponsor and regulatory authority(ies) with any reports required.

8.12 Records Retention

All correspondence (e.g., with sponsor, IRB/IEC, or clinical research associates) relating to this clinical study will be kept in appropriate file folders. Records of patients, source documents, eCRF, and drug inventory sheets pertaining to the study must be kept on file.

Essential documents should be retained until at least 15 years after the date on which the results of the study are submitted to the regulatory authorities in support of an allocation for a research or marketing permit, or completion date for study by approval or disapproval of any application, whichever is later. These documents should be retained for a longer period, however, if required by the applicable regulatory requirements or by an agreement with the sponsor. It is the responsibility of the sponsor to inform the investigator/institution as to when these documents no longer need to be retained.

If an investigator moves, withdraws from an investigation, or retires, the responsibility for maintaining the records may be transferred to another person, who will accept the responsibility. Notice of transfer must be made to and agreed upon by the sponsor.

8.13 Patient Identification Register

The investigator agrees to complete a patient identification register, which will be used for the purpose of long-term follow-up, if needed. This form will be treated as confidential and will be filed by the investigator in the Study Center Master File. Otherwise, all reports and communications relating to the study will identify patients by assigned number only.

8.14 Publications

After completion of the study, the data may be considered for reporting at a scientific meeting or for publication in a scientific journal. In these cases, the sponsor will be responsible for these activities and may work with the investigators to determine how the manuscript is written and edited, the number and order of authors based on SOPs of CELLTRION, Inc., the publication to which it will be submitted, and other related issues. The sponsor has final approval authority over all such issues.

Data are the property of the sponsor and cannot be published without prior authorization from the sponsor, but data and publication thereof will not be unduly withheld.

9 Study Management

9.1 Sponsor

[redacted]

9.2 Vendor Contact

[redacted]

SAE Reporting

[redacted]

The names and addresses of the investigators and clinical study centers involved in the study are presented separately together with the investigators' signatures.

9.3 Analytical Facilities

Any analytical facilities and procedures utilized for this study must be Good Laboratory Practice compliant. Details of analytical facilities are presented in the ICF.

9.4 Monitoring

9.4.1 Data Safety Monitoring Board

This study will be monitored by an independent DSMB consisting of a PK specialist, statistician, independent physician, and an independent chairing physician. The DSMB will review and evaluate accumulating safety data to ensure the safety of study patients.

Additionally, study results when the clinical study report (CSR) is available will be reviewed by the DSMB.

Further details will be provided in the independent DSMB charter.

9.4.2 Monitoring of the Study

The clinical monitor, as a representative of the sponsor, has the obligation to follow the study closely. In doing so, the monitor will visit the investigator and study center at periodic intervals or perform remote monitoring, in addition to maintaining necessary telephone and letter (or e-mail) contact. The monitor will maintain current personal knowledge of the study

through observation, review of study records and source documentation (on-site or remotely), and discussion of the conduct of the study with the investigator and staff.

All aspects of the study will be carefully monitored, by the sponsor or its designee, for compliance with applicable government regulation with respect to current ICH E6(R2) and current SOPs.

9.4.3 Inspection of Records

Investigators and institutions involved in the study will permit study-related monitoring, audits, IRB/IEC review, and regulatory inspections by providing direct access to all study records. In the event of an audit, the investigator agrees to allow the sponsor, representatives of the sponsor, or a regulatory agency access to all study records.

The investigator should promptly notify the sponsor and CRO of any audits scheduled by any regulatory authorities.

9.5 Management of Protocol Amendments and Deviations

9.5.1 Modification of the Protocol

Any changes in this research activity, except those necessary to remove an apparent, immediate hazard to the patient, must be reviewed and approved by the sponsor or its designee. Amendments to the protocol must be submitted in writing to the investigator's IRB/IEC for approval before patients are enrolled under an amended protocol. This will be fully documented.

The investigator must not implement any deviation from or change to the protocol without discussion and agreement from CELLTRION, Inc. or its designee, and prior review, documented approval, and favorable opinion of the amendment from the relevant IRB/IEC and/or regulatory authorities, except where it is necessary to eliminate an immediate hazard to patients or where the changes involve only logistical or administrative aspects of the clinical study. The eCRF and source documents will describe any departure from the protocol and the circumstances requiring it.

Protocol amendments will be submitted to the appropriate authorities as required by the applicable regulatory requirements.

