Clinical Study Protocol

A Phase III, Randomised, Double-blind, Multicentre Clinical Study to Evaluate the Efficacy, Safety, Tolerability, Pharmacokinetics, and Immunogenicity of SB17 (proposed ustekinumab biosimilar) Compared to Stelara® in Subjects with Moderate to Severe Plaque Psoriasis

Product	SB17 (proposed ustekinumab biosimilar)	
EudraCT Number	2020-006115-19	
US IND Number (if applicable)	N/A	
Protocol Number	SB17-3001	
Study Phase	Phase III	
Version and Effective Date	Version 2.0	Feb 15, 2021
	Version 1.0	Dec 30, 2020
Sponsor	Samsung Bioepis Co., Ltd 76, Songdogyoyuk-ro, Yeonsu-gu, Incheon, 21987 Republic of Korea	

SYNOPSIS

Name of Sponsor/Company:	Samsung Bioepis Co., Ltd.
Name of Finished Product:	SB17 (proposed ustekinumab biosimilar)
Name of Active Ingredient:	Ustekinumab

Title of Study:

A Phase III, randomised, double-blind, multicentre clinical study to evaluate the efficacy, safety, tolerability, pharmacokinetics, and immunogenicity of SB17 (proposed ustekinumab biosimilar) compared to Stelara® in subjects with moderate to severe plaque psoriasis

Protocol No:	SB17-3001	**Phase:**	III
Investigator sites:	Approximately 70 Investigator sites globally		

Planned Study Period: Approximately 56 weeks

Screening period will be 4 weeks. SB17 or Stelara® will be administered up to Week 40, and the last assessment will be done at Week 52.

Objectives:

Primary Objective

The primary objective is to demonstrate the equivalence of SB17 to Stelara®, in terms of the percent change from baseline in Psoriasis Area and Severity Index (PASI) at Week 12 in subjects with moderate to severe plaque psoriasis

Secondary Objective(s)

The secondary objectives are:

- To evaluate the efficacy of SB17 compared to Stelara®
  - Percent change from baseline in PASI other than Week 12
  - Physician's Global Assessment (PGA)
  - PASI50, PASI75, and PASI90 response rate
  - Change from baseline in Dermatology Life Quality Index (DLQI)
- To evaluate safety and tolerability of SB17 compared to Stelara®
- To evaluate the pharmacokinetics (PK) of SB17 compared to Stelara® in subjects participating in PK evaluation
- To evaluate the immunogenicity of SB17 compared to Stelara®
- To evaluate safety and immunogenicity in subjects who transitioned to SB17 and who maintained Stelara® at Week 28 for the transition period

Study Design:

This is a randomised, double-blind, multicentre clinical study to evaluate the efficacy, safety, tolerability, PK, and immunogenicity of SB17 compared to Stelara® in subjects with moderate to severe plaque psoriasis.

Subjects will be randomised in a 1:1 ratio to receive either SB17 or Stelara® via subcutaneous injection. Investigational products (IPs) (SB17 or Stelara®) will be administered at Week 0, 4, and then every 12 weeks up to Week 40, and the last assessment will be done at Week 52.

Name of Sponsor/Company:	Samsung Bioepis Co., Ltd.
Name of Finished Product:	SB17 (proposed ustekinumab biosimilar)
Name of Active Ingredient:	Ustekinumab

At Week 28, subjects who achieved a PASI50 response and are considered eligible will enter the transition period. In the transition period, subjects receiving Stelara® will be randomised again in a 1:1 ratio to either continue on Stelara® (Stelara®/Stelara®) or be transitioned to SB17 (Stelara®/SB17), up to Week 40. Subjects receiving SB17 will continue to receive SB17 up to Week 40 but they will follow the randomisation procedure in order to maintain blinding.

Number of Subjects:

Sufficient subjects will be screened so that approximately 464 subjects will be randomised in the study.

Target Population:

Moderate to severe plaque psoriasis indicated for systemic therapy for psoriasis

Eligibility Criteria for Main Period:

Inclusion Criteria

Subjects must meet all of the following criteria to be eligible for the study:

1. Aged 18 years or older at Screening (defined as the time of signing the informed consent form [ICF]).
2. Have plaque psoriasis diagnosed at least 6 months prior to Screening, with or without psoriatic arthritis.
3. Have plaque psoriasis at Screening and Randomisation with the involvement and severity defined as the following:
    a. Total affected body surface area (BSA) ≥ 10%.
    b. PASI score of ≥ 12.
    c. PGA score of ≥ 3 (moderate).
4. Considered to be a candidate for phototherapy or systemic therapy for psoriasis at Screening.
5. Be less than 95 kg of body weight at Screening and at Randomisation.
6. Adequate haematological function at Screening defined as the following by central lab:
    a. White blood cell count ≥ 3.5×10^3 cells/μL (≥ 3.5×10^9 cells/L).
    b. Neutrophil count ≥ 1.5×10^3 cells/μL (≥ 1.5×10^9 cells/L).
    c. Haemoglobin ≥ 10 g/dL.
    d. Platelet count ≥ 125,000/mm^3 (≥ 125×10^9/L).
7. Adequate renal and hepatic function at Screening defined as the following by central lab:
    a. Serum creatinine < 1.5 × upper limit of normal (ULN).
    b. Serum alanine transaminase (ALT) and aspartate transaminase (AST) < 2 × ULN.
8. Non-childbearing potential female (e.g., permanently sterilised, postmenopausal [defined as amenorrhea of at least 12 months without an alternative medical cause prior to Screening and a follicle stimulating hormone (FSH) level of > 40 IU/L at Screening]), OR childbearing potential

Name of Sponsor/Company:	Samsung Bioepis Co., Ltd.
Name of Finished Product:	SB17 (proposed ustekinumab biosimilar)
Name of Active Ingredient:	Ustekinumab

female subjects or male subjects with their (respectively male or childbearing female) partners who agree to use at least two forms of appropriate contraception method (e.g., established use of oral, injected, intravaginal, transdermal, or implanted hormonal contraceptive, placement of an intrauterine device or intrauterine hormone-releasing system, physical barrier [Note: female condom and male condom should not be used together]) from Screening until 15 weeks after the last dose of IP. Vasectomy alone will be allowed for male subjects and female subjects of childbearing potential with a sole vasectomised male partner. Vasectomised subjects or partners should be medically confirmed for sterilisation. True abstinence alone will be allowed if this is in line with the preferred and usual lifestyle of the subject, or for subjects who do not have a partner.

9. Have provided informed consent and must be able to, in the opinion of the Investigator, understand the implications of taking part in the study and be willing to follow the study requirements.

Exclusion Criteria

Subjects meeting any of the following criteria are not eligible for the study:

1. Have nonplaque forms of psoriasis, including erythrodermic, pustular, guttate, or drug-induced psoriasis at Screening.
2. Have other skin disease than psoriasis that:
    a. Requires topical or systemic corticosteroid or other immunosuppressive therapy at Screening.
    b. May confound the efficacy evaluation per Investigator discretion at Screening.
3. Have used biologics (any therapeutic monoclonal antibody or fusion receptor protein) such as;
    a. Any tumour necrosis factor (TNF) inhibitors within the previous 6 months prior to Randomisation.
    b. Any interleukin (IL)-12 or IL-23 inhibitor biologics (including ustekinumab/ustekinumab biosimilars, guselkumab, tildrakizumab, or rizankizumab), IL-17 inhibitor (including secukinumab, ixekizumab, or brodalumab), rituximab, or integrin inhibitor biologics at any time prior to Randomisation.
    c. Other biologics within the longer of either 5 half-lives or 3 months prior to Randomisation.
4. Known allergic reactions or hypersensitivity to ustekinumab or to any ingredients of Stelara® or SB17 at Screening.
5. History of a systemic allergic reaction or hypersensitivity to prior biologic therapies at Screening.
6. History of asthma that:
    a. Required intubation at any time prior to Screening.
    b. Required hospitalisation or 14 days or more of oral corticosteroids use (cumulatively) within 6 months prior to Randomisation.
    c. Requires oral corticosteroids or considered to be corticosteroid-dependent in the opinion of the Investigator at Randomisation.
7. History of exfoliative dermatitis, Reversible Posterior Leukoencephalopathy Syndrome (RPLS), facial palsy, allergic alveolitis, or non-infectious pneumonia including interstitial pneumonia,

Name of Sponsor/Company:	Samsung Bioepis Co., Ltd.
Name of Finished Product:	SB17 (proposed ustekinumab biosimilar)
Name of Active Ingredient:	Ustekinumab

cryptogenic organizing pneumonia, or eosinophilic pneumonia, etc. at Screening.

8. Have received phototherapy (including ultraviolet B [UVB], psoralen and ultraviolet A [PUVA], or sunbaths/tanning beds, etc.) or conventional systemic therapy (including corticosteroids, methotrexate [MTX], calcineurin inhibitors, retinoids, vitamin D analogues, fumaric acid esters, apremilast, 6-thioguanine, hydroxyurea, etc.) for psoriasis within 4 weeks prior to Randomisation.
9. Have received topical therapy for psoriasis (including corticosteroids, vitamin D analogues, retinoids, calcineurin inhibitors, coal tar, anthralin, urea, alpha-hydroxy acid, or salicylic acid, etc.) within 2 weeks prior to Randomisation.
10. Have received any disease-modifying anti-rheumatic drugs (DMARDs), any systemic immunosuppressants (including those mentioned above in systemic psoriasis therapy, antimalarials, sulfasalazine, Janus kinase [JAK] inhibitors, gold, minocycline, azathioprine, 6-mercaptopurine, mycophenolate mofetil, etc.) or any other injectable or enema corticosteroids, within 4 weeks prior to Randomisation (except for leflunomide: within 12 weeks from Randomisation).
11. Have received non-biologic IP from another study within 5 half-lives of that product prior to Randomisation or use of an investigational device at Randomisation.
12. Women who are pregnant or nursing at Screening, or men and women planning pregnancy during the study period and until 15 weeks after the last dose of IP.
13. Have received a live or live attenuated viral vaccine or a live bacterial vaccine (except Bacille Calmette-Guerin [BCG] vaccination) within 4 weeks prior to Randomisation or plan to do so within 15 weeks after the last dose of IP. For BCG vaccination, subjects who have received BCG within 12 months prior to Randomisation or plan to do so within 12 months after the last dose of IP.
14. Have active or latent tuberculosis (TB) at Screening, by known history or any of the following:
    a. Positive QuantiFERON®-Gold Plus test.
    b. Positive chest X-ray findings (radiographs taken within 3 months prior to Randomisation with radiologist confirmation will be accepted) determined by a qualified physician such as radiologist or pulmonologist, including active TB, untreated or inadequately treated old, inactive or healed TB.
    c. By any other positive findings determined by TB specialist, including suggestive signs or symptoms of TB or recent close contact with active TB patients.
15. History of ongoing infection or a positive test of hepatitis B virus (HBV, defined as hepatitis B surface antigen [HBsAg] positive or HBsAg negative and hepatitis B core antibody [HBcAb] positive), hepatitis C virus (HCV; for subjects who have previously received anti-HCV treatment must have a sustained virologic response [SVR] for at least 24 weeks post-treatment and no evidence of significant liver fibrosis [i.e., must be METAVIR F0 or F1] in addition to negative HCV-ribonucleic acid (RNA) at Screening to be eligible), or human immunodeficiency virus (HIV) infection, or any history of primary immunodeficiency at Screening.
16. History of sepsis (defined as a life-threatening organ dysfunction caused by infection), chronic or recurrent infection, conditions that require regular antibiotic prophylaxis (such as rheumatic heart disease), opportunistic, granulomatous (for TB, please see above), or invasive fungal infection at Screening.

Name of Sponsor/Company:	Samsung Bioepis Co., Ltd.
Name of Finished Product:	SB17 (proposed ustekinumab biosimilar)
Name of Active Ingredient:	Ustekinumab

17. History of other bacterial, fungal, viral, parasitic, or helminthic infection requiring oral antimicrobial within 2 weeks prior to Randomisation or a serious infection (a bacterial, fungal, viral, parasitic, or helminthic infection that requires hospitalisation or treatment with parenteral antimicrobials) within 8 weeks prior to Randomisation. Other mild infections should be resolved before Randomisation. For Coronavirus Disease 2019 (COVID-19), please see below.
18. History of lymphoproliferative disease or leukaemia at Screening.
19. History of malignancy (except for squamous or basal cell carcinoma of the skin that has been treated and not recurred within 3 months prior to Screening, or surgically treated cervical carcinoma *in situ*) within the last 5 years prior to Screening.
20. History of myocardial infarction, New York Heart Association (NYHA) III/IV congestive heart failure, or stroke within 12 months prior to Randomisation.
21. Have uncontrolled hypertension (defined as systolic blood pressure [SBP] ≥ 160 mmHg or diastolic blood pressure [DBP] ≥ 100 mmHg confirmed after repeat measurement) at Screening.
22. Have uncontrolled diabetes mellitus (defined as having history of diabetic peripheral neuropathy or diabetic foot, or otherwise considered uncontrolled in the opinion of the Investigator) at Screening.
23. History of organ transplantation at Screening.
24. Evidence of alcohol or substance abuse within the last 12 months prior to Screening.
25. History of a major surgery in the opinion of the Investigator within 12 weeks prior to Randomisation or have a plan to do so during the study period.
26. Have psychiatric disease at Screening defined as:
    a. Current uncontrolled mental disorder (including depression) in the opinion of the Investigator.
    b. History of suicidal attempts or ideation.
    c. Considered to be at risk of suicide in the opinion of the Investigator.
27. Have other major organ dysfunction or failure such as liver cirrhosis, dialysis-dependent renal failure, any cardiopulmonary disease with functional disability of NYHA III/IV equivalent, aplastic anaemia or any other transfusion-dependent/stimulating factor dependent haematological disorders, or dementia at Screening.
28. Considered to be at risk of progressive weight gain or widely fluctuating body weight, in the opinion of the Investigator, at Screening.
29. History of COVID-19 as:
    a. History of asymptomatic, mild or moderate COVID-19 within 8 weeks prior to Randomisation.
    b. Any history of severe or critical COVID-19, or hospitalisation due to COVID-19 at Randomisation.
    c. Any history of COVID-19 complications or sequalae including lung fibrosis, thromboembolism, cardiac, gastrointestinal, neuropsychiatric, ‘long COVID’, or

Name of Sponsor/Company:	Samsung Bioepis Co., Ltd.
Name of Finished Product:	SB17 (proposed ustekinumab biosimilar)
Name of Active Ingredient:	Ustekinumab

dermatologic manifestations, etc. at Randomisation.

Note: COVID-19 severity grade is according to World Health Organization (WHO) COVID-19 disease severity classification. Subjects who have suggestive signs or symptoms of COVID-19 must be evaluated and determined to be COVID-19 negative per local regulations before Screening.

30. Have any other disease or disorder, that will put the subject at risk if they are enrolled, in the opinion of the Investigator, at Screening.
31. Have poor venous access or unwillingness to undergo multiple venepuncture and blood sampling at Screening.

Eligibility Criteria for Transition Period:

Inclusion Criteria

1. Achieve PASI50 response on Week 28 visit assessment.
2. Willing to participate in the rest of study and able to follow the study procedure with the opinion of the Investigator.

Exclusion Criteria

1. Subject is considered to be of increased risk when entered in the Transition Period, in the opinion of the Investigator.

Investigational Products:

- Name: SB17 (proposed ustekinumab biosimilar) or European Union (EU) sourced Stelara®
- Formulation: 0.5 mL of 90 mg/mL solution of ustekinumab in a pre-filled syringe (PFS)
- Route of administration: Subcutaneous injection in abdomen, upper thighs, or upper arm
- Injection volume: 0.5 mL
- Dose regimen: 45 mg at Week 0, 4, and then every 12 weeks up to Week 40. If the subject becomes > 100 kg at subsequent dosing visits the subject will receive 90 mg in the form of two doses of 45 mg.

Main Criteria for Evaluation

Primary Endpoint

- Percent change from baseline in PASI at Week 12

Secondary Endpoints

The secondary efficacy endpoints are:

- PGA at Week 2, 4, 8, 12, 16, 20, 24, 28, 40, and 52
- PASI50, PASI75, and PASI90 response rate at Week 2, 4, 8, 12, 16, 20, 24, 28, 40, and 52
- Percent change from baseline in PASI at Week 2, 4, 8, 16, 20, 24, 28, 40, and 52

Name of Sponsor/Company:	Samsung Bioepis Co., Ltd.
Name of Finished Product:	SB17 (proposed ustekinumab biosimilar)
Name of Active Ingredient:	Ustekinumab

- Change from baseline in DLQI at Week 4, 12, 16, 28, 40, and 52

The safety endpoints are:

- Incidence of adverse events (AEs)
- Incidence of serious AEs (SAEs)
- Changes in vital signs and clinical laboratory parameters

The PK endpoints are:

- Serum ustekinumab concentration at Week 0, 2, 4, 8, 12, 16, and 28

The immunogenicity endpoints are:

- Incidence of anti-drug antibodies (ADAs) at Week 0, 4, 8, 12, 16, 28, 40, and 52
- Incidence of neutralising antibodies (NAbs) at Week 0, 4, 8, 12, 16, 28, 40, and 52

Statistical Methods

Analysis Sets for Efficacy Analyses

Full Analysis Set (FAS) consists of all subjects who are randomised. Following the intent-to-treat principle, subjects will be analysed according to the treatment group they are assigned to at Randomisation. However, subjects who do not have any efficacy assessment result after randomisation or do not receive IP during the study period will be excluded from FAS.