9.5.2 Protocol Deviations

The investigator or designee must document and explain in the patient's source documentation any deviation from the approved protocol. The investigator may implement a deviation from, or a change of, the protocol to eliminate an immediate hazard to study patients without prior IRB/IEC approval. As soon as possible after such an occurrence, the implemented deviation or change, the reasons for it, and any proposed protocol amendments should be submitted to the IRB/IEC for review and approval, to the sponsor for agreement, and to the regulatory authorities, if required.

A deviation from the protocol is an unintended or unanticipated departure from the procedures or processes approved by the sponsor and the IRB/IEC and agreed to by the investigator. A major deviation occurs when there is non-adherence to the protocol by the patient or investigator that may results in a significant impact on the completeness, accuracy, reliability of study data or additional risk to the patient's rights, safety, and well-being. Major protocol deviations include the followings, and can lead to the patient being withdrawn from the study (Section 4.2) or exclusion from the statistical analysis (Section 7.2).

- Mis-randomization (defined as patients who received the opposite treatment to which they were assigned at any point during the study)
- Non-adherence to inclusion or exclusion criteria
- Significant ICH GCP non-compliance
- Receipt of prohibited medication or treatment

Protocol deviations will be documented by the clinical monitor throughout the course of monitoring visits. Deviations will be defined prior to unblinding. Principal investigators will be notified in writing by the monitor of deviations. The IRB/IEC should be notified of all protocol deviations in a timely manner.

9.6 Study Termination

Although CELLTRION, Inc. has every intention of completing the study, CELLTRION, Inc. reserves the right to discontinue the study at any time for clinical or administrative reasons.

The end of the study is defined as the date that the final database lock with no further database change for the final CSR.

9.7 Final Report

Whether the study is completed or prematurely terminated, the sponsor will ensure that the CSRs are prepared and provided to the regulatory agency(ies) as required by the applicable regulatory requirement(s). The sponsor will also ensure that the CSRs in marketing applications meet the standards of the ICH harmonised tripartite guideline E3: Structure and content of CSRs.

CELLTRION, Inc. plans to prepare 2 CSRs, but additional CSRs will be generated upon requirements for regulatory or academic purposes, including but not limited to the following:

- Data for each patient up to Week 28
- All data after completion of the study (up to Week 52)

10 References

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11 Appendices

11.1 Schedule of Events

Table 11-1 Schedule of Events

	Screening	Treatment Period I					Treatment Period II			EOS[1]
Visit Number		**1**	**2**	**3**	**4**	**5**	**6**	**7**	**8**	
Study Week	**–6**	**0**	**2**	**4**	**8**	**12[2]**	**16**	**28[3]**	**40**	**52**
Study Day	**–42 to –1**	**1**	**15**	**29**	**57**	**85**	**113**	**197**	**281**	**365**
Visit Window (days)[4]			**± 3**	**± 3**	**± 3**	**± 3**	**± 7**	**± 7**	**± 7**	**± 7**
Screening/Baseline assessments										
Informed consent	X									
Demographics, height	X									
Medical history	X									
Inclusion/exclusion criteria	X	X[11]								
% BSA involvement	X	X[11]								
Randomization[5]		X[11]					X[11]			
Hepatitis B[6]	X						(X[11])			(X)
Hepatitis C and HIV-1 & -2 test[7]	X									
Serum pregnancy test[8]	X									X
Chest X-ray[9]	X									
Interferon-γ release assay[10]	X						X[11]			
Study drug/Related assessments										
Study drug (CT-P43 or Stelara) administration[11]		X		X			X	X	X	
Hypersensitivity/injection site reactions monitoring[12]		X		X			X	X	X	
Local injection site pain by VAS[13]		X		X			X	X	X	
Efficacy assessments										

	Screening	Treatment Period I					Treatment Period II			EOS[1]
Visit Number		**1**	**2**	**3**	**4**	**5**	**6**	**7**	**8**	
Study Week	**–6**	**0**	**2**	**4**	**8**	**12[2]**	**16**	**28[3]**	**40**	**52**
Study Day	**–42 to –1**	**1**	**15**	**29**	**57**	**85**	**113**	**197**	**281**	**365**
Visit Window (days)[4]			**± 3**	**± 3**	**± 3**	**± 3**	**± 7**	**± 7**	**± 7**	**± 7**
Psoriasis Area Severity Index[14]	X	X[11]	X	X[11]	X	X	X[11]	X[11]	X[11]	X
Static Physician's Global Assessment[14]	X	X[11]	X	X[11]	X	X	X[11]	X[11]	X[11]	X
Dermatology Life Quality Index[15]		X[11]	X	X[11]	X	X	X[11]	X[11]	X[11]	X
Patient pain VAS for PsA[15]		X[11]				X	X[11]	X[11]		X
Patient Global Assessment VAS for PsA[15]		X[11]				X	X[11]	X[11]		X
PK/Immunogenicity/ Biomarker assessments										
Pharmacokinetic sampling[16]		X[11]		X[11]		X	X[11]	X[11]	X[11]	X
Immunogenicity sampling[17]		X[11]		X[11]		X	X[11]	X[11]	X[11]	X
Biomarker sampling[18]		X[11]								
Safety assessments										
Vital signs, body weight[19]	X	X[11]		X[11]	X	X	X[11]	X[11]	X[11]	X
Physical examination	X	X[11]		X[11]	X	X	X[11]	X[11]	X[11]	X
Urine pregnancy test[20]		X[11]		X[11]			X[11]	X[11]	X[11]	
Clinical laboratory tests[21]	X	X[11]		X[11]	X	X	X[11]	X[11]	X[11]	X
12-Lead ECG[22]	X					X		X		X
Prior, concomitant medications[23]	X									
Tuberculosis clinical monitoring[24]	X									
Adverse event monitoring[25]	X									

Abbreviations: BSA, body surface area; ECG, electrocardiogram; EOS, end-of-study; HIV, human immunodeficiency virus; ICF, informed consent form; IGRA, interferon- γ release assay; sPGA, static Physician's Global Assessment; PK, pharmacokinetic; PsA, psoriatic arthritis; TB, tuberculosis; VAS, visual analog scale.

Note: For all patients who discontinue study drug early, every effort should be made to have the patient continue in the study and complete regularly scheduled study visits. If a patient cannot or is unwilling to attend any visit(s), a safety follow-up (i.e., adverse events, concomitant medications) will be conducted by telephone according to the study visit schedule. If a patient discontinues study drug prior to Week 12, when the primary endpoint is assessed, they should return to the site at Week 12 for the primary efficacy endpoint assessment, even if they initiated psoriasis medication changes (including those prohibited by the protocol).

1. The End-of-Study (EOS) visit will be performed at the Week 52 visit for the patients who completed or discontinued study drug.
2. At Week 12, it is recommended that patients who achieve at least PASI 50 continue study drug administration in the Treatment period II in all groups.
3. At Week 28, it is recommended that patients who achieve at least PASI 75 continue further study drug administration in all groups.
4. A dose visit window of ±3 days is recommended up to and including Week 12 and a visit window of ±7 days is recommended thereafter, based on the baseline visit, including the EOS visit. If any study visit has to be rescheduled, subsequent visits should follow the original visit date scheduled.
5. Patients will be randomly assigned to receive CT-P43 (45 or 90 mg) or Stelara (45 or 90 mg) on Day 1 (Week 0) prior to the study drug administration. A second randomization will be performed at the Week 16 visit prior to the study drug administration. Patients in the Stelara group will be randomly assigned again to either continue Stelara or undergo transition to CT-P43 from Week 16. All patients who were initially randomly assigned to the CT-P43 group on Day 1 (Week 0) will continue their treatment with CT-P43.
6. At Screening, HBsAg, HBsAb, and HBcAb must be assessed in all patients (mandatory). If the HBsAg test result is positive, the patient must be excluded from the study. If a patient has HBsAg (negative), HBsAb (negative or positive), and HBcAb (positive), a HBV DNA test will be performed at Screening. If the HBV DNA test result is positive, the patient will be excluded from the study; if the HBV DNA test result is negative, the patient can be included in the study. For patients who are enrolled based on the HBV DNA test, testing of HBsAg, HBsAb, HBV DNA, aspartate aminotransferase, alanine aminotransferase, and total bilirubin will be performed at the Week 16 and EOS visits. If the patient develops hepatitis B reactivation, a study drug should be discontinued. Hepatitis B analysis will be performed at the central laboratory.
7. At Screening, hepatitis C antibody will be assessed in all patients. If the HCV test results is positive, HCV RNA will be performed at Screening. If the HCV RNA test result is negative, the patient can be included in the study at the investigator's discretion. Further evaluation for the patients who are enrolled based on HCV RNA test can be done depending on the investigator's discretion during the study. If the HIV test result is positive, the patient must be excluded from the study. Hepatitis C and HIV analysis will be performed at the central laboratory.
8. A serum pregnancy test for women of childbearing potential should be conducted at Screening and at the EOS visit. Patients who are of childbearing potential with only negative results from a serum pregnancy test can be enrolled. A serum pregnancy test will be performed at the central laboratory.
9. A chest X-ray (both posterior–anterior and lateral views) is not required at Screening if a chest X-ray from within 12 weeks prior to the first administration of the study drug (Day 1) is available.
10. The IGRA analysis will be performed at the central laboratory. No further IGRA testing is required during the treatment period for patients who have at least 1 positive IGRA result and have completed the country-specific TB prophylaxis. For patient who early discontinued study drug, IGRA test is unnecessary after the discontinuation.
11. For study drug administration visits, procedures will be performed prior to the study drug administration. Study drug will be administered by a predefined unblinded staff at the site during the study.
12. Additional vital signs including BP, pulse and respiratory rates, and body temperature (prior to the beginning of the study drug administration and 1 hour [±10 minutes] after the end of the study drug administration) will be monitored for possible hypersensitivity reactions. In addition, hypersensitivity will be monitored by routine continuous clinical monitoring, including patient-reported signs and symptoms. In case of hypersensitivity, emergency equipment, such as adrenaline, antihistamines, corticosteroids, and respiratory support including inhalational therapy, oxygen, and artificial ventilation must be available; in addition, any types of ECG can be performed. Hypersensitivity that may occur after the administration of the study drug will be monitored. If the patient experiences any of