Per-Protocol Set (PPS) consists of all FAS subjects who weight ≤ 100 kg and received 45 mg IP at Week 0 and Week 4 and have PASI assessment result at Baseline and Week 12 without any major protocol deviations (PDs) that have impact on primary efficacy assessment. Major PDs that will lead to exclusion from this set will be pre-defined prior to unblinding the treatment group assignment for analyses.

Efficacy Analyses

The primary efficacy analysis will aim to demonstrate equivalence in terms of percent change from baseline in PASI at Week 12 between SB17 and EU sourced Stelara®.

Equivalence between the two treatment groups will be declared if the 95% confidence interval (CI) of the mean difference is entirely contained within the pre-defined equivalence margin of [-15%, 15%]. The 95% CI of the mean difference between the two treatment groups in relation to the percent change from baseline in PASI will be estimated for the both PPS and FAS.

Additionally, the 90% CI of the mean difference between the two treatment groups will be estimated for both FAS and PPS with a narrower pre-defined equivalence margin of [-10%, 10%] as a sensitivity analysis. For those subjects who drop out of the study prematurely, a multiple imputation will be used with the assumption of monotone missing pattern and regression method for FAS under the missing at random assumption. Complete case analysis will also be performed for FAS.

As the secondary efficacy endpoints, PGA, PASI50, PASI75, PASI90 response rate, percentage change from baseline in PASI, and change from baseline in DLQI will be summarised by treatment group and visit for the FAS and PPS.

Safety Analyses

Name of Sponsor/Company:	Samsung Bioepis Co., Ltd.
Name of Finished Product:	SB17 (proposed ustekinumab biosimilar)
Name of Active Ingredient:	Ustekinumab

All reported terms for AEs will be coded using the Medical Dictionary for Regulatory Activities (MedDRA). All AEs, including SAEs, will be summarised descriptively by treatment group. No statistical test will be performed for AEs.

A treatment-emergent AE (TEAE) will be defined as any AE with an onset date on or after the date of first dose of IP. AEs which are conditions or findings already present during the pre-treatment period but increase in severity during the treatment period will be considered as treatment-emergent. Pre-existing AEs before the treatment period with no increase in severity during the treatment period will not be considered as treatment-emergent.

All AEs, TEAEs, SAEs, AEs of special interest (AESIs), and other AEs will be summarised by the number and percentage of subjects experiencing events by system organ class, preferred term, causality, and severity. All AEs including those existing during the pre-treatment period will be listed by subject. COVID-19 related AEs and SAEs in COVID-19 infected subjects will be summarised by treatment group to determine possible causal relationship with the IP, if needed.

Changes in vital signs and clinical laboratory measurements parameters will be summarised descriptively by treatment group and visit. Other safety variables will be summarised descriptively by treatment group and visit and listed.

PK Analyses

Descriptive statistics will be used to summarise serum drug concentration by treatment group and visit and listed for the PK Analysis Set (PKS).

Immunogenicity Analyses

The incidence of ADAs and NAbs will be summarised by treatment group and visit and listed.

Sample Size Calculation

Approximately 464 subjects will be randomised into the study with a 1:1 ratio.

A statistical equivalence margin is obtained by fixed-effects meta-analysis of five randomised controlled studies of ustekinumab, which estimates a risk difference of CCI with a CCI An equivalence limit of CCI is statistically calculated to preserve CCI of the effect of ustekinumab over and above placebo, but a clinical equivalence margin of [-15%, 15%] was set for the comparison with the 95% CI of the mean difference in the percent change from baseline in PASI at Week 12.

Based on this equivalence margin, a sample size of 192 subjects per treatment group was calculated with the assumptions of common standard deviation (SD) of 31.11, 10% loss from the primary analysis and approximately 100 remainders per treatment group after transition at the overall 5% significance level, providing over 90% power. Overall 464 subjects (232 per treatment group) will be randomised into the study to determine equivalence of percent change from baseline in PASI at Week 12.

The equivalence margin for the comparison with the 90% CI of the difference in the percent change from baseline in PASI at Week 12 will be [-10%, 10%] by the agency recommendation.

Based on this equivalence margin, a sample size of 169 subjects per treatment group was calculated with the assumption of the common SD of 31.11 at the overall 10% significance level, providing 80% power. Overall 338 subjects (169 per treatment group) will be randomised into the study to determine equivalence of percent change from baseline in PASI at Week 12.

Therefore, the sample size of 464 allows enough power to detect the equivalence in both situations.

GRAPHICAL STUDY DESIGN AND SCHEDULE OF ACTIVITIES

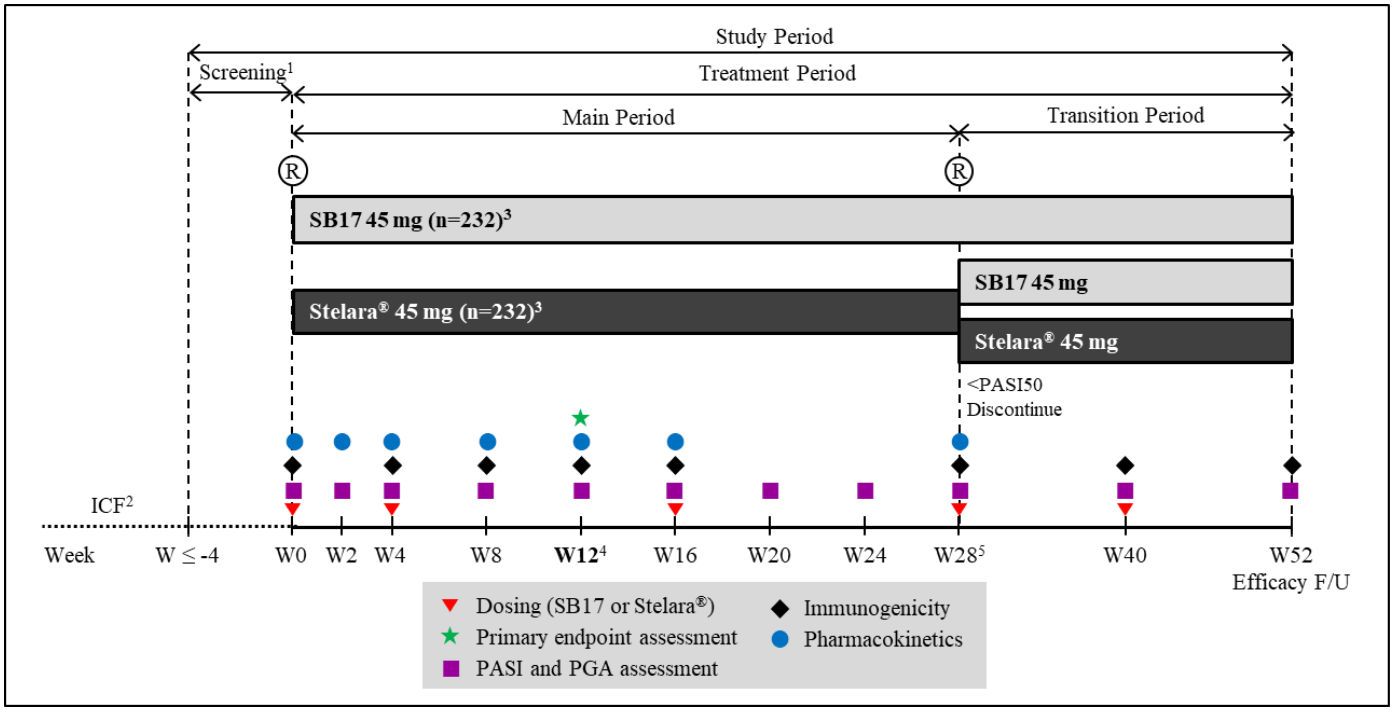

Figure 1. Graphical Study Design

F/U = Follow-up; ICF = Informed Consent Form; PASI = Psoriasis Area and Severity Index; PGA = Physician's Global Assessment; ® = Randomisation

1. Screening will be done within 4 weeks prior to Randomisation.
2. Informed consent should be obtained prior to any study related procedures.
3. SB17 or Stelara® 45mg at Week 0, 4, and then every 12 weeks up to Week 40. If the subject becomes > 100 kg at subsequent dosing visits the subject will receive 90 mg in the form of two doses of 45 mg.
4. The primary endpoint (percent change from baseline in PASI) is assessed at Week 12.
5. At Week 28 subjects who achieved a PASI50 response and are considered eligible will enter the transition period. Subjects receiving Stelara® will be randomised in a 1:1 ratio to either continue to receive Stelara® or be transitioned to SB17. Subjects receiving SB17 will continue to receive SB17 up to Week 40, but they will also follow the randomisation procedure in order to maintain blinding.

Table 1. Schedule of Activities

Assessment	Screening	Treatment Period										
Visit	**0**	**1**	**2**	**3**	**4**	**5**	**6**	**7**	**8**	**9**	**10**	**11 or ET[16]**
Day (± Visit Window)	**−28 to −1**	**1**	**15 (±3)**	**29 (±3)**	**57 (±3)**	**85 (±3)**	**113 (±5)**	**141 (±5)**	**169 (±5)**	**197 (± 5)**	**281 (±7)**	**365 (±7)**
Week	**−4 to 0**	**0**	**2**	**4**	**8**	**12**	**16**	**20**	**24**	**28**	**40**	**52**
Written informed consent[1]	✓											
Demographic information	✓											
Medical and surgical history[2]	✓											
Psoriasis BSA involvement (%)	✓	✓										
Physical examination[3]	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓
Height and weight[4]	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓
12-lead ECG	✓											
Vital signs[5]	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓
Chest X-ray	✓											
TB evaluation[6]	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓
Assessment of eligibility	✓	✓								✓		
Randomisation		✓								✓[15]		
IP administration		✓		✓			✓			✓	✓	
Previous and concomitant medications[7]	Continuously											
AE monitoring[8]	Continuously											
EFFICACY ASSESSMENTS												
PASI	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓
PGA	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓
DLQI		✓		✓		✓	✓			✓	✓	✓
LABORATORY ASSESSMENTS												
Virology screen[9]	✓											
QuantiFERON®-Gold Plus test[10]	✓											
Pregnancy test and FSH test[11]	✓	✓		✓			✓			✓	✓	✓
Clinical laboratory test[12]	✓	✓		✓		✓	✓			✓	✓	✓
PK assessment[13]		✓	✓	✓	✓	✓	✓			✓		
Immunogenicity assessment[14]		✓		✓	✓	✓	✓			✓	✓	✓

AE = Adverse event; BSA = Body surface area; DLQI = Dermatology Life Quality Index; ECG = Electrocardiogram; ET = Early termination; FSH = Follicle stimulating hormone; IP =

Investigational product; PASI = Psoriasis Area and Severity Index; PGA = Physician's Global Assessment; PK = Pharmacokinetic(s); TB = Tuberculosis

1. Informed consent must be obtained prior to any study related procedures.
2. Medical history includes menopausal status, clinically significant diseases, surgical procedures, and lifestyle measures (smoking and alcohol).
3. Complete physical examination at Screening visit; abbreviated physical examination at subsequent visits (the abbreviated physical examination must include general appearance, cardiovascular, respiratory systems, and abdomen; other body systems to be examined at the discretion of the Investigator). The result for physical examinations must be confirmed by the Investigator.
4. Body weight will be measured at Screening and every visit (recommended to be done after overnight fasting state) but height will be measured only at Screening.
5. Vital signs include blood pressure (BP), pulse rate, and body temperature.
6. If TB is suspected at any point during the study, a chest X-ray and QuantiFERON®-Gold Plus test should be performed and the Sponsor should be informed.
7. Previous and concomitant medication or therapy at Screening and concomitant medication or therapy only at visits until Week 52 or ET (visit or safety follow-up phone call, if done). Medications before randomisation should be reported as much to ensure eligibility. All ongoing medications at Randomisation should be reported.
8. AEs will be collected from the time of signing the informed consent (even if this is prior to IP administration) until Week 52 or ET (visit or safety follow-up phone call, if done).
9. Virology screening will be performed at Screening only. HBV (HBsAg, HBcAb), HCV (HCV antibody [HCV Ab]), and HIV (HIV antibody [HIV Ab]) will be tested. Those who are HCV Ab positive will be tested for HCV RNA. Subjects who are HIV Ab positive will do a confirmatory HIV RNA test.
10. If the QuantiFERON®-Gold Plus test is indeterminate, one retest should be done. If the follow-up test is still indeterminate, the subject will be screen failed. Retests are not allowed for positive tests.
11. Serum pregnancy test should be performed at Screening for women of childbearing potential. For women with amenorrhea of at least 12 months without an alternative medical cause, serum FSH test should be performed at Screening. From Randomisation, a urine pregnancy test will be performed and must be negative before each IP administration. Additional pregnancy test(s) may be performed besides the schedule after Randomisation at the Investigator's discretion.
12. Blood and urine samples for clinical laboratory test will be collected at Screening, Week 12, and 52 (or ET visit), and prior to IP administration at Week 0, 4, 16, 28, and 40.
    - Haematology: Haemoglobin, haematocrit, platelet count, white blood cell count (total and differential);
    - Chemistry: Sodium, potassium, calcium, phosphorus, creatinine, glucose, total bilirubin, albumin, ALT, AST, alkaline phosphatase (ALP), C-reactive protein (CRP);
    - Urinalysis (dipstick): Protein, blood, leucocytes, nitrite, glucose, ketone, pH, specific gravity, bilirubin, urobilinogen
13. For PK subgroup only (approximately 140 subjects), blood samples for PK analysis will be collected at Week 2, 8, and 12, and prior to IP administration at Week 0, 4, 16, and 28.
14. Blood samples for immunogenicity will be collected at Week 8, 12, and 52 (or ET visit) and prior to IP administration at Week 0, 4, 16, 28, and 40.
15. At Week 28, subjects who achieved PASI50 response and are considered eligible will enter the transition period. Subjects who are receiving Stelara® will be re-randomised in a 1:1 ratio to either continue to receive Stelara® or be transitioned to SB17. Subjects who are receiving SB17 will continue to receive SB17 up to Week 40 but they will also follow the randomisation procedure in order to maintain blinding.
16. Subjects who prematurely discontinue from the study at any time post 1st IP administration will be required to have an ET visit. ET visit will be performed at 12 weeks from the last IP administration. If ET visit happens to occur before 11 weeks, a phone call for safety follow-up will be performed at 12 weeks (± 7 days) from the last IP administration.

LIST OF ABBREVIATIONS

ADA	Anti-drug antibody
AE	Adverse event
AESI	Adverse event of special interest
ALP	Alkaline phosphatase
ALT	Alanine transaminase
AST	Aspartate transaminase
BCG	Bacille Calmette-Guerin
BP	Blood pressure
BSA	Body surface area
CHO	Chinese Hamster Ovary
CI	Confidence interval
COVID-19	Coronavirus Disease 2019
CRO	Contract research organisation
CRP	C-reactive protein
CSR	Clinical study report
DBP	Diastolic blood pressure
DLQI	Dermatology Life Quality Index
DMARD	Disease-modifying anti-rheumatic drug
DNA	Deoxyribonucleic acid
DSMB	Data and Safety Monitoring Board
ECG	Electrocardiogram
eCRF	Electronic case report form
EMA	European Medicine Agency
EOS	End of the study
ET	Early termination
EU	European Union
FAS	Full Analysis Set
FDA	Food and Drug Administration
FSH	Follicle stimulating hormone

GCP	Good Clinical Practice
GMP	Good Manufacturing Practice
HBcAb	Hepatitis B core antibody
HBsAg	Hepatitis B surface antigen
HBV	Hepatitis B virus
HCV	Hepatitis C virus
HCV Ab	Hepatitis C virus antibody
HIV	Human immunodeficiency virus
HIV Ab	Human immunodeficiency virus antibody
IB	Investigator's brochure
ICF	Informed consent form
ICH	International Council for Harmonization
IEC	Independent Ethics Committee
IL	Interleukin
IP	Investigational product
IRB	Institutional Review Board
IWRS	Interactive Web Response System
JAK	Janus kinase
MedDRA	Medical Dictionary for Regulatory Activities
MRHD	Maximum recommended human subcutaneous dose
MTX	Methotrexate
NAb	Neutralising antibody
NYHA	New York Heart Association
PASI	Psoriasis Area and Severity Index
PD	Protocol deviation
PFS	Pre-filled syringe
PGA	Physician's Global Assessment
PK	Pharmacokinetic(s)
PKS	Pharmacokinetic Analysis Set
PPS	Per-Protocol Set
PUVA	Psoralen and ultraviolet A

QOL	Quality of life
RAN	Randomised Set
RNA	Ribonucleic acid
RPLS	Reversible Posterior Leukoencephalopathy Syndrome
SAE	Serious adverse event
SAF	Safety Set
SAP	Statistical analysis plan
SARS-CoV-2	Severe acute respiratory syndrome coronavirus 2
SBP	Systolic blood pressure
SD	Standard deviation
SmPC	Summary of Product Characteristics
SOP	Standard operating procedure
SVR	Sustained virologic response
TB	Tuberculosis
TEAE	Treatment-emergent adverse event
TNF	Tumour necrosis factor
TOST	Two one-sided equivalence tests
ULN	Upper limit of normal
US	United States of America
UV	Ultraviolet
UVB	Ultraviolet B
WHO	World Health Organization

TABLE OF CONTENTS

LIST OF TABLES

LIST OF FIGURES

LIST OF STUDY STAFF

SPONSOR:	**Samsung Bioepis Co., Ltd.** 76, Songdogyoyuk-ro, Yeonsu-gu, Incheon, 21987 Republic of Korea
Clinical Project Manager	PPD
Clinical Development Lead	PPD
Clinical Research Scientist	PPD
Statistician	PPD
Safety Physician	PPD
Project Safety Lead	PPD

1. Introduction

1.1. Background

Plaque psoriasis is a chronic immune-mediated inflammatory disease with predominantly skin and joint manifestations affecting approximately 2-3% of the population. Psoriasis can occur at any age, and is most common in the age group 50-69. The reported prevalence of psoriasis in countries ranges between 0.09% and 11.4%, making psoriasis a serious global problem [1].