hypersensitivity signs and symptoms outside study center, the patient can visit the study center for further assessment. Injection site reactions will be assessed 30 minutes (± 10 minutes) after the end of the study drug administration. For the patients who early discontinued study drug, monitoring of hypersensitivity/injection site reactions are unnecessary after the study drug discontinuation.

13. Local site pain by patient using 100 mm VAS will be assessed immediately (within 15 minutes) after the study drug administration. For patient who early discontinued study drug, this assessment is unnecessary after the discontinuation.
14. The investigator-reported outcomes assessments (i.e., PASI, sPGA) will be performed by a qualified efficacy assessor at the site. If possible, it is recommended that the same assessor perform the investigator-reported outcomes assessments throughout the entire study period.
15. The patient-reported outcomes/quality of life questionnaires should be completed by the patient prior to any of the other study-related assessments being performed, that is, physical examinations, blood sampling, and other efficacy evaluations, and study drug administration.
16. Blood samples for PK analysis will be collected at predose (prior to the beginning of study drug administration) except Week 12 and EOS at which the blood sample will be taken at any time. For patients who early discontinued the study drug, PK sampling will only be collected until the next scheduled dosing visit and further PK sampling is unnecessary. However, if a patient is discontinued the study drug at Week 40, PK sampling will be required at the EOS visit.
17. Serum samples for immunogenicity testing will be drawn at the same time as the clinical laboratory tests before dosing except Week 12 and EOS at which the sample will be taken at any time, where applicable. Additional serum samples for immunogenicity testing may be collected if a patient experiences immune-related AEs. Analysis will be performed at the central laboratory. For patient who early discontinued study drug, immunogenicity sampling will only be collected until the next scheduled dosing visit and further immunogenicity sampling is unnecessary. However, if a patient is discontinued the study drug at Week 40, immunogenicity sampling will be required at the EOS visit.
18. Only for patients who sign a separate ICF for the biomarker assessment, a blood sample for evaluation of any necessary genotypes will be collected prior to dosing on Day 1 (Week 0).
19. Vital signs (including systolic and diastolic BP, pulse and respiratory rates, and body temperature) will be measured after 5 minutes of rest (sitting). In addition, weight will be measured prior to study drug administration.
20. A urine pregnancy test for women of childbearing potential will be used to confirm that patients are not pregnant before the study drug administration on each visit date or more frequently if required by country-specific legislation. A urine pregnancy test will be performed locally. If a urine pregnancy test result is positive, a confirmatory serum pregnancy test will be performed at the central laboratory. For patient who early discontinued study drug, urine pregnancy test is unnecessary after the discontinuation.
21. Clinical laboratory (clinical chemistry, hematology, and urinalysis) test samples will be analyzed at the central laboratory.