The major manifestation of psoriasis is chronic inflammation of the skin. It is characterised by disfiguring, thick, scaly, erythematous plaques that may be painful or often severely pruritic and may cause significant quality of life (QOL) issues. Psoriasis is a chronic disease that waxes and wanes during a patient's lifetime, and is often modified by treatment initiation and cessation and has few spontaneous remissions [2]. Before biologics, psoriasis was treated with topical steroids, or when severe, systemic agents such as methotrexate (MTX), cyclosporin, or psoralen and ultraviolet A (PUVA). However, such treatments were limited by liver or renal toxicity or risk of skin cancers. Tumour necrosis factor (TNF) antagonists changed the landscape of systemic treatment but also have significant toxicities such as serious infections and activation of tuberculosis (TB).

The interleukin (IL)-23 pathway is central to the pathogenesis of psoriasis. Stelara® (ustekinumab) is an IL12/23 inhibitor indicated for the treatment of moderate to severe plaque psoriasis in adults who failed to respond to, or who have a contraindication to, or are intolerant to other systemic therapies including cyclosporine, MTX, or PUVA [3]. The recommended doses of Stelara® for psoriasis is 45 mg administered via subcutaneous injection at Weeks 0 and 4, then every 12 weeks thereafter. A dose of 90 mg may be used in patients with a body weight greater than 100 kg [4]. Stelara® has a longer dose interval, that may be favourable for patient compliance, and has a better efficacy profile compared with TNF inhibitors and is a significant treatment for psoriasis management [5]. A biosimilar is a biological medicine highly similar to another already approved biological medicine (the 'reference medicine') [6]. Biosimilars have the potential to increase accessibility of biologics to a wider patient population.

1.1.1. Background to Coronavirus Disease-2019

There is currently an outbreak of respiratory disease, Coronavirus Disease 2019 (COVID-19), caused by a novel virus called severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) that was first detected in Wuhan City, Hubei Province, China in 2019. This new virus has rapidly spread across the globe, causing the World Health Organization (WHO) to declare a pandemic situation on March 12, 2020. The countermeasures initiated by national and local governments worldwide and the recommendations issued by the health authorities have impacted current and new clinical studies. As the threat of pandemic burden, including new outbreaks, locally or globally, will impact the further conduct of clinical studies, appropriate risk assessments and mitigation measures will need to be taken into consideration in all clinical studies to protect subjects, site staff, and society as a whole.

Both the European Medicine Agency (EMA) [7] and the United States of America (US) Food and Drug Administration (FDA) [8], as well as national health authorities in Europe, have issued new guidelines that aim to provide recommendations for actions for conduct of clinical studies of medical products during COVID-19 pandemic. Since the pandemic situation is evolving, guidelines, recommendations, national laws, and local restrictions may change at a high pace. Given the circumstances of a potentially relapsing pandemic or epidemic situation with regard to the spread of COVID-19 in the future, special attention will be paid to protect subjects participating in the study and site staff involved in the investigations against infection with SARS-CoV-2 in accordance to such guidance.

1.2. Overview of SB17

SB17 has been developed as a similar biological medicinal product to Stelara® having ustekinumab as the active substance. Stelara® is currently indicated for plaque psoriasis, paediatric plaque psoriasis, psoriatic arthritis, Crohn's disease, and ulcerative colitis [3, 9].

SB17 is produced by recombinant deoxyribonucleic acid (DNA) technology. SB17 is manufactured by suspension culture of Chinese Hamster Ovary (CHO) mammalian cells and purified by several steps including specific viral inactivation and removal procedures.

According to the guideline International Council for Harmonization (ICH) Q6B, characterisation of a biological therapeutic must involve its physicochemical properties, biological activities, purity, impurities, and quantity. The characterisation study will employ the 'state-of-the-art' analytical methods in order to investigate the primary, secondary, and higher-order structures, as well as the post-translational modifications, structural heterogeneity, charge variants, purity, and biological activities.

1.2.1. Non-Clinical Studies of SB17

As outlined in the "Guideline on similar biological medicinal products containing biotechnology-derived proteins as active substance: non-clinical and clinical issues" [10], a risk-based approach was taken to the non-clinical evaluation of SB17. A series of *in vitro* biologic activity studies have been performed in order to demonstrate non-clinical similarity between SB17 and Stelara®. As a result, observation from above studies has established solid non-clinical evidence of similarity, and therefore *in vivo* studies were thought to be not required in line with the guideline. Also, non-clinical safety pharmacology, reproductive and developmental toxicity, and carcinogenicity studies were not performed, as they are not required for non-clinical testing of biosimilars as outlined in the guideline [10].

1.3. Comparator Investigational Product: Stelara®

1.3.1. Non-Clinical Data of Reference Product

Animal studies have not been conducted to evaluate the carcinogenic or mutagenic potential of Stelara®. Published literature showed that administration of murine IL-12 caused an antitumor effect in mice that contained transplanted tumours and IL-12/IL-23p40 knockout mice or mice treated with anti-IL-12/IL-23p40 antibody had decreased host defence to tumours. Mice genetically manipulated to be deficient in both IL-12 and IL-23 or IL-12 alone developed ultraviolet (UV)-induced skin cancers earlier and more frequently compared to wild-type mice. The relevance of these experimental findings in mouse models for malignancy risk in humans is unknown.

No effects on fertility were observed in male cynomolgus monkeys that were administered ustekinumab at subcutaneous doses up to 45 mg/kg twice weekly (45 times the maximum recommended human subcutaneous dose [MRHD] on a mg/kg basis) prior to and during the mating period. However, fertility and pregnancy outcomes were not evaluated in mated females.

No effects on fertility were observed in female mice that were administered an analogous IL-12/IL-23p40 antibody by subcutaneous administration at doses up to 50 mg/kg, twice weekly, prior to and during early pregnancy.

In a 26-week toxicology study, one out of 10 monkeys subcutaneously administered 45 mg/kg ustekinumab twice weekly for 26 weeks had a bacterial infection [9].

1.3.2. Clinical Data of Reference Product in Psoriasis

Two multicentre, randomised, double-blind, placebo-controlled studies (PHOENIX 1 and PHOENIX 2) enrolled a total of 1,996 subjects 18 years of age and older with plaque psoriasis who had a minimum body surface area (BSA) involvement of 10%, and Psoriasis Area and Severity Index (PASI) score ≥ 12, and who were candidates for phototherapy or systemic therapy. Subjects with guttate, erythrodermic, or pustular psoriasis were excluded from the studies [3].

PHOENIX 1 enrolled 766 subjects and PHOENIX 2 enrolled 1,230 subjects [11, 12]. The studies had the same design through Week 28. In both studies, subjects were randomised in equal proportion to placebo, 45 mg or 90 mg of Stelara®. Subjects randomized to Stelara® received 45 mg or 90 mg doses, regardless of weight, at Weeks 0, 4, and 16. Subjects randomised to receive placebo at Weeks 0 and 4 crossed over to receive Stelara® (either 45 mg or 90 mg) at Weeks 12 and 16. In both studies, the endpoints were the proportion of subjects who achieved at least a 75% reduction in PASI score (PASI75) from baseline to Week 12 and treatment success (cleared or minimal) on the Physician's Global Assessment (PGA). The PGA is a 6-category scale ranging from 0 (cleared) to 5 (severe) that indicates the physician's overall assessment of psoriasis focusing on plaque thickness/induration, erythema, and scaling.

In both studies, subjects in all treatment groups had a median baseline PASI score ranging from approximately 17 to 18. Baseline PGA score was marked or severe in 44% of subjects in PHOENIX 1 and 40% of subjects in PHOENIX 2. Approximately two-thirds of all subjects had received prior phototherapy, 69% had received either prior conventional systemic or biologic therapy for the treatment of psoriasis, with 56% receiving prior conventional systemic therapy and 43% receiving prior biologic therapy. A total of 28% of subjects had a history of psoriatic arthritis.

Examination of age, gender, and race subgroups did not identify differences in response to Stelara® among these subgroups.

In subjects who weighed 100 kg or less, response rates were similar with both the 45 mg and 90 mg doses; however, in subjects who weighed greater than 100 kg, higher response rates were seen with 90 mg dosing compared with 45 mg dosing.

Subjects in PHOENIX 1 who were PASI75 responders at both Weeks 28 and 40 were re-randomised at Week 40 to either continued dosing of Stelara® (Stelara® at Week 40) or to withdrawal of therapy (placebo at Week 40). At Week 52, 89% (144/162) of subjects re-randomised to Stelara® treatment achieved PASI75 compared with 63% (100/159) of 24 subjects re-randomised to placebo (treatment withdrawal after Week 28 dose). The median time to loss of PASI75 response among the subjects randomised to treatment withdrawal was 16 weeks [9].

The PSOLAR study found no increased risk of malignancy associated with Stelara® use in humans [13].

1.4. Study Rationale

A biosimilar is a biological medicinal product that is highly similar to an already authorised original biological medicinal product (reference medicinal product) in terms of quality, tolerability, and efficacy based on a comprehensive comparability exercise [10, 14]. The EMA and the US FDA have developed specific guidelines for a biologic drug to be approved as a biosimilar [14, 15]. These guidelines recommend a stepwise approach in developing a biosimilar starting with extensive physicochemical and biological characterisation before initiating clinical studies for the comparison of the efficacy, tolerability, pharmacokinetic (PK) properties, and immunogenicity of the biosimilar. The purpose of this study is to demonstrate the equivalence in efficacy of SB17 compared to Stelara® and to evaluate the safety and immunogenicity in subjects with moderate to severe plaque psoriasis. In addition,

systemic exposure of SB17 to Stelara® will also be evaluated in subjects participating in PK evaluation.

1.5. Risk and Benefit Assessment

1.5.1. Known Potential Risks

According to the European Union (EU) Stelara® Summary of Product Characteristics (SmPC), the most common adverse reactions (> 5%) in controlled periods of the adult psoriasis, psoriatic arthritis, Crohn's disease, and ulcerative colitis clinical studies with ustekinumab were nasopharyngitis and headache. Most were considered to be mild and did not necessitate discontinuation of study treatment. The most serious adverse reaction that has been reported was serious hypersensitivity reactions including anaphylaxis. Specific safety precautions include infections, TB, malignancies, systemic and respiratory hypersensitivity reactions, and serious skin conditions such as exfoliative dermatitis. The overall safety profile was similar for patients with psoriasis, psoriatic arthritis, Crohn's disease, and ulcerative colitis.

In order to ensure the safety of subjects who participate in the study, specific conditions such as TB, malignancy, and history of certain pulmonary or cutaneous conditions are excluded from enrolment, and the subjects should be instructed to report their symptoms related to adverse events of special interest (AESIs) in Section 8.3 without delay and should be managed appropriately.

Participation in clinical study may require more frequent visits than usual medical practice, thus, additional risk under the COVID-19 should be considered, if needed. The Sponsor will consider whether to start, continue, temporarily halt, or close the study at some or all clinical study sites based on the risk assessment with relevant parties' input on an ongoing basis.

This study will take place at multicentre clinical sites with accessible medical facilities which will allow immediate treatment of medical emergencies including systemic hypersensitivity. All study related procedures will be conducted by medical staffs with appropriate level of training and expertise and an understanding of the investigational products (IPs), its target, and mechanism of action. An independent Data and Safety Monitoring Board (DSMB) will convene at pre-specified intervals to conduct interim monitoring of accumulating safety data. Following each data review, the DSMB will make recommendations regarding the conduct of the study, including continuation of the study without modifications, modification of the protocol, pausing of subject enrolment until the resolution of an issue, or termination of the study for safety reasons.

1.5.2. Known Potential Benefits

Stelara® binds and subsequently inhibits the bioactivity of the human cytokines IL-12 and IL-23. Thus, Stelara® prevents abnormal regulation of IL-12 and IL-23 associated with immune mediated diseases, such as psoriasis, psoriatic arthritis, Crohn's disease, and ulcerative colitis.

The efficacy of Stelara® in PASI and PGA scores was statistically significant in plaque psoriasis after 12 weeks of treatment. The proportion of patients achieving PASI75 response at Week 12 was 72.2% and 65% on 45 mg and 90 mg, respectively. Approximately 35 to 50% of subjects achieved a PASI90 response at Week 12. Similar efficacy was observed when efficacy was assessed using the PGA.

Although clinical data is currently unavailable, as a proposed ustekinumab biosimilar, SB17 is expected to have similar clinical outcome to Stelara® based on the physicochemical and biological similarity. Therefore, all subjects who participate in this study would be expected to enjoy similar clinical benefits anticipated for Stelara® treatment.

1.5.3. Assessment of Potential Risks and Benefits

The available data demonstrate a high degree of physicochemical and biological similarity of SB17

with the reference medicinal product (Stelara®). The suitability of the methodology employed to evaluate the similarity of SB17 and Stelara® in a pharmaceutical setting were confirmed by EMA and the US FDA. The known and potential risks of receiving SB17 are expected to be similar to those seen with Stelara®. As Stelara® is an approved drug for psoriasis, and assuming SB17 having a similar risk/benefit profile to that of Stelara®, the risk/benefit balance of this study is expected to be favourable. In conclusion, sufficient evidence exists for the justification of the administration of SB17, as a similar biological medicinal product of Stelara®, to subjects with psoriasis.

The study protocol provides adequate instructions for the detection and treatment of adverse events (AEs) arising following the administration of the IPs (SB17 or Stelara®).

Risk assessment for the COVID-19 will be documented on an ongoing basis in relevant documents. The risk assessment and associated mitigation measures based on inputs from relevant stakeholders will be prioritised to consider the rights, safety, and wellbeing of the study subjects.

2. Study Objectives and Endpoints

2.1. Study Objectives

2.1.1. Primary Objective

The primary objective is to demonstrate the equivalence of SB17 to Stelara®, in terms of the percent change of baseline in PASI at Week 12 in subjects with moderate to severe plaque psoriasis.

2.1.2. Secondary Objectives

The secondary objectives are:

- To evaluate the efficacy of SB17 compared to Stelara®
  - Percent change from baseline in PASI other than Week 12
  - PGA
  - PASI50, PASI75, and PASI90 response rate
  - Change from baseline in Dermatology Life Quality Index (DLQI)
- To evaluate safety and tolerability of SB17 compared to Stelara®
- To evaluate the PK of SB17 compared to Stelara® in subjects participating in PK evaluation
- To evaluate the immunogenicity of SB17 compared to Stelara®
- To evaluate safety and immunogenicity in subjects who transitioned to SB17 and who maintained Stelara® at Week 28 for the transition period

2.2. Study Endpoints

2.2.1. Primary Endpoint

- Percent change from baseline in PASI at Week 12

2.2.2. Secondary Endpoints

<u>Efficacy Endpoints</u>

- PGA at Week 2, 4, 8, 12, 16, 20, 24, 28, 40, and 52
- PASI50, PASI75, and PASI90 response rate at Week 2, 4, 8, 12, 16, 20, 24, 28, 40, and 52
- Percent change from baseline in PASI at Week 2, 4, 8, 16, 20, 24, 28, 40, and 52
- Change from baseline in DLQI at Week 4, 12, 16, 28, 40, and 52

Safety Endpoints

- Incidence of AEs
- Incidence of serious AEs (SAEs)
- Changes in vital signs and clinical laboratory parameters

PK Endpoints

- Serum ustekinumab concentration at Week 0, 2, 4, 8, 12, 16, and 28

Immunogenicity Endpoints

- Incidence of anti-drug antibodies (ADAs) at Week 0, 4, 8, 12, 16, 28, 40, and 52
- Incidence of neutralising antibodies (NAbs) at Week 0, 4, 8, 12, 16, 28, 40, and 52

3. Study Design

3.1. Overview of Study Design

This is a randomised, double-blind, multicentre clinical study to evaluate the efficacy, safety, tolerability, PK, and immunogenicity of SB17 compared to Stelara® in subjects with moderate to severe plaque psoriasis.

Subjects will be randomised in a 1:1 ratio to receive either SB17 or Stelara® via subcutaneous injection. IPs (SB17 or Stelara®) will be administered at Week 0, 4, and then every 12 weeks up to Week 40, and the last assessment will be done at Week 52.

At Week 28, subjects who achieved a PASI50 response and are considered eligible will enter the transition period. In the transition period, subjects receiving Stelara® will be randomised again in a 1:1 ratio to either continue on Stelara® or be transitioned to SB17 up to Week 40. Subjects receiving SB17 will continue to receive SB17 up to Week 40 but they will follow the randomisation procedure in order to maintain blinding.

Screening period will be 4 weeks. IPs (SB17 or Stelara®) will be administered up to Week 40, and the last assessment will be done at Week 52.

3.2. Rationale for Study Design

3.2.1. Scientific Rationale for Study Design

The purpose of this study is to demonstrate the equivalence in clinical efficacy of SB17 and Stelara® in subjects with psoriasis.

According to EMA and FDA guideline, the study population should generally be representative of approved therapeutic indications of the reference product and be sensitive for detecting potential differences between the biosimilar and the reference product. For Stelara®, psoriasis is an indication approved by both EMA and the US FDA. Also, psoriasis population has the largest effect size which is

considered as sensitive, compared to other approved indications such as psoriatic arthritis, Crohn's disease, and ulcerative colitis. Therefore, psoriasis population is selected for this study to assess the biosimilarity in efficacy, safety, and immunogenicity between SB17 and Stelara®.

This study is a randomised, double-blind, and parallel group study for 52 weeks. And transition will be performed at Week 28 to investigate the clinical impact (safety and immunogenicity) of switching.

3.2.2. Rationale for Dose Selection

The recommended dose of Stelara® for psoriasis is 45 mg administered via subcutaneous injection initially and 4 weeks later, followed by 45 mg every 12 weeks. A dose of 90 mg (in the form of 2 doses of 45 mg) may be used in subjects with a body weight being greater than 100 kg during the study. The primary analysis will be done with subjects ≤ 100 kg and receiving only 45 mg doses (see Section 9.4). Therefore, it is highly recommended to maintain a body weight of ≤ 100 kg.

3.2.3. Rationale for Pharmacokinetic Assessments

A randomised, double-blind, three-arm, parallel group, single-dose Phase I comparative PK study will be conducted in healthy subjects to demonstrate similarity in PK profiles of SB17, EU sourced Stelara®, and US sourced Stelara®. However, that Phase I study is a single dose study, and to evaluate the PK profiles at steady state with repeated dose in a patient population, PK assessment in this Phase III study is considered necessary. The evaluation is a descriptive in nature and no hypothesis testing will be done.

3.2.4. Rationale for Immunogenicity Assessments

Biological/biotechnology-derived proteins can induce an unwanted immune response that is triggered by more than a single factor and the consequence of immunogenicity may vary considerably, ranging from irrelevant to therapy to serious and life-threatening. Immune responses may affect both safety and effectiveness such as altering PK, inducing anaphylaxis, or promoting development of NAbs that neutralise that as well as its endogenous protein counterpart.

Approximately 6 to 12.4% of subjects treated with Stelara® in psoriasis and psoriatic arthritis clinical studies developed antibodies to ustekinumab, which were generally low-titre. In psoriasis clinical studies, antibodies to ustekinumab were associated with reduced or undetectable serum ustekinumab concentrations and reduced efficacy. In psoriasis studies, the majority of patients who were positive for antibodies to ustekinumab had NAbs. There is no apparent correlation between the presence of anti-ustekinumab antibodies and the occurrence of injection site reactions.

For subject safety and for demonstrating biosimilarity, immunogenicity will be assessed in this study according to the recommended guideline [10, 14].

3.3. Duration of Study Participation

The duration of study participation will be 4 weeks of Screening and up to 52 weeks of study treatment period (including 24 weeks transition period) per subject.

3.4. Number of Subjects

Approximately 464 subjects are planned to be randomised from approximately 70 sites for study duration.

3.5. End of Study Definition

A subject is considered to have completed the study if he or she has completed all period of the study

including the last scheduled visit shown in Table 1. The end of the study (EOS) is defined as completion of the last subject's Week 52 visit or the last activity (e.g., visit procedure or safety follow-up phone call) for early termination (ET) if the last subject prematurely discontinues the IP.

4. Study Population

4.1. Overview

The study population for this study is subjects with moderate to severe plaque psoriasis. Eligibility for participation in this study will be based on the inclusion/exclusion criteria. For exclusionary conditions to be assessed at Screening, if the subject or Investigator becomes aware of the condition occurring during the Screening period before Randomisation, it will be considered exclusionary.

4.2. Inclusion Criteria for Main Period

Subjects must meet all of the following criteria to be eligible for the study:

1. Aged 18 years or older at Screening (defined as the time of signing the informed consent form [ICF]).
2. Have plaque psoriasis diagnosed at least 6 months prior to Screening, with or without psoriatic arthritis.
3. Have plaque psoriasis at Screening and Randomisation with the involvement and severity defined as the following:
    a. Total affected BSA ≥ 10%.
    b. PASI score of ≥ 12.
    c. PGA score of ≥ 3 (moderate).
4. Considered to be a candidate for phototherapy or systemic therapy for psoriasis at Screening.
5. Be less than 95 kg of body weight at Screening and at Randomisation.
6. Adequate haematological function at Screening defined as the following by central lab:
    a. White blood cell count ≥ 3.5×10^3 cells/μL (≥ 3.5×10^9 cells/L).
    b. Neutrophil count ≥ 1.5×10^3 cells/μL (≥ 1.5×10^9 cells/L).
    c. Haemoglobin ≥ 10 g/dL.
    d. Platelet count ≥ 125,000/mm^3 (≥ 125×10^9/L).
7. Adequate renal and hepatic function at Screening defined as the following by central lab:
    a. Serum creatinine < 1.5 × upper limit of normal (ULN).
    b. Serum alanine transaminase (ALT) and aspartate transaminase (AST) < 2 × ULN.
8. Non-childbearing potential female (e.g., permanently sterilised, postmenopausal [defined as amenorrhea of at least 12 months without an alternative medical cause prior to Screening and a follicle stimulating hormone (FSH) level of > 40 IU/L at Screening]), OR childbearing potential female subjects or male subjects with their (respectively male or childbearing female) partners who agree to use at least two forms of appropriate contraception method (e.g., established use of oral, injected, intravaginal, transdermal, or implanted hormonal

contraceptive, placement of an intrauterine device or intrauterine hormone-releasing system, physical barrier [Note: female condom and male condom should not be used together]) from Screening until 15 weeks after the last dose of IP. Vasectomy alone will be allowed for male subjects and female subjects of childbearing potential with a sole vasectomised male partner. Vasectomised subjects or partners should be medically confirmed for sterilisation. True abstinence alone will be allowed if this is in line with the preferred and usual lifestyle of the subject, or for subjects who do not have a partner.

9. Have provided informed consent and must be able to, in the opinion of the Investigator, understand the implications of taking part in the study and be willing to follow the study requirements.

4.3. Exclusion Criteria for Main Period

Subjects meeting any of the following criteria are not eligible for the study:

1. Have nonplaque forms of psoriasis, including erythrodermic, pustular, guttate, or drug-induced psoriasis at Screening.
2. Have other skin disease than psoriasis that:
    a. Requires topical or systemic corticosteroid or other immunosuppressive therapy at Screening.
    b. May confound the efficacy evaluation per Investigator discretion at Screening.
3. Have used biologics (any therapeutic monoclonal antibody or fusion receptor protein) such as;
    a. Any TNF inhibitors within the previous 6 months prior to Randomisation.
    b. Any IL-12 or IL-23 inhibitor biologics (including ustekinumab/ustekinumab biosimilars, guselkumab, tildrakizumab, or rizankizumab), IL-17 inhibitor (including secukinumab, ixekizumab, or brodalumab), rituximab, or integrin inhibitor biologics at any time prior to Randomisation.
    c. Other biologics within the longer of either 5 half-lives or 3 months prior to Randomisation.
4. Known allergic reactions or hypersensitivity to ustekinumab or to any ingredients of Stelara® or SB17 at Screening.
5. History of a systemic allergic reaction or hypersensitivity to prior biologic therapies at Screening.
6. History of asthma that:
    a. Required intubation at any time prior to Screening.
    b. Required hospitalisation or 14 days or more of oral corticosteroids use (cumulatively) within 6 months prior to Randomisation.
    c. Requires oral corticosteroids or considered to be corticosteroid-dependent in the opinion of the Investigator at Randomisation.

7. History of exfoliative dermatitis, Reversible Posterior Leukoencephalopathy Syndrome (RPLS), facial palsy, allergic alveolitis, or non-infectious pneumonia including interstitial pneumonia, cryptogenic organizing pneumonia, or eosinophilic pneumonia, etc. at Screening.

8. Have received phototherapy (including ultraviolet B [UVB], PUVA, or sunbaths/tanning beds, etc.) or conventional systemic therapy (including corticosteroids, MTX, calcineurin inhibitors, retinoids, vitamin D analogues, fumaric acid esters, apremilast, 6-thioguanine, hydroxyurea, etc.) for psoriasis within 4 weeks prior to Randomisation.

9. Have received topical therapy for psoriasis (including corticosteroids, vitamin D analogues, retinoids, calcineurin inhibitors, coal tar, anthralin, urea, alpha-hydroxy acid, or salicylic acid, etc.) within 2 weeks prior to Randomisation.

10. Have received any disease-modifying anti-rheumatic drugs (DMARDs), any systemic immunosuppressants (including those mentioned above in systemic psoriasis therapy, antimalarials, sulfasalazine, Janus kinase [JAK] inhibitors, gold, minocycline, azathioprine, 6-mercaptopurine, mycophenolate mofetil, etc.) or any other injectable or enema corticosteroids, within 4 weeks prior to Randomisation (except for leflunomide: within 12 weeks from Randomisation).

11. Have received non-biologic IP from another study within 5 half-lives of that product prior to Randomisation or use of an investigational device at Randomisation.

12. Women who are pregnant or nursing at Screening, or men and women planning pregnancy during the study period and until 15 weeks after the last dose of IP.

13. Have received a live or live attenuated viral vaccine or a live bacterial vaccine (except Bacille Calmette-Guerin [BCG] vaccination) within 4 weeks prior to Randomisation or plan to do so within 15 weeks after the last dose of IP. For BCG vaccination, subjects who have received BCG within 12 months prior to Randomisation or plan to do so within 12 months after the last dose of IP.

14. Have active or latent TB at Screening, by known history or any of the following:

    a. Positive QuantiFERON®-Gold Plus test.

    b. Positive chest X-ray findings (radiographs taken within 3 months prior to Randomisation with radiologist confirmation will be accepted) determined by a qualified physician such as radiologist or pulmonologist, including active TB, untreated or inadequately treated old, inactive or healed TB.

    c. By any other positive findings determined by TB specialist, including suggestive signs or symptoms of TB or recent close contact with active TB patients.

15. History of ongoing infection or a positive test of hepatitis B virus (HBV, defined as hepatitis B surface antigen [HBsAg] positive or HBsAg negative and hepatitis B core antibody [HBcAb] positive), hepatitis C virus (HCV; for subjects who have previously received anti-HCV treatment must have a sustained virologic response [SVR] for at least 24 weeks post-treatment and no evidence of significant liver fibrosis [i.e., must be METAVIR F0 or F1] in addition to negative HCV-ribonucleic acid (RNA) at Screening to be eligible), or human immunodeficiency virus (HIV) infection, or any history of primary immunodeficiency at Screening.

16. History of sepsis (defined as a life-threatening organ dysfunction caused by infection), chronic or recurrent infection, conditions that require regular antibiotic prophylaxis (such as rheumatic heart disease), opportunistic, granulomatous (for TB, please see above), or invasive fungal infection at Screening.
17. History of other bacterial, fungal, viral, parasitic, or helminthic infection requiring oral antimicrobial within 2 weeks prior to Randomisation or a serious infection (a bacterial, fungal, viral, parasitic, or helminthic infection that requires hospitalisation or treatment with parenteral antimicrobials) within 8 weeks prior to Randomisation. Other mild infections should be resolved before Randomisation. For COVID-19, please see below.
18. History of lymphoproliferative disease or leukaemia at Screening.
19. History of malignancy (except for squamous or basal cell carcinoma of the skin that has been treated and not recurred within 3 months prior to Screening, or surgically treated cervical carcinoma in situ) within the last 5 years prior to Screening.
20. History of myocardial infarction, New York Heart Association (NYHA) III/IV congestive heart failure, or stroke within 12 months prior to Randomisation.
21. Have uncontrolled hypertension (defined as systolic blood pressure [SBP] ≥ 160 mmHg or diastolic blood pressure [DBP] ≥ 100 mmHg confirmed after repeat measurement) at Screening.
22. Have uncontrolled diabetes mellitus (defined as having history of diabetic peripheral neuropathy or diabetic foot, or otherwise considered uncontrolled in the opinion of the Investigator) at Screening.
23. History of organ transplantation at Screening.
24. Evidence of alcohol or substance abuse within the last 12 months prior to Screening.
25. History of a major surgery in the opinion of the Investigator within 12 weeks prior to Randomisation or have a plan to do so during the study period.
26. Have psychiatric disease at Screening defined as:
    a. Current uncontrolled mental disorder (including depression) in the opinion of the Investigator.
    b. History of suicidal attempts or ideation.
    c. Considered to be at risk of suicide in the opinion of the Investigator.
27. Have other major organ dysfunction or failure such as liver cirrhosis, dialysis-dependent renal failure, any cardiopulmonary disease with functional disability of NYHA III/IV equivalent, aplastic anaemia or any other transfusion-dependent/stimulating factor dependent haematological disorders, or dementia at Screening.
28. Considered to be at risk of progressive weight gain or widely fluctuating body weight, in the opinion of the Investigator, at Screening.
29. History of COVID-19 as:
    a. History of asymptomatic, mild or moderate COVID-19 within 8 weeks prior to Randomisation.

b. Any history of severe or critical COVID-19, or hospitalisation due to COVID-19 at Randomisation.

c. Any history of COVID-19 complications or sequalae including lung fibrosis, thromboembolism, cardiac, gastrointestinal, neuropsychiatric, 'long COVID', or dermatologic manifestations, etc. at Randomisation.

Note: COVID-19 severity grade is according to WHO COVID-19 disease severity classification. Subjects who have suggestive signs or symptoms of COVID-19 must be evaluated and determined to be COVID-19 negative per local regulations before Screening.

30. Have any other disease or disorder, that will put the subject at risk if they are enrolled, in the opinion of the Investigator, at Screening.

31. Have poor venous access or unwillingness to undergo multiple venepuncture and blood sampling at Screening.

4.4. Eligibility Criteria for Transition Period

4.4.1. Inclusion criteria

1. Achieve PASI50 response on Week 28 visit assessment.

2. Willing to participate in the rest of study and able to follow the study procedure with the opinion of the Investigator.

4.4.2. Exclusion Criteria for Transition Period

1. Subject is considered to be of increased risk when entered in the Transition Period, in the opinion of the Investigator.

4.5. Lifestyle Considerations

During this study, subjects should:

- Refrain from exposure to UV rays, including sunbathing and suntanning (see Section 5.3.2).
- Avoid excessive alcohol consumption.
- While subjects who become > 100 kg will receive 90 mg in the form of two 45 mg doses, it is highly recommended not to become overweight and maintain a bodyweight of 100 kg or below.
- Subjects are advised to adhere to local requirements for reduction of the public COVID-19 exposure while ambulatory. All subjects should self-assess whether they have any signs or symptoms consistent with COVID-19, and to check if they have had any contact with COVID-19 patients before visiting the clinical study site. If there are suspected signs or symptoms of COVID-19 or potential contact with COVID-19 patients, the subjects should not visit the site and should contact the site remotely (via phone, email, etc.) first. If applicable, subjects will be referred to the local health care system. Physical distancing and person-to-person contact restrictions will be applied and explained to subjects while staying at the site. Study participants will be asked to use surgical face masks and/or gloves if deemed appropriate by the Investigator and site staff and guided by local requirements.

4.6. Screen Failures, Retesting, and Rescreening

4.6.1. Screen Failures

Screen failures are defined as subjects who consent to participate in the clinical trial but do not meet one or more criteria required for participation in the trial during the screening procedures. A minimal set of screen failure information is required. If the subject is not randomised within 28 days after signing the ICF, the subject will be screen failed.