Clinical chemistry	Total protein, serum bilirubin (total and direct), alanine aminotransferase, aspartate aminotransferase, alkaline phosphatase, γ-glutamyltransferase, blood urea nitrogen, creatinine, albumin, sodium, potassium, calcium, chloride, inorganic phosphorus, glucose, lactate dehydrogenase, total cholesterol, triglyceride, high-density lipoprotein cholesterol, C reactive protein, and uric acid
Hematology	Red blood cells, total and differential white blood cell count, absolute neutrophil count, platelet count, hemoglobin, and hematocrit
Urinalysis	Bilirubin, blood, glucose, ketones, leukocytes, nitrite, pH, protein, specific gravity, and urobilinogen

22. All scheduled 12-lead ECGs must be performed locally after the patient has rested quietly for at least 5 minutes in the supine position. Regardless of the 12-lead ECG result, further cardiological evaluation can be conducted at the investigator's discretion.
23. Use of all prior and concomitant medications and/or therapies for the treatment of psoriasis and the systemic agents that could affect psoriasis, from the diagnosis of disease until the EOS visit, will be recorded in both the source documents and the eCRF. Use of all medications for other purposes, taken from 42 days prior to the first administration of study drug will be recorded until the EOS visit in both the source documents and the eCRF.
24. Throughout the study, patients will be monitored for the clinical signs and symptoms of TB. An additional IGRA or chest X-ray can be performed at the investigator's discretion based on the judgment per the signs and symptoms of TB monitoring. The investigator will confirm the absence of active TB prior to the subsequent dose

administration.

25. Adverse events will be assessed from the date the informed consent form is signed until up to EOS visit, regardless of the relationship to the study drug. After the EOS visit, serious adverse drug reaction will be reported to CELLTRION, Inc. or its designee.

*If a study center is not equipped to perform the specified tests, this will be discussed and arranged with the sponsor or the sponsor's designee

11.2 Psoriasis Area and Severity Index (PASI)

The Psoriasis Area and Severity Index (PASI) is a quantitative rating score for measuring the severity of psoriatic lesions based on area coverage and plaque appearance.

Plaque characteristic	Lesion score	Head	Upper Limbs	Trunk	Lower Limbs
Erythema	0 = None 1 = Slight 2 = Moderate 3 = Severe 4 = Very severe				
Induration/Thickness					
Scaling					
Add together each of the 3 scores for each body region to give 4 separate sums (A).					
Lesion Score Sum (A)					

Percentage area affected	Area score	Head	Upper Limbs	Trunk	Lower Limbs
Area Score (B) *Degree of involvement as a percentage for each body region affected (score each region with score between 0-6)*	0 = 0% 1 = 1% - 9% 2 = 10% - 29% 3 = 30% - 49% 4 = 50% - 69% 5 = 70% - 89% 6 = 90% - 100%				
Multiply Lesion Score Sum (A) by Area Score (B), for each body region, to give 4 individual subtotals (C).					
Subtotals (C)					
Multiply each of the Subtotals (C) by amount of body surface area represented by that region, i.e. x 0.1 for head, x 0.2 for upper limbs, x 0.3 for trunk, and x 0.4 for lower limbs.					
Body Surface Area		x 0.1	x 0.2	x 0.3	x 0.4
Totals (D)					
Add together each of the scores for each body region to give the final PASI Score.					

PASI Score = ☐

11.3 Static Physician's Global Assessment (sPGA)

The sPGA is is a 5-point score ranging from 0 to 4, based on the physician's assessment of the erythema, average thickness, and scaling of all psoriatic lesions at a given time point. The sum of the 3 scales will be divided by 3 to obtain a final sPGA score. A lower score indicates less body coverage, with 0 being clear and 1 being almost clear.

Erythema (averaged over all lesions)

0 = Normal (post-inflammatory hyper/hypopigmentation may be present)
1 = Faint, diffuse pink or slight red coloration
2 = Mild (light red coloration)
3 = Definite red coloration (Dull to bright red)
4 = Bright to Deep red coloration of lesions

Induration (averaged over all lesions)

0 = None
1 = Just detectable (slight elevation above normal skin)
2 = Mild thickening (slight but definite elevation, typically edges are indistinct or sloped)
3 = Clearly distinguishable to moderate thickening (marked definite elevation with rough or sloped edges)
4 = Severe thickening with hard edges (marked elevation typically with hard or sharp edges)

Scaling (averaged over all lesions)

0 = No scaling
1 = Minimal focal scaling (surface dryness with some desquamation)
2 = Predominately fine scaling (fine scale partially or mostly covering lesions)
3 = Moderate scaling (coarser scale covering most or all of the lesions)
4 = Severe /coarse scaling covering almost all or all lesions (coarse, non-tenacious scale predominates)

Scoring

Clear	0 = 0 = for all three
Almost clear	1 = mean >0, <1.5
Mild	2 = mean >= 1.5, <2.5
Moderate	3 = mean >= 2.5, <3.5
Severe	4 = mean >= 3.5

11.4 Dermatology Life Quality Index (DLQI)

DERMATOLOGY LIFE QUALITY INDEX

DLQI

Hospital No: Date:
Name: Score:
Address: Diagnosis:

The aim of this questionnaire is to measure how much your skin problem has affected your life OVER THE LAST WEEK. Please tick one box for each question.