4.6.2. Retesting

All laboratory-related eligibility criteria (including QuantiFERON®-Gold Plus tests, serum FSH test, and serum pregnancy test) will be determined only by central lab measurement. Eligibility related laboratory tests are not allowed for retesting unless the laboratory finding was due to technical error (e.g., missing value due to sample mishandling, etc.) or retesting is required per protocol (e.g., indeterminate QuantiFERON®-Gold Plus test result).

4.6.3. Rescreening

Rescreening is allowed for a technical issue (e.g., repeated laboratory error that makes eligibility confirmation difficult within 28 days after signing the ICF, COVID-19 related travel or transport restrictions that makes the screening procedure infeasible after signing the ICF, etc.) and not a medical issue. Such subjects can be rescreened only once, based on Investigator recommendation and after discussion with medical monitor. The rescreened subject will have to undergo the full screening procedures (including ICF consent) again.

4.7. Replacement

Subjects who are discontinued from IP after randomisation will not be replaced.

5. Treatment and Investigational Product

5.1. Treatment of the Subjects

5.1.1. Dosing and Treatment Schedule

Subjects will be administered SB17 or Stelara® 45 mg at Week 0, Week 4, followed by every 12 weeks up to Week 40. By eligibility criteria, all subjects will receive 45 mg at Week 0 (Randomisation). If the subject gains weight and becomes > 100 kg in subsequent dosing visits the subject will receive two doses of 45 mg (total of 90 mg). Each injection should be done in different sites.

No visit window will be allowed at Week 0 for first IP administration. Visit window for dosing visit except for Week 0 will be allowed as follows:

- ± 3 days for Week 4
- ± 5 days for Week 16 and Week 28
- ± 7 days for Week 40

IP administration delay must be avoided as much as possible. If IP dose delay requiring out-of-window administration is necessary due to AE, etc., administer the IP as soon as possible. IP dose delay is possible up to 4 weeks from scheduled dosing date. If 4 weeks is exceeded, the IP administration should be skipped. Subsequent visit schedules will not be changed due to administration delay or skip. However, if the last scheduled IP (Week 40) cannot be given even after a 4-week delay, an ET visit should be

made. Even if IP administration is not skipped, out-of-window administration will be still a protocol deviation (PD).

5.1.2. Assignment of Subjects to Treatment Group

A unique subject number will be assigned to subjects at Screening. The subject number will be used to register the subject using the Interactive Web Response System (IWRS) and the subject will then be randomised (in a ratio of 1:1) to either SB17 or Stelara®.

At Week 28, subjects who achieved a PASI50 response will enter the transition period. Subjects receiving Stelara® will be randomised again in a 1:1 ratio to either continue to receive Stelara® or be transitioned to SB17 up to Week 40. Subjects receiving SB17 will continue to receive SB17 up to Week 40 but they will also follow the randomisation procedure to maintain blinding.

A unique randomisation number will be assigned to the subject number by the IWRS at randomisation to ensure that treatment group assignment is unbiased and concealed from subjects, Investigators, and other study personnel. The subject number will not be changed after re-randomisation at Week 28. The randomisation number is linked to the treatment group assignment, which in turn is linked to IP kit number.

The assigned subject number(s) and randomisation number(s) will not be reused.

5.1.3. Blinding

This study is double-blinded. Subjects, Investigators, and other study personnel will be unaware of the treatment group assignments throughout the study treatment period after randomisation. Emergency unblinding is referred to Section 8.5.

To ensure the blinding of the treatment group assignment, blinding cap will be applied to IP (SB17 or Stelara®). The carton and IP pre-filled syringe (PFS) will be packed and labelled in identical appearance.

5.2. Investigational Product

5.2.1. Identity of Investigational Product

The IPs will be supplied to investigational sites as a PFS.

Details of the IPs are provided in Table 2.

Table 2. Investigation Product Description

	SB17	EU Sourced Stelara®
Formulation	Solution for subcutaneous injection in PFS	Solution for subcutaneous injection in PFS
Fill volume	0.5 mL	0.5 mL
Active compound	45 mg ustekinumab	45 mg ustekinumab

5.2.2. Formulation, Packaging, and Labelling

Ustekinumab is supplied for use as a solution for injection in PFS (45 mg per PFS for SB17 and EU sourced Stelara®).

These IP PFSs will be packed and labelled in a double-blinded manner for clinical use. The labels for carton and PFS will contain the protocol number, unique identifier, Sponsor company name, expiry or retest date, storage condition, and all other details according to the Good Manufacturing Practice (GMP)

and other relevant local laws and/or regulations.

The temperature will be monitored properly during the study period. The IP should be stored in a secure area and clearly labelled and stored away from other IP or medication to prevent confusion (e.g., in a clearly marked box on a separate shelf of the refrigerator).

A detailed guideline for IP preparation, administration, storage, and destruction will be provided in the Pharmacy Manual.

5.2.3. Product Storage and Stability

SB17 or Stelara® should be stored at 2°C to 8°C (36°F to 46°F) in the original carton until time of use to protect from light. The temperature will be monitored properly during the study period. If continuous monitoring is not available then manual temperature logs should be generated and recorded to ensure proper storage conditions. If a temperature deviation occurred, responsible person should contact the Sponsor to determine if the drug is still appropriate for use.

Do not freeze SB17 or Stelara® PFS. Do not shake SB17 or Stelara® PFS. The IPs must not be used beyond the expiration date.

5.2.4. Preparation and Administration of Investigational Products

IPs should be inspected visually for particulate matter or discoloration prior to administration. SB17 or Stelara® is a colourless to light yellow solution and may contain a few small translucent or white particles. If it is discoloured or cloudy, or if other particulate matter is present, the IPs must not be used. Do not shake SB17 or Stelara® PFS. Strong shaking may damage the IPs. If it has been shaken strongly, the IPs must not be used.

Prior to administration, IPs should be removed from the refrigerator and brought to room temperature. Do not remove the syringe's needle cover while allowing it to reach room temperature. The needle cover should not be removed until you are ready to inject the dose.

IPs will be administered as a single subcutaneous injection in the abdomen (divided by quadrants, avoiding the navel), upper thighs, or upper arm. Only the Investigator or trained designee can perform and monitor the IP administration.

Each injection should be administered at a different anatomic location (such as upper arms, upper thighs, or any quadrant of abdomen) than the previous injection, and not into areas where the skin is tender, bruised, erythematous, or indurated.

A detailed guideline for IP preparation, administration, storage, and destruction will be provided in the Pharmacy Manual.

5.2.5. Treatment Compliance and Investigational Product Accountability

Compliance will be assessed by the subject's source documents and electronic case report form (eCRF). All dosing information including the exact date and time of IP administration must be recorded in the source document and eCRF.

The Investigator or designee should maintain the documents of IP accountability and record the IP kit number administered to subjects. IP accountability and dispensing records must be kept and contain the following information:

- The identification of the subjects to whom the drug was dispensed.

- The date(s) and quantity of the drug dispensed and exact package to the subject.
- The dispensing and inventory logs must be available for review.

The used IP will be destructed at the investigational site according to local regulation after drug accountability is done. All unused IPs should be returned to the Sponsor or designated vendor unless local destruction at site is approved by the Sponsor. If destruction is authorised at the investigational site, the Investigator must ensure that the materials are destroyed in compliance with all applicable environmental regulations, institutional policies, and any instructions provided by the Sponsor. Destruction of the IP must be adequately documented.

5.3. Concomitant Medication or Treatment

5.3.1. Permitted Concomitant Medications or Treatment

Any other medications and treatments (except for prohibited concomitant medications or treatments) that are considered necessary for the subject's welfare, and that are not expected to interfere with the evaluation of the IP may be given at the Investigator's discretion.

Corticosteroid nasal spray, eye drops, ear drops, and inhalers are permitted.

Emollients, moisturisers, or shampoos that do not contain ingredients that are prohibited are allowed except within 24 hours before the time of PASI/PGA evaluation.

5.3.2. Prohibited Concomitant Medications or Treatment

Medications that are prohibited prior to Randomisation and throughout the study are presented in Table 3. Corticosteroids are described in more detail in Table 4. By principle, corticosteroids should not be used as much as possible, and subjects who cannot discontinue systemic corticosteroids during the study should not be enrolled.

Major surgeries in the opinion of the Investigator are prohibited from 12 weeks prior to Randomisation, and during the study period unless necessary for AE management.

Table 3. Prohibited Medications prior to Randomisation and throughout the Study

Medication	Time Prohibited prior to Randomisation
Phototherapy (including UVB, PUVA, or sunbaths/ tanning beds, etc.) or systemic therapy for psoriasis (including oral/injectable corticosteroids, MTX, calcineurin inhibitors, retinoids, vitamin D analogues, fumaric acid esters, apremilast, 6-thioguanine, hydroxyurea, etc.)[a]	4 weeks
Topical therapy for psoriasis (including corticosteroids, vitamin D analogues, retinoids, calcineurin inhibitors, coal tar, anthralin, urea, alpha-hydroxy acid, or salicylic acid, etc.)	2 weeks
DMARDs/systemic immunosuppressant (including those mentioned above in systemic psoriasis therapy, antimalarials, sulfasalazine, JAK inhibitors, gold, minocycline, azathioprine, 6-mercaptopurine, mycophenolate mofetil, etc.)	4 weeks
Leflunomide	12 weeks
TNF inhibitors	6 months
IL-12, IL-23, IL-17, integrin inhibitors, rituximab	At any time
Any other therapeutic monoclonal antibodies	5 half-lives of that product or 3 months,

Medication	Time Prohibited prior to Randomisation
or fusion receptor protein	whichever is longer
Non-biologic IP from another study	5 half-lives of that product
Live or live attenuated viral vaccine or a live bacterial vaccine	4 weeks (until 15 weeks after last IP)
BCG vaccination	12 months (until 12 weeks after last IP)

[a] Common immunosuppressants such as systemic corticosteroids, MTX, calcineurin inhibitors, etc. are also prohibited for pre-existing medical histories as part of DMARDs/systemic immunosuppressants.

Table 4. Prohibited Corticosteroids prior to Randomisation and throughout the Study

Medication	Time Prohibited prior to Randomisation	Other Considerations
Topical corticosteroids for psoriasis[a]	2 weeks	• After the Week 12 evaluation, low potency topical corticosteroids (corresponding to US Class 6 or 7) may be used on the face and groin only. Such topical steroids should not be used within 24 hours before the time of PASI/PGA evaluation. • If topical corticosteroids for other than psoriasis are needed during the study it should be discussed with the Sponsor before use.
Systematic corticosteroids (oral, intravenous, and intramuscular injection)	4 weeks	• If necessary for other reasons (e.g., AE management), a short-term use is allowed, cumulatively up to 14 days. Longer term uses should be considered for IP discontinuation. • Systemic corticosteroids as a prophylactic premedication to prevent hypersensitivity to the IP without a prior event are not allowed. • Subjects who develop hypersensitivity to the IP and are considered to require prophylactic systemic corticosteroids to prevent future hypersensitivity reactions should consider IP discontinuation.
Intralesional corticosteroids	4 weeks	• If intralesional steroids for other than psoriasis is needed it should be discussed with the Sponsor before use.
Intra-articular corticosteroids (including tendon or bursa injections)	4 weeks	• After the Week 12 evaluation, these are allowed up to 2 times, 1 joint per time.
All other routes (enema, etc.) except for permitted ones	4 weeks	• Corticosteroids for any reason must be avoided as much as possible during the study.

[a] It is to be noted that any other dermatologic disease that requires corticosteroids are excluded at Screening.

5.3.3. Rescue Medications

The use of rescue medication is not allowable at any time throughout study. There are certain medications permitted after Week 12, please refer to Section 5.3.2. If the subject cannot continue the study without prohibited medications due to lack of efficacy or for other reasons, discontinuation of IP should be considered.

6. Study Assessment

6.1. Efficacy Assessment

6.1.1. Psoriasis Area Severity Index

PASI incorporates the extent of psoriasis at four anatomic sites with the signs of erythema, scale, and elevation. PASI scores range from 0 to 72. The PASI assessment will be performed by the Investigator at the time points outlined in Table 1. PASI is highly recommended to be assessed by the same person for each subject throughout the study. The severity of the disease is calculated as follows.

In the PASI system, the body is divided into 4 areas: The head (h), trunk (t), upper extremities (u), and lower extremities (l), which account for 10%, 30%, 20%, and 40% of the total BSA, respectively.

The area of psoriatic involvement of these four areas (A_h, A_t, A_u, and A_l) is given a numerical value:

- 0 = No involvement
- 1 = 1% to < 10% involvement
- 2 = 10% to < 30% involvement
- 3 = 30% to < 50% involvement
- 4 = 50% to < 70% involvement
- 5 = 70% to < 90% involvement
- 6 = 90% to 100% involvement

Regarding area assessments, please note the following conventions:

- The neck is considered part of the head area
- The axillae and groin are considered part of the trunk area
- The buttocks are considered part of the lower extremities area

The signs of severity, erythema (E), induration (plaque thickness, I), and scaling (desquamation, S) of these four areas are assessed using a numeric scale 0 to 4:

- 0 = No symptoms
- 1 = Slight
- 2 = Moderate
- 3 = Severe
- 4 = Very severe

The PASI score is calculated according to the following formula:

$$\mathbf{PASI = 0.1 \times (E_h + I_h + S_h) \times A_h + 0.3 \times (E_t + I_t + S_t) \times A_t + 0.2 \times (E_u + I_u + S_u) \times A_u + 0.4 \times (E_l + I_l + S_l) \times A_l}$$

A PASI50, PASI75, and PASI90 response is defined as a ≥ 50%, ≥ 75%, and ≥ 90% improvement of PASI score from baseline.

6.1.2. Physician's Global Assessment

The PGA is used to determine the subject's psoriasis lesions overall. The PGA assessment will be performed by the Investigator at the time points outlined in Table 1. PGA is highly recommended to be assessed by the same person for each subject throughout the study.

Overall lesions will be graded for induration, erythema, and scaling based on scales as below. The sum of the 3 scales will be divided by 3 to obtain a final PGA score.

Induration (I) (averaged over all lesions)

- 0 = No evidence of plaque elevation
- 1 = Minimal plaque elevation, = 0.25 mm
- 2 = Mild plaque elevation, = 0.5 mm
- 3 = Moderate plaque elevation, = 0.75 mm
- 4 = Marked plaque elevation, = 1 mm
- 5 = Severe plaque elevation, = 1.25 mm or more

Erythema (E) (averaged over all lesions)

- 0 = No evidence of erythema, hyperpigmentation may be present
- 1 = Faint erythema
- 2 = Light red coloration
- 3 = Moderate red coloration
- 4 = Bright red coloration
- 5 = Dusky to deep red coloration

Scaling (S) (averaged over all lesions)

- 0 = No evidence of scaling
- 1 = Minimal; occasional fine scale over less than 5% of the lesion
- 2 = Mild; fine scale dominates
- 3 = Moderate; coarse scale predominates
- 4 = Marked; thick, nontenacious scale dominates
- 5 = Severe; very thick tenacious scale predominates

Total Average = (I + E + S)/3

Physician's Static Global Assessment based upon above Total Average

- 0 = Cleared, except for residual discoloration
- 1 = Minimal - majority of lesions have individual scores for (I + E + S)/3 that averages 1
- 2 = Mild - majority of lesions have individual scores for (I + E + S)/3 that averages 2

- 3 = Moderate - majority of lesions have individual scores for (I + E + S)/3 that averages 3
- 4 = Marked - majority of lesions have individual scores for (I + E + S)/3 that averages 4
- 5 = Severe - majority of lesions have individual scores for (I + E + S)/3 that averages 5

***Note**: Scores should be rounded to the nearest whole number. If total ≤ 1.49, score = 1; if total ≥ 1.50, score = 2.*

6.1.3. Dermatology Life Quality Index

The DLQI will be self-reported by the subjects at the time points outlined in Table 1.

The DLQI is a dermatology-specific quality of life instrument designed to measure the health-related quality of life of adult patients suffering from a skin disease [16]. The DLQI consists of 10 questions concerning patients' perception of the impact of skin diseases on different aspects of their health-related quality of life over the last week.

The scoring of each question is as follows:

- Very much = 3 points
- A lot = 2 points
- A little = 1 point
- Not at all, Not relevant, or unanswered = 0 point
- For Question 7, if 'prevented work or studying' is Yes = 3 points

The DLQI is calculated by summing the score of each question resulting in a maximum of 30 and a minimum of 0.

The questionnaire is provided in APPENDIX I.

6.2. Safety Assessment

6.2.1. Adverse Events

AE will be assessed throughout the study period in accordance as described in Section 8.

6.2.2. Clinical Laboratory Evaluations

Blood and urine samples for clinical laboratory test will be collected at the time points outlined in Table 1. Detail instructions of collecting, processing, storage, and shipment for blood samples are described in the Central Laboratory Manual. For urinalysis, collecting and processing urine samples will be proceeded in accordance with local practice or local standard operating procedures (SOP)s.

The parameters for clinical laboratory tests are listed in Table 5.

Table 5. Parameters for Clinical Laboratory Tests

Haematology	• Haemoglobin • Haematocrit • Platelet count • White blood cell count (total and differential)
Chemistry	• Sodium • Potassium • Creatinine

	• Glucose • Calcium • Phosphorus • Total bilirubin • Albumin • ALT • AST • Alkaline phosphatase (ALP) • C-reactive protein (CRP)
Urinalysis (Dipstick)[a]	• Protein • Blood • Leucocytes • Nitrite • Glucose • Ketone • pH • Specific gravity • Bilirubin • Urobilinogen
Virology[b, c]	• HBsAg • HBcAb, total • HCV antibody (HCV Ab) • HIV antibody (HIV Ab)

[a] Urinalysis will be performed by a local laboratory.
[b] At Screening only
[c] HBV (HBsAg and HBcAb), HCV Ab, and HIV Ab test will be performed. Those who are HCV Ab positive will be tested for RNA. Subjects who are HIV Ab positive will do a confirmatory HIV RNA test.

The Investigator will check any laboratory values which have potential significance in subject's safety during the study period. The Investigator will also evaluate any change in laboratory values. Each out of range result should be assessed as not clinically significant or clinically significant by Investigator. All laboratory abnormalities that require intervention (e.g., temporal or permanent discontinuation of IP, need additional concomitant medications or procedures) should be assessed as clinically significant and the clinically significant abnormalities should be recorded as AEs.

Clinical laboratory test including haematology, chemistry, urinalysis can be tested additionally for patient's safety purpose during the study period at the Investigator's discretion.

When a scheduled laboratory test result (after Screening) would not be available due to the subject missing the visit or to technical issues (e.g., sampling error, handling error, tube breakage), it is recommended to perform or repeat the test as soon as available (e.g., at the next scheduled visit) at discretion of the Investigator or Sponsor recommendation.

For laboratory tests required for eligibility determination at Screening, any missing result must be repeated within the screening period to confirm eligibility.

6.2.3. Physical Examination

Physical examinations and abbreviated physical examinations must be performed by trained medical personnel at the time points outlined in Table 1. It is preferable for the same person to perform the physical examination throughout the study (i.e., for all subjects at each visit). The result for physical examinations must be confirmed by the Investigator. The physical examination should include an assessment of the subject's general appearance, skin, head, neck, throat, lymph nodes, cardiovascular, neurological, thyroid, musculoskeletal/extremities, respiratory systems, and the subject's abdomen.

Pelvic, breast, and rectal exams are not required unless medically indicated. The abbreviated physical examination should include an assessment of the subject's general appearance, cardiovascular, respiratory systems, and the subject's abdomen. Other body systems may be examined at the discretion of the Investigator.

Abnormal findings will be documented on the source document, and any clinically significant abnormality or worsening of a previously noted abnormality should be recorded as an AE.

Body weight will be measured at Screening and every visit (recommended to be done after overnight fasting state) but height will be measured only at Screening.

6.2.4. Twelve-lead Electrocardiogram

Twelve-lead electrocardiogram (ECG) measurements will be performed and reviewed by a cardiologist, Investigator, or designee at Screening.

6.2.5. Vital Signs

Vital signs include blood pressure (BP), pulse rate, and body temperature. Vital signs will be assessed at the time points outlined in Table 1.

The Investigator should assess all vital signs and any clinically significant abnormalities should be reported as an AE. If SBP is ≥ 160 mmHg or DBP is ≥ 100 mmHg at Screening, it should be confirmed after a repeat measure after being seated comfortably without talking for at least 5 minutes apart from initial measurement. If repeat test result is still above SBP ≥ 160 mmHg or DBP ≥ 100 mmHg, the subject will be screen failed.

6.2.6. Chest X-ray

Posterior-anterior and lateral chest X-rays should be obtained and reviewed by qualified physician such as radiologist or pulmonologist at Screening and the results reviewed by the Investigator or designee. If chest X-rays were taken within 3 months prior to Randomisation and show no clinically significant abnormality, and there are no signs or symptoms suggestive of pulmonary disease, particularly TB or malignancy, by qualified physician review, that would exclude the subject from the study, then a chest X-ray does not need to be repeated at Screening.

6.2.7. Tuberculosis Evaluation

The Investigator, or designee, will evaluate the subject for signs and symptoms of TB at the time points outlined in Table 1.

This evaluation may be performed in conjunction with the complete or abbreviated physical examination. The following series of questions are suggested for use during the evaluation, but not limited to:

- Please indicate if you are having any of the following problems since last visit.
  - New cough of > 14 days duration or a chronic cough of > 3 weeks
  - Production of sputum
  - Blood-streaked sputum
  - Unexplained weight loss
  - Fever

- Fatigue/tiredness
- Night sweats
- Shortness of breath

- Have you had close contact with an individual with active TB?

If TB is suspected at any point during the study, a chest X-ray and QuantiFERON®-Gold Plus test should be performed. Any diagnostic uncertainties should be clarified with TB specialist. In addition, QuantiFERON®-Gold Plus test will be performed at Screening. Subjects who have indeterminate QuantiFERON®-Gold Plus test result at the first time should have the test repeated. If the subject has an indeterminate result for the repeat test at Screening, the subject will be screen failed.

If a subject is diagnosed as having active TB, it should be reported to the Sponsor according to the instructions in Section 8.1.3. The subject must immediately discontinue administration of IP and should be referred for appropriate treatment.

If a subject is considered to have latent TB from a positive QuantiFERON®-Gold Plus test result at Screening, the subject must be excluded from the study. And subjects who have positive QuantiFERON®-Gold Plus test result after Week 0 must discontinue the IP. Positive QuantiFERON®-Gold Plus test results after Week 0 will be collected as AEs.

6.2.8. Pregnancy Test and Follicle Stimulating Hormone Test

For women of childbearing potential, serum pregnancy test should be performed at Screening. For women with amenorrhea of at least 12 months without an alternative medical cause, a serum FSH test should be performed at Screening. From Randomisation, a urine pregnancy test will be performed locally at the time points outlined in Table 1 and should have a negative result before each IP administration.

Additional pregnancy test(s) may be performed besides the schedule after Randomisation at the Investigator's discretion.

When a pregnancy test result at Screening would not be available due to technical issues (e.g., handling error, sampling error, tube breakage), the test shall be repeated in all circumstances (missing results at Screening would be considered as screening failure).

6.3. Other Assessments

6.3.1. Pharmacokinetic Assessment

Blood samples for PK assessment will be collected at the time points outlined in Table 1. PK assessment will be performed in approximately 140 subjects (70 subjects per treatment group in initial randomisation at Week 0 [Day 1]) participating in PK evaluation.

Only subjects who consent to the PK blood sampling will be enrolled in PK sub-study.

Blood samples for PK assessment will be collected prior to IP administration at the day of IP administration (Week 0, 4, 16, and 28). Blood samples for PK assessment at Week 2, 8, and 12 will be collected at any time during when subject is staying at investigational sites. Subjects' samples may be used for method development, method validation and/or investigation, only for this study.

In all cases, the exact date and time of the PK sampling and IP administration must be carefully recorded in the source documents and eCRF. Detail instructions of collecting, handling, storage, and shipment

for PK samples are described in the Central Laboratory Manual.

6.3.2. Immunogenicity Assessment

Blood samples for immunogenicity assessment will be collected at the time points outlined in Table 1. Immunogenicity assessment will be performed in all randomised subjects.

Blood samples for immunogenicity assessment will be collected prior to IP administration at the day of IP administration (Week 0, 4, 16, 28, and 40). Blood samples for immunogenicity assessment at Week 8, 12, and 52/ET visit will be collected at any time during when subject is staying at investigational sites. Subjects' samples may be used for method development, method validation and/or investigation, only for this study.

In all cases, the exact date and time of the immunogenicity sampling and IP administration must be carefully recorded in the source documents and eCRF. Detail instructions of collecting, handling, storage, and shipment for immunogenicity samples are described in the Central Laboratory Manual.

7. Study Procedures

7.1. Study Flow and Visit Schedule

During this study, efficacy, safety, PK, immunogenicity assessments will be performed at the time points outlined in Table 1. Unless otherwise specified all procedures should be performed pre-dose and highly recommended to be done on the same day with IP dosing. Detail instructions of collecting, processing, storing, and shipping for blood samples are described in the Central Laboratory Manual. Local SOPs will be used for collecting and processing urine samples. All results should be recorded in the source documents along with the date and time the procedures were performed.

7.1.1. Screening Visit

Screening should be performed within 28 days before randomisation. The Investigator must discuss the study with the subject and obtain written informed consent from the subject prior to any study related procedures. Any pre-existing chronic diseases (such as hypertension or diabetes) should be well evaluated and controlled to ensure subject's safety during the study. Any new conditions discovered during the Screening process should be adequately assessed and managed.

The following procedures should be performed:

- Written informed consent
- Demographic information
- Review of medical and surgical history and lifestyle measures (smoking and alcohol history)
- Physical examination (including height and weight; weight is recommended to be measured at overnight fasting state)
- Psoriasis BSA involvement
- Serum pregnancy test for women of childbearing potential
- Serum FSH test for women with amenorrhea of at least 12 months without an alternative medical cause
- 12-lead ECG

- Vital signs
- TB evaluation (refer to Section 6.2.7)
- Chest X-ray (radiographs taken within 3 months from Randomisation with radiologist confirmation will be accepted)
- Blood sampling for QuantiFERON®-Gold Plus test
- Blood and urine sampling for clinical laboratory tests (haematology, chemistry, urinalysis, and virology)
- Eligibility assessment
- Efficacy assessment: PASI and PGA
- Documentation of AEs
- Documentation of all previous and concomitant medications

If the subject is not randomised within 28 days after signing the ICF, the subject must be screen failed (please see Section 4.6).

Once the subject is confirmed eligible for the study, the subject will be reminded in particular of the study restrictions such as contraception, prohibited medications, and other study requirements. The Investigator shall pay attention to each subject's particular needs in order to provide the necessary training and advice and foster protocol compliance.

7.1.2. Treatment Period

7.1.2.1. Visit 1 (Week 0/Day 1)

The following procedures should be performed:

Prior to randomisation

- Physical examination (including weight; weight is recommended to be measured at overnight fasting state)
- Psoriasis BSA involvement
- Urine pregnancy test for women of childbearing potential
- Vital signs
- TB evaluation (refer to Section 6.2.7)
- Blood and urine sampling for clinical laboratory tests (haematology, chemistry, and urinalysis)
- Blood sampling for PK assessment
- Blood sampling for immunogenicity assessment
- Efficacy assessment: PASI, PGA, and DLQI
- Eligibility assessment

Randomisation and IP administration

- Randomisation
  - Randomisation must proceed after all screening procedures including eligibility assessment.
- IP administration
  - The Investigator (or trained designee) must be present at the time of the injection and for at least 30 minutes after the injection and all subjects must be observed carefully for symptoms of an allergic reaction.

Any time regardless of IP administration

- Documentation of AEs
- Documentation of all concomitant medications

7.1.2.2. Visit 2 (Week 2/Day 15 ± 3 days)

The following procedures should be performed:

- Physical examination (including weight; weight is recommended to be measured at overnight fasting state)
- Vital signs
- TB evaluation (refer to Section 6.2.7)
- Blood sampling for PK assessment
- Efficacy assessment: PASI and PGA
- Documentation of AEs
- Documentation of all concomitant medications

7.1.2.3. Visit 3 (Week 4/Day 29 ± 3 days)

The following procedures should be performed:

Prior to IP administration

- Physical examination (including weight; weight is recommended to be measured at overnight fasting state)
- Urine pregnancy test for women of childbearing potential
- Vital signs
- TB evaluation (refer to Section 6.2.7)
- Blood and urine sampling for clinical laboratory tests (haematology, chemistry, and urinalysis)
- Blood sampling for PK assessment
- Blood sampling for immunogenicity assessment
- Efficacy assessment: PASI, PGA, and DLQI

IP administration

- IP administration
  - The Investigator (or trained designee) must be present at the time of the injection and for at least 30 minutes after the injection and all subjects must be observed carefully for symptoms of an allergic reaction.

Any time regardless of IP administration

- Documentation of AEs
- Documentation of all concomitant medications

7.1.2.4. Visit 4 (Week 8/Day 57 ± 3 days)

The following procedures should be performed:

- Physical examination (including weight; weight is recommended to be measured at overnight fasting state)
- Vital signs
- TB evaluation (refer to Section 6.2.7)
- Blood sampling for PK assessment
- Blood sampling for immunogenicity assessment
- Efficacy assessment: PASI and PGA
- Documentation of AEs
- Documentation of all concomitant medications

7.1.2.5. Visit 5 (Week 12/Day 85 ± 3 days)

The following procedures should be performed:

- Physical examination (including weight; weight is recommended to be measured at overnight fasting state)
- Vital signs
- TB evaluation (refer to Section 6.2.7)
- Blood and urine sampling for clinical laboratory tests (haematology, chemistry, and urinalysis)
- Blood sampling for PK assessment
- Blood sampling for immunogenicity assessment
- Efficacy assessment: PASI, PGA, and DLQI
- Documentation of AEs
- Documentation of all concomitant medications

7.1.2.6. Visit 6 (Week 16/Day 113 ± 5 days)

The following procedures should be performed:

Prior to IP administration

- Physical examination (including weight; weight is recommended to be measured at overnight fasting state)
- Urine pregnancy test for women of childbearing potential
- Vital signs
- TB evaluation (refer to Section 6.2.7)
- Blood and urine sampling for clinical laboratory tests (haematology, chemistry, and urinalysis)
- Blood sampling for PK assessment
- Blood sampling for immunogenicity assessment
- Efficacy assessment: PASI, PGA, and DLQI

IP administration

- IP administration
  - The Investigator (or trained designee) must be present at the time of the injection and for at least 30 minutes after the injection and all subjects must be observed carefully for symptoms of an allergic reaction.

Any time regardless of IP administration

- Documentation of AEs
- Documentation of all concomitant medications

7.1.2.7. Visit 7 (Week 20/Day 141 ± 5 days)

The following procedures should be performed:

- Physical examination (including weight; weight is recommended to be measured at overnight fasting state)
- Vital signs
- TB evaluation (refer to Section 6.2.7)
- Efficacy assessment: PASI and PGA
- Documentation of AEs
- Documentation of all concomitant medications

7.1.2.8. Visit 8 (Week 24/Day 169 ± 5 days)

The following procedures should be performed:

- Physical examination (including weight; weight is recommended to be measured at

overnight fasting state)

- Vital signs
- TB evaluation (refer to Section 6.2.7)
- Efficacy assessment: PASI and PGA
- Documentation of AEs
- Documentation of all concomitant medications

7.1.2.9. Visit 9 (Week 28/Day 197 ± 5 days)

The following procedures should be performed:

Prior to re-randomisation

- Physical examination (including weight; weight is recommended to be measured at overnight fasting state)
- Urine pregnancy test for women of childbearing potential
- Vital signs
- TB evaluation (refer to Section 6.2.7)
- Blood and urine sampling for clinical laboratory tests (haematology, chemistry, and urinalysis)
- Blood sampling for PK assessment
- Blood sampling for immunogenicity assessment
- Efficacy assessment: PASI, PGA, and DLQI
- Eligibility assessment
    - If a subject who does not achieve PASI50 response at Week 28, the subject has to discontinue and ET will occur at Week 28 visit. Accordingly, the subject needs to complete the ET procedures (Section 7.1.3)

Re-randomisation and IP administration

- Re-randomisation
    - Only subjects who achieved at least a PASI50 response at Week 28 assessment will be re-randomised and enter the transition period. Subjects receiving Stelara® will be randomised in a 1:1 ratio to either continue to receive Stelara® or be transitioned to SB17. Subjects receiving SB17 will continue to receive SB17 up to Week 40 but they will also follow the randomisation procedure in order to maintain blinding.
- IP administration
    - The Investigator (or trained designee) must be present at the time of the injection and for at least 30 minutes after the injection and all subjects must be observed carefully for symptoms of an allergic reaction.

Any time regardless of IP administration

- Documentation of AEs
- Documentation of all concomitant medications

7.1.2.10. Visit 10 (Week 40/Day 281 ± 7 days)

The following procedures should be performed:

Prior to IP administration

- Physical examination (including weight; weight is recommended to be measured at overnight fasting state)
- Urine pregnancy test for women of childbearing potential
- Vital signs
- TB evaluation (refer to Section 6.2.7)
- Blood and urine sampling for clinical laboratory tests (haematology, chemistry, and urinalysis)
- Blood sampling for immunogenicity assessment
- Efficacy assessment: PASI, PGA, and DLQI

IP administration

- IP administration
  - The Investigator (or trained designee) must be present at the time of the injection and for at least 30 minutes after the injection and all subjects must be observed carefully for symptoms of an allergic reaction.