1.	Over the last week, how **itchy, sore, painful** or **stinging** has your skin been?	Very much A lot A little Not at all	☐ ☐ ☐ ☐	
2.	Over the last week, how **embarrassed** or **self conscious** have you been because of your skin?	Very much A lot A little Not at all	☐ ☐ ☐ ☐	
3.	Over the last week, how much has your skin interfered with you going **shopping** or looking after your **home** or **garden**?	Very much A lot A little Not at all	☐ ☐ ☐ ☐	 Not relevant ☐
4.	Over the last week, how much has your skin influenced the **clothes** you wear?	Very much A lot A little Not at all	☐ ☐ ☐ ☐	 Not relevant ☐
5.	Over the last week, how much has your skin affected any **social** or **leisure** activities?	Very much A lot A little Not at all	☐ ☐ ☐ ☐	 Not relevant ☐
6.	Over the last week, how much has your skin made it difficult for you to do any **sport**?	Very much A lot A little Not at all	☐ ☐ ☐ ☐	 Not relevant ☐
7.	Over the last week, has your skin prevented you from **working** or **studying**?	Yes No	☐ ☐	 Not relevant ☐
	If "No", over the last week how much has your skin been a problem at **work** or **studying**?	A lot A little Not at all	☐ ☐ ☐	
8.	Over the last week, how much has your skin created problems with your **partner** or any of your **close friends** or **relatives**?	Very much A lot A little Not at all	☐ ☐ ☐ ☐	 Not relevant ☐
9.	Over the last week, how much has your skin caused any **sexual difficulties**?	Very much A lot A little Not at all	☐ ☐ ☐ ☐	 Not relevant ☐
10.	Over the last week, how much of a problem has the **treatment** for your skin been, for example by making your home messy, or by taking up time?	Very much A lot A little Not at all	☐ ☐ ☐ ☐	 Not relevant ☐

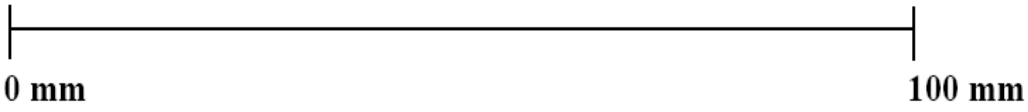
Please check you have answered EVERY question. Thank you.

11.5 Patient Pain Visual Analog Scale for Psoriatic Arthritis

Instructions:

Consider the following question: How much pain have you had because of your psoriatic arthritis in the past week?

Place a vertical (|) mark on the line to indicate the severity of the pain.



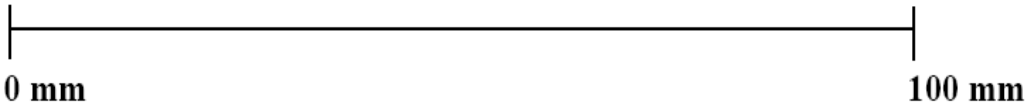
No pain Most severe pain

11.6 Patient Global Assessment Visual Analog Scale for Psoriatic Arthritis

Instructions:

Think about the following question: Considering all the ways your psoriatic arthritis affects you, how would you rate the condition you felt over the past week?

Place a vertical (|) mark on the line to indicate how you felt.

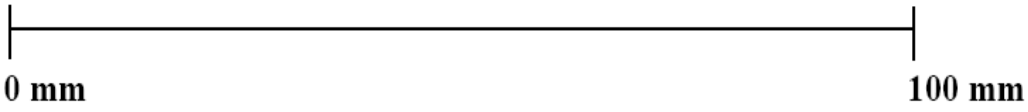


0 mm **100 mm**

Very well Very poor

11.7 Patient's Assessment Visual Analog Scale of Local Site Pain

Patient assessment of local site pain is measured by the patient indicating the extent of their current pain by marking one line (|) through the 100-mm line (0 mm equals no pain and 100 mm equals most severe pain). The length of the line is measured from the left (in mm) and the value (in mm) recorded in the patient's eCRF.



No pain Most severe pain