Any time regardless of IP administration

- Documentation of AEs
- Documentation of all concomitant medications

7.1.2.11. Visit 11 (Week 52/Day 365 ± 7 days)

Visit 11 (Week 52) is defined as 12 weeks (± 7 days) after the last scheduled IP administration (i.e., Week 40). All subjects who complete the last scheduled IP administration at Week 40 will conduct Visit 11.

The following procedures should be performed:

- Physical examination (including weight; weight is recommended to be measured at overnight fasting state)
- Urine pregnancy test for women of childbearing potential
- Vital signs
- TB evaluation (refer to Section 6.2.7)
- Blood and urine sampling for clinical laboratory tests (haematology, chemistry, and urinalysis)

- Blood sampling for immunogenicity assessment
- Efficacy assessment: PASI, PGA, and DLQI
- Documentation of AEs
- Documentation of all concomitant medications

After study completion, subjects should discuss with their physician to switch to the most appropriate psoriasis treatment after their last study visit.

7.1.3. Early Termination

Subjects who discontinue from the study at any time post 1st IP administration will be required to attend an ET visit.

The ET visit is recommended to be performed at 12 weeks (± 7 days) after the last IP administration. When this schedule cannot be done within time (e.g., due to subject not available or other reasons), the ET visit should still be performed as soon as possible and no later than the initially scheduled Week 52 visit date. For subjects who have permanently discontinued the IP between Week 4 and Week 12, it is highly recommended to also complete the Week 12 visit before ET.

The following procedures should be performed:

- Physical examination (including weight; weight is recommended to be measured at overnight fasting state)
- Urine pregnancy test for women of childbearing potential
- Vital signs
- TB evaluation (refer to Section 6.2.7)
- Blood and urine sampling for clinical laboratory tests (haematology, chemistry, and urinalysis)
- Blood sampling for immunogenicity assessment
- Efficacy assessment: PASI, PGA, and DLQI
- Documentation of AEs
- Documentation of all concomitant medications

If the ET visit happens to occur before 11 weeks after the last IP administration, a phone call for safety follow-up will be performed at 12 weeks (± 7 days) after the last IP administration in order to collect AEs and related concomitant medications. If a subject is not available, a phone call for safety follow-up will be performed as soon as possible, but no later than Week 52 from the first IP administration. If the subject refused ET visit, it should be recorded in the subject's medical records and the eCRF. In all cases, the reason for IP discontinuation must be recorded in the subject's medical records and the eCRF. Subjects should discuss with their physician to switch to the most appropriate psoriasis treatment after their last study visit/phone call.

7.1.4. Unscheduled visit

Unscheduled visit is allowed during study period at the discretion of the Investigator, if deemed clinically necessary for the patient's safety. Any tests, procedures, or assessments performed at the

unscheduled visits must be recorded in the source documents and eCRF.

7.2. Discontinuation

7.2.1. Subject Discontinuation

The subject ***must be*** permanently discontinued from IPs in the event of any of the following:

- Consent withdrawal by subject
  - If the subject withdraws his/her consent, the Investigator must inquire the reasons for consent withdrawal as to whether it is related to the study (e.g., AE); however, the subject could refuse to provide such reason.
  - If the main reason for consent withdrawal is considered related to the study, the Investigator may select the appropriate reason for withdrawal (other than just consent withdrawal) from a pre-defined list as below.
- Lost to follow-up
- Pregnancy of study subject
- Serious toxicity (including serious hypersensitivity such as anaphylaxis, TB, exfoliative dermatitis, RPLS, malignancy, pulmonary toxicity such as allergic alveolitis, eosinophilic pneumonia, interstitial pneumonia, or cryptogenic organizing pneumonia, etc.)
- Failure to achieve PASI50 response on Week 28 visit assessment
- Serious lack of IP compliance (Note: if related with toxicity, then toxicity should be selected as main reason for IP discontinuation)
  - A subject missed any of first two doses (at Week 0 [Day 1] and Week 4 [Day 29]) after randomisation.
  - A subject missed two or more doses after Week 12.
- Using or switching to another psoriasis biologic
- Unblinding the study treatment allocation to subject or the Investigator (i.e., breaking the double-blind)
- Any other reasons per the Investigator or the Sponsor determination
- Severe or critical COVID-19, or COVID-19 with sequalae

In addition, the subject ***should be considered to be*** permanently discontinued from IPs in the event of any of the following:

- Other unacceptable toxicity determined by subject or the Investigator (including recurrent or serious infections, etc.)
- Lack of efficacy other than Week 28 determined by subject or the Investigator
- Other lack of protocol compliance (such as 2 or more dose delays or using other prohibited medications/treatment [see Section 5.3.2], etc.)

Subjects who have active COVID-19 infection (regardless of severity) should have the IP temporarily discontinued until the infection resolves. If the condition becomes severe, critical or develops sequalae

the subject should permanently discontinue.

If a subject is prematurely discontinued from IP due to any of the above described reasons, the subject needs to complete the ET procedures (Section 7.1.3).

7.2.2. Discontinuation of Study Sites

Investigational site participation may be discontinued if the Sponsor, the Investigator, or the Institutional Review Board (IRB)/Independent Ethics Committee (IEC) of the investigational site judge it necessary for any reason. Health authorities and IRB/IEC will be informed about the discontinuation of the study sites in accordance with applicable regulations.

7.2.3. Lost to Follow-up

A subject will be considered lost to follow-up if he or she fails to return for scheduled visits and is unable to be contacted by the study site staff. Determination of subject's status as lost to follow-up should be based on Investigator's discretion. Some examples when making consideration could be

- If a subject fails to visit for 2 consecutive scheduled visits (for Week 40, if Week 52 visit is not made) without any notification, loss to follow-up may be considered.
- Before a subject is deemed lost to follow-up, the Investigator or designee should make every effort to regain contact with the subject (such as 3 telephone calls or any other equivalent methods of contact). These contact attempts should be documented in the subject's medical record or study file.
- Should the participant continue to be unreachable, he or she will be considered to have withdrawn from the study with a primary reason of lost to follow-up.

7.2.4. Discontinuation of the Study

The Sponsor may terminate this study prematurely for reasonable cause provided that written notice is submitted to the Investigator, IRB/IEC, and relevant authorities in advance of the intended termination:

- Poor enrolment of subjects making completion of the study within acceptable time frame
- Discontinuation of development of the study drug
- The decision by the Sponsor to terminate the study based on medical/ethical, business decision/strategic, or study conduct-related reasons

If the study is terminated or discontinued prematurely, the Sponsor will promptly notify to the Investigator. The Investigator may be informed of additional procedures to be followed in order to assure that adequate consideration is given to the protection of the subject's welfare and best interests.

Health authorities and IRB/IEC will be informed about the discontinuation of the study in accordance with applicable regulations.

8. Safety Monitoring and Reporting

8.1. Adverse Events

8.1.1. Definition of Adverse Event

An AE is any untoward medical occurrence in a patient or clinical investigation subject administered the medicinal (investigational) product or other protocol-imposed intervention and which does not

necessarily have to have a causal relationship with this treatment or intervention. An AE can therefore be an unfavourable and unintended sign (including an abnormal laboratory finding), symptom, or disease temporally associated with the use of any dose of a medicinal (investigational) product or other protocol-imposed intervention regardless of attribution.

All AEs during the period of observation (as specified in Section 8.1.2) including the events that occurred prior to administration of an IP should be reported as an AE in the AE section of the eCRF.

Pre-existing conditions which worsen (i.e., increase in severity) that meet the definition of an AE during the study are to be reported as AEs.

Diagnostic and therapeutic non-invasive and invasive procedures, such as surgery, should not be reported as AEs. However, the medical condition for which the procedure was performed should be reported if it meets the definition of an AE. For example, an acute appendicitis that begins during the AE reporting period should be reported as an AE and the resulting appendectomy should be recorded as treatment of the AE.

The AEs that emerge during treatment with an IP (i.e., treatment-emergent AE [TEAE]) will be analysed for the purposes of safety analyses.

8.1.1.1. Clinically Significant Abnormality

If there are any abnormalities discovered during the laboratory test, physical examination, vital signs, and/or other safety assessments and the abnormality is assessed clinically significant by the Investigator, it should be reported as an AE. This does not apply to pre-existing conditions which have been documented at Screening or if the abnormality is consistent with a current diagnosis (underlying disease or other AEs). If it is not specified or defined elsewhere in the protocol, clinically significant abnormality may include the events that led to an *intervention*, including withdrawal of the IP treatment, dose reduction, additional concomitant medication, and others evaluated as clinically significant by the Investigator.

If the clinically significant laboratory or other abnormality from safety assessment is not a sign of a disease or syndrome, the abnormality itself should be reported as an AE in the eCRF. If the abnormality can be characterised by a precise clinical term, the clinical term should be reported as the AE. For example, an elevated serum potassium level of 7.0 mEq/L should be reported as 'hyperkalaemia'. Observations of the same clinically significant abnormality from visit to visit should not be repeatedly reported as AEs in the eCRF, unless their aetiology changes (e.g., when the AE severity increases, the maximum severity for the total duration of the event shall be recorded). However, if the AE started before the first IP administration and its severity increases after IP treatment start, a new AE shall be reported and the date of severity increase shall correspond to the new AE onset date (while the pre-existing AE, with the lower severity, shall be stopped).

8.1.2. Period of Observation for Adverse Events

AEs will be reported from the time the ICF is signed until Week 52 or ET (visit or safety follow-up phone call, if done).

The Investigator should observe the AEs for appropriate medical care of the subject until AE resolution or stabilisation. Unresolved AEs during the study period should be followed up until Week 52 or ET and recorded in the eCRF. Thus, the Investigator does not need to actively monitor subjects for AEs once the clinical study has ended.

However, if the subject has an ongoing SAE until Week 52 or ET, these cases should be followed up until event resolution or stabilisation after clinical study end, and reported through the SAE paper form

(see Section 8.2.2).

In addition, SAEs that occurred after the subject had completed the clinical study and are deemed related to the IP in the opinion of the Investigator should be reported to the Sponsor or its designated representative if the Investigator becomes aware of the SAEs (see Section 8.2.2).

8.1.3. Reporting Adverse Events

AEs are to be reported in the eCRF and reviewed by the Investigator. When reporting an AE, a diagnosis (when possible and appropriate) rather than each individual sign and symptom should be reported.

Each AE is to be assessed to determine if it meets the criteria of an SAE (see Section 8.2.1 for SAE definition). If an AE is classified as an SAE, it must be reported to Sponsor, or its designated representative, promptly according to the timeline specified in Section 8.2.2. For an SAE, a diagnosis with a description of signs and symptoms as well as other supporting information that led to the diagnosis should be described in the SAE form provided by the Sponsor (see Section 8.2.2.).

8.1.4. Severity Assessment

The Investigator is responsible for assessing and reporting the severity of AEs.

Following classifications should be used to classify AEs:

- Mild events are usually transient and do not interfere with the subject's daily activities,
- Moderate events introduce a low level of inconvenience or concern to the subject and may interfere with daily activities,
- Severe events interrupt the subject's usual daily activities.

8.1.5. Causality Assessment

The Investigator is responsible for assigning a causal relationship to each AE. The causal relationship between the IP and the AE should be defined as not related (no) or related (yes).

Events should be classified as 'related' if there is a reasonable possibility that the IP caused the AE. This means that there are facts (evidence) or arguments to suggest a causal relationship.

Events should be classified as 'not related' if there is no reasonable possibility that the IP caused the AE.

8.1.6. Expectedness Assessment

Expectedness of AEs will be assessed by referring to the safety information in the Investigator's brochure (IB) of the relevant safety section of IB, as required. More detailed information on expectedness assessment will be explained in the IB.

8.1.7. Withdrawal due to Adverse Events

Subject withdrawal from the study due to an AE should be distinguished from withdrawal due to personal reasons and recorded on the appropriate eCRF section. Subjects withdrawn due to an AE should be followed up until the time point specified in the protocol. When a subject withdraws from the study due to an SAE, the SAE must be reported and followed in accordance with the requirements outlined in Section 8.2.2.

Subjects who discontinue the administration of IPs because of serious or significant safety issues should

be followed closely until the events are fully and permanently resolved or stabilised.

8.2. Serious Adverse Events

8.2.1. Definition of Serious Adverse Event

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

- Results in death,
- Is life-threatening,
- Requires inpatient hospitalisation or prolongation of existing hospitalisation,
- Results in persistent or significant disability/incapacity,
- Results in congenital anomaly/birth defects,
- Is medically important.

Medical and scientific judgement should be exercised in deciding whether expedited reporting is appropriate in other situations, such as important medical events that may not be immediately life-threatening or result in death or hospitalisation. However, if it is determined that the event may jeopardise the subject and may require intervention to prevent one of the other outcomes listed in the definition above, the important medical event should be reported as serious. Examples of such events are intensive treatment in an emergency room or at home for allergic bronchospasm, blood dyscrasias, or convulsions that do not result in hospitalisation or development of drug dependency or drug abuse.

The term ‘severe’ is often used to describe the intensity (severity) of a specific event (as in mild, moderate, or severe myocardial infarction); the event itself, however, may be of relatively minor medical significance (such as severe headache). This is not the same as ‘serious’, which is based on subject/event outcome or action criteria usually associated with events that pose a threat to a subject’s life or functioning.

8.2.1.1. Life-threatening

The term ‘life-threatening’ in the definition of ‘serious’ refers to an event in which the subject was at risk of death at the time of the event; it does not refer to an event which hypothetically might have caused death if it were more severe.

8.2.1.2. Hospitalisation

AEs reported from clinical studies associated with inpatient hospitalisation or prolongations of hospitalisation are considered serious. Staying at an observation unit in the emergency room for more than 24 hours qualifies for hospitalisation. Any events leading to subsequent emergency room visit for less than 24 hours should be in the discretion of Investigator to assess serious as medically important.

Hospitalisation or prolongation of hospitalisation in the absence of a precipitating clinical AE is not in itself an SAE. Examples include:

- Admission for treatment of a pre-existing condition not associated with the development of a new AE or with a worsening of the pre-existing condition (e.g., for work-up of persistent pre-treatment lab abnormality),
- Social admission for convenience (e.g., admission of a subject who does not have a carer),

- Administrative admission (e.g., for a yearly physical exam),
- Optional admission not associated with a precipitating clinical AE (e.g., for elective cosmetic surgery).

Pre-planned treatments or surgical procedures should be noted in the Screening documentation for the individual subject.

8.2.2. Reporting Serious Adverse Events

SAEs must be immediately reported at least within 24 hours of the Investigator becoming aware of the event to Sponsor or its designated representative in the eCRF. In any case when the electronic form would not be available, a paper SAE form can be used as backup.

Date and time (wherever possible) of the Investigator becoming aware of the SAE will be recorded in the source document and SAE form properly.

In particular, if the SAE is fatal or life-threatening, Sponsor must be notified immediately, irrespective of the extent of available AE information. This timeframe also applies to additional (follow-up) information that becomes available on previously forwarded SAE reports. Sponsor will then follow expedited safety reporting procedures according to local and international regulations as appropriate.

The Investigator is obligated to pursue and provide information to Sponsor on all SAEs in accordance with the timeframes for reporting specified above. In addition, an Investigator may be requested by Sponsor to obtain specific additional follow-up information in an expedited fashion. This information may be more detailed than that captured on eCRF. In general, this will include a description of the SAE, which should be provided in sufficient detail so as to allow for a complete medical assessment of the case and independent determination of possible causality. Information on other possible causes of the event, such as concomitant medications and illnesses must be provided. In the case of a subject death, a summary of available autopsy findings must be submitted as soon as possible to Sponsor or its designated representative.

All SAEs will be followed until event resolution or stabilisation (for chronic events), if possible, even when a subject is withdrawn from treatment. For chronic events that do not fully resolve until years later, the outcome should be reported as ‘resolved with sequelae’ as soon as the event has stabilised or returned to baseline. Follow-up information for the SAE should be actively sought and submitted as the information becomes available.

When SAE is not resolved or stabilised until Week 52 or ET, SAE should also be followed-up as appropriate and the information should be submitted to the Sponsor when the information becomes available. If the Investigator detects an SAE in a subject after the Week 52 or ET, and considers the event to be related to the IP or study-related procedures, the Investigator should contact the Sponsor to determine how the SAE should be documented and reported using the paper SAE form.

8.3. Adverse Events of Special Interest

The following AEs will be classified as AESI in this study:

- Systemic hypersensitivity
- Infections
- Pulmonary events

- Injection site reaction

8.3.1. Hypersensitivity

Systemic hypersensitivity reactions, including anaphylaxis and angioedema, have been reported with ustekinumab, in some cases several days after treatment. The site must have trained personnel and equipment/medications to manage serious hypersensitivity reactions such as anaphylaxis. The Investigator (or trained designee) must be present from the time of the injection to at least 30 minutes post-injection to detect any immediate hypersensitivity reaction. Mild or moderate hypersensitivity reactions may be first treated with paracetamol, nonsteroidal anti-inflammatory drugs or antihistamines. If an anaphylactic or other clinically significant hypersensitivity reaction occurs, institute appropriated therapy and discontinue IPs.

8.3.2. Infections

Ustekinumab may have the potential to increase the risk of infections and reactivate latent infections, and serious infections have occurred. Subjects should be instructed to seek medical advice if signs or symptoms suggestive of an infection occur. If a subject develops a serious infection, the subject should be closely monitored and ustekinumab should not be administered until the infection resolves.

8.3.3. Pulmonary Events

Cases of allergic alveolitis and non-infectious pneumonia including interstitial pneumonia, cryptogenic organizing pneumonia, and eosinophilic pneumonia have been reported during post-approval use of ustekinumab. Clinical presentations included cough, dyspnoea, and interstitial infiltrates following one to three doses. Serious outcomes have included respiratory failure and prolonged hospitalisation. Improvement has been reported after discontinuation of ustekinumab and also, in some cases, administration of corticosteroids. If infection has been excluded and diagnosis is confirmed, institute appropriated therapy and discontinue IPs.

8.3.4. Injection Site Reaction

Injection site reactions have been reported with ustekinumab. There is no apparent correlation between the presence of anti-ustekinumab antibodies and the occurrence of injection site reactions.

8.4. Pregnancy

Any pregnancy, including those of female partners of male subjects treated with the IP, should be reported to the Sponsor. If the female partner of a male subject becomes pregnant, a written consent must be obtained from the female partner before collecting any pregnancy-related information. All subjects, from the time the subject receives the first dose of IP until Week 52 or ET visit should be actively monitored for pregnancy. Subjects who were prescribed birth control methods by the Investigator, should be instructed to spontaneously report to the Investigator if a pregnancy occurs up to 15 weeks after the last IP administration. Pregnancies shall be reported to Sponsor, and the IP must be discontinued. Pregnancy reports should be made within 24 hours of the Investigator becoming aware of the pregnancy using the pregnancy report form.

Although pregnancy is not an AE, all pregnancies must be followed up until 6-8 weeks after the outcome of the pregnancy becomes available, unless the subject is lost to follow-up. The pregnancy outcome should be notified to Sponsor by submitting a follow-up pregnancy report form. If the outcome of the pregnancy meets SAE criteria then the Investigator should report this case according to the SAE reporting process (Section 8.2.2).

8.5. Emergency or Accidental Unblinding of Assigned Treatment

Unblinding should be considered only when knowledge of the treatment assignment is deemed essential for the subject's safety by their Investigator or a regulatory body. Emergency unblinding should be decided based on the medical judgement by Investigator considering subjects safety. In general, unblinding of subjects during the conduct of the clinical study should only be performed where there are compelling medical or safety reasons to do so. The responsibility to break the treatment code in emergency situations resides solely with the Investigator.

The IWRS will be used to break the blind and details on how to do this are provided in the IWRS manual including back-up method enabling unblinding. The Sponsor must be notified immediately after a subject and/or the Investigator is unblinded during the course of the study along with the reason for breaking the blind. Pertinent information regarding the circumstances of unblinding of a subject's treatment code must be documented in the subject's source documents. This includes who performed the unblinding, the subject(s) affected, the reason for the unblinding, the date of the unblinding, and the relevant IP information.

Similarly, in case of accidental unblinding (i.e., accidental in that it occurred but it was not deliberated by the Investigator), the Investigator should promptly document the accidental unblinding and inform the Sponsor and the contract research organisation (CRO) of the unblinding occurrence.

Important Note: Unblinding (emergency or accidental) is one of the reasons for subject's discontinuation from study treatment (Section 7.2.1).

8.6. Independent Data and Safety Monitoring Board

An independent DSMB will be assigned for this study. The DSMB will consist of external experts and will review the safety and tolerability data from the study at pre-specified intervals. The details of the safety data and time points for review will be described in the DSMB Charter and in the DSMB statistical analysis plan (SAP).

In addition, an ongoing blinded review of AEs, including clinical laboratory data will be continuously undertaken by the Sponsor medical monitor and project safety monitor.

9. Statistical Methods and Data Analysis

Further information on the statistical methods to be used in this study will be provided in the SAP, which will be finalised prior to the database lock for reporting the main clinical study report (CSR).

Statistical analysis and reporting will be performed as follows:

- **Interim safety analysis for independent DSMB meeting:**

  A DSMB SAP, describing the methodology and presentation of results and access to results will be prepared as a separate document. The safety reports for the DSMB data review meetings will be prepared according to the DSMB SAP.

  The statistical analysis will be performed by an independent statistical reporting team and the results will be communicated to the DSMB directly by an independent unblinded statistician.

- **Main CSR:**

  The main analysis will take place once all subjects complete the procedures at Week 28, or its corresponding visit. Available efficacy, safety, PK, and immunogenicity data will

be analysed and reported.

At the time of this reporting, a limited number of identified individuals of the Sponsor or CRO will be unblinded for reporting purpose. However, subjects, Investigators, and other study personnel will remain blinded throughout the entire study period.

- **Final CSR:**

  The final analysis will take place after the last subject completes the procedures at Week 52 or the corresponding visit. All study data will be analysed and reported for final CSR.

9.1. Statistical Hypotheses

This is a study to demonstrate equivalence in percent change from baseline in PASI at Week 12 between SB17 and Stelara®. The null hypothesis tested for the primary efficacy analysis is that either (1) SB17 is inferior to Stelara® or (2) SB17 is superior Stelara® based on a pre-specified equivalence margin.

9.2. Analysis Sets

The following sets will be used for the analyses performed in the study:

- Randomised Set (RAN) consists of all subjects who receive a randomisation number.
- Full Analysis Set (FAS) consists of all subjects who are randomised. Following the intent-to-treat principle, subjects will be analysed according to the treatment group they are assigned to at Randomisation. However, subjects who do not have any efficacy assessment result after randomisation or do not receive IP during the study period will be excluded from FAS.
- Per-Protocol Set (PPS) consists of all FAS subjects who weight ≤ 100 kg and received 45 mg IP at Week 0 and Week 4 and have PASI assessment result at Baseline and Week 12 without any major PDs that have impact on the primary efficacy assessment. Major PDs that will lead to exclusion from this set will be pre-defined prior to unblinding the treatment group assignment for analyses.
- Safety Set 1 (SAF1) consists of all subjects who receive at least one IP during the study period. Subjects will be analysed according to the IP received.
- Safety Set 2 (SAF2) consists of all subjects in the SAF1 who receive at least one IP after re-randomisation at Week 28. Subjects will be analysed according to the IP received.
- PK Analysis Set (PKS) consists of all subjects in the SAF1 who have at least one serum concentration data.

9.3. Subject Demographic and Baseline Characteristics

Subject demographics and baseline characteristics will be summarised by treatment group for the RAN. Continuous variables (e.g., age, weight, height) will be summarised with descriptive statistics (n, mean, standard deviation [SD], median, minimum, maximum) and categorical variables (e.g., gender, race, ethnicity) will be summarised with frequency and percentage.

Comparison between treatment groups in baseline characteristics will be performed using the chi-square test or *F*-test as appropriate. The results of these tests will be provided including the *p*-value only for descriptive purposes and will not be used as a formal basis to determine the factors to be included in primary or secondary efficacy analysis models. If baseline imbalances are detected for any of the factors,

additional analyses may be performed to adjust for these baseline differences.

Relevant medical history will be summarised by treatment group for the RAN.

9.4. Analysis of the Primary Objective

The primary efficacy analysis will aim to demonstrate equivalence in terms of percent change from baseline in PASI at Week 12 between SB17 and Stelara®.

The primary efficacy analysis will be performed for the PPS with the percent change from baseline in PASI at Week 12 using generalised linear model with the baseline value of PASI as a covariate and site (or pooled centres) and treatment group as factors. The equivalence between the two treatment groups will be declared if the two-sided 95% confidence interval (CI) of the mean difference of percent change from baseline in PASI at Week 12 is entirely contained within the pre-defined equivalence margin of [−15%, 15%]. The similar analysis will be performed for the FAS to support the primary analysis.

Additionally, the two-sided 90% CI of the mean difference between the two treatment groups will be estimated for both PPS and FAS with a narrower pre-defined equivalence margin of [-10%, 10%] as a sensitivity analysis.

To conduct the sensitivity analysis for the FAS, missing data will be imputed using multiple imputation method with the assumption of monotone missing pattern and regression method for subjects who drop out for the study prior to the primary analysis time point. Available case analysis will also be performed for the FAS.

9.5. Analysis of the Secondary Objectives

9.5.1. Efficacy Variable Analyses

As the secondary efficacy endpoints, PGA, PASI50, PASI75, PASI90 response rate, percentage change from baseline in PASI, and change from baseline in DLQI will be summarised by treatment group and visit for the FAS and PPS.

9.5.2. Safety Analyses

Analysis for AE and concomitant medications will be performed for main period, transition period, and overall study period. Analyses for main and transition period will be performed in the SAF1 and SAF2 respectively and analyses for the overall study period will be performed in the SAF1.

All reported terms for AEs will be coded using the Medical Dictionary for Regulatory Activities (MedDRA). For all AE and SAE tables, subjects will be counted once for each preferred term and each system organ class.

A TEAE will be defined as any AE with an onset date on or after the date of the initiation of study drug. AEs which are already present before the initiation of study drug and increase in severity after the initiation of study drug will be considered as TEAEs. Pre-existing AEs before the initiation of study drug with no increase in severity after the initiation of study drug will not be considered as TEAEs.

Other AE will be defined as all TEAEs excluding SAEs.

All AEs, TEAEs, SAEs, AESIs, and other AEs with incidence by preferred term > 5% within any treatment group will be summarised by the number and percentage of subjects experiencing events by system organ class, preferred term, and treatment group. COVID-19 related AEs and SAEs in COVID-19 infected subjects will be summarised by treatment group to determine possible causal relationship with the IP, if needed. SAEs leading to IP discontinuation and TEAEs by causality and

severity will be summarised similarly. All AEs including those existing during the pre-treatment period will be listed by subject.

Changes in vital signs and clinical laboratory measurements parameters will be summarised descriptively by treatment group and visit. Other safety variables will be summarised descriptively by treatment group and visit unless otherwise specified and listed.

Duration of exposure to IP and number of injections will be summarised descriptively by treatment group for the SAF1. Prior and concomitant medications will be summarised by treatment group with frequency and percentage.

9.5.3. Pharmacokinetic Analyses

PK analyses will be performed for the PKS. Serum drug concentration will be summarised descriptively by treatment group and visit.

9.5.4. Immunogenicity Analyses

ADA and NAb results will be summarised with frequency and percentage by treatment group and visit. In addition, incidence of overall ADA will be summarised by treatment group.

9.6. Sample Size Calculations

To calculate equivalence margin, the percent change from baseline in PASI at Week 12 were referred from five randomised controlled studies of ustekinumab.

As seen in Table 6, a fixed-effect meta-analysis of the above five studies estimates a risk difference of CCI with a CCI. Although an equivalence limit of CCI is statistically calculated to preserve CCI of the effect of ustekinumab over and above placebo, a clinical equivalence margin [-15%, 15%] was set for the comparison with the 95% CI of the mean difference in the percent change from baseline in PASI at Week 12.

Table 6. Percent Change from Baseline in PASI at Week 12 from Reference Studies

Reference	Ustekinumab 45 mg		Placebo	
	N	Mean (SD)	N	Mean (SD)
CCI				
Meta-analysis for risk difference with CCI	CCI			

Based on this equivalence margin, a sample size of 192 subjects per treatment group was calculated with the assumptions of common SD of 31.11, 10% loss from the primary analysis and approximately 100 remainders per treatment group after transition at Week 28 at the overall 5% significance level, providing over 90% power. Overall 464 subjects (232 per treatment group) will be randomised into the study to determine equivalence of percent change from baseline in PASI at Week 12.

The nQuery Advisor® option two one-sided equivalence tests (TOST) for two-group design gives the following statement to estimate the n per group to show the equivalence: "*When the sample size in each group is 232, a two group design will have 99.86% power to reject both the null hypothesis that the test mean minus the standard mean is below -15 and the null hypothesis that the test mean minus the*

standard mean is above 15 i.e., that the test and standard are not equivalent, in favor of the alternative hypothesis that the means of the two groups are equivalent, assuming that the expected difference in means is 0, the common standard deviation is 31.33 and that each test is made at the 2.5% level."

The equivalence margin for the comparison with the 90% CI of the difference in the percent change from baseline in PASI at Week 12 will be [-10%, 10%] by the agency recommendation.

Based on this equivalence margin, a sample size of 169 subjects per treatment group was calculated with the assumption of the common SD of 31.11 at the overall 10% significance level, providing 80% power. Overall 338 subjects (169 per treatment group) will be randomised into the study to determine equivalence of percent change from baseline in PASI at Week 12.

The nQuery Advisor® option TOST for two-group design gives the following statement to estimate the n per group to show the equivalence: "*When the sample size in each group is 169, a two group design will have 80% power to reject both the null hypothesis that the test mean minus the standard mean is below -10 and the null hypothesis that the test mean minus the standard mean is above 10 i.e., that the test and standard are not equivalent, in favor of the alternative hypothesis that the means of the two groups are equivalent, assuming that the expected difference in means is 0, the common standard deviation is 31.33 and that each test is made at the 5% level.*"

Therefore, the sample size of 464 allows enough power to detect the equivalence in both situations.

10. Data Collection and Management

10.1. Data Confidentiality

Study information will be labelled with a code number, and will not include the subject's name, hospital number or other information that could identify them. A list linking the code and the subject's name will be kept in the site files as required by ICH E6 (R2) Good Clinical Practice (ICH-GCP).

The coded information will be sent to the Sponsor (or designee) who will analyse it and report the study results both to regulatory and ethical authorities. The Sponsor may also place data on public websites or publish journal articles based upon these results. Care will be taken to prevent subjects being identified through these publications. In addition, data may be shared with other companies or researchers to aid further research. Such data sharing practices will be covered by confidentiality agreements. No-one outside the Investigator site will have access to subject-identifiable information.

10.2. Monitoring

The Sponsor has engaged the services of CRO to perform all monitoring functions within this clinical study. The monitors will work in accordance with the CRO SOPs (and/or Sponsor SOP, if applicable) and have the same rights and responsibilities as monitors from the Sponsor organisation. Monitors will establish and maintain regular contact between the Investigator and the Sponsor.

Monitors will evaluate the competence of each Investigator site and inform the Sponsor about any problems relating to facilities, technical equipment, or medical staff. During the study, monitors will check that written informed consent has been obtained correctly from all subjects and that data are recorded correctly and completely. Monitors will also perform source data verification by comparing entries in the eCRF with corresponding source data and informing the Investigator of any errors or omissions. Monitors will verify adherence to the protocol at the Investigator site. All PDs will be reported to the Sponsor. Monitors will arrange for the supply of IP and ensure appropriate storage conditions are maintained.

Monitoring visits will be conducted at regular intervals according to ICH-GCP and monitoring plan.

The monitor will provide written reports to the Sponsor on each occasion they contact with the Investigator regardless of whether it is by phone or in person.

Further details on the monitoring processes and the level of source data verification to be performed will be outlined in the monitoring plan.

10.3. Data Handling and Record Keeping

The Investigator must maintain essential study documents (protocol and protocol amendments, completed eCRFs, signed ICFs, relevant correspondence, and all other supporting documentation) until at least 2 years after the last approval of a marketing application in an ICH region and until there are no pending or contemplated marketing applications in an ICH region or at least 2 years after the formal discontinuation of clinical development of the IP. These documents should be retained for a longer period if required by the applicable regulatory requirements or the hospital, institution or private practice in which the study is being conducted. Subject identification codes (subject names and corresponding study numbers) will be retained for the same period of time. These documents may be transferred to another responsible party, deemed acceptable by the Sponsor, and who agrees to abide by the retention policies. Written notification of transfer must be submitted to the Sponsor. The Investigator must contact the Sponsor prior to disposing of any study records and obtain written permission to do so.

10.4. Future Use of Stored Specimens and Data

The Sponsor or designated representative can store PK and/or immunogenicity samples for maximum 10 years after the end of the clinical study (refer to Section 3.5). The Sponsor or designated representative should operate under the same regulations related to and take the same responsibility to save personal data. The sample may be used for additional assay to be performed if considered scientifically relevant or requested by regulatory authorities in order to have the possibility to perform the assay.

10.5. Database Management and Coding

Data generated within this clinical study will be handled according to the relevant SOPs of the data management and biostatistics departments of the Sponsor (or an appropriate company designated by the Sponsor to perform these activities). Subject data will be captured in an eCRF and reviewed by the monitor in order to check adherence to the protocol and to detect any data inconsistency or discrepancy.

The Investigator must ensure that the clinical data required by the study protocol are carefully reported in the eCRF. He/she must also check that the data reported in the eCRF correspond to those in the medical records.

Data must be entered into eCRFs in English by the designated Investigator site personnel in a timely manner. Forms should be available during periodic visits by study monitors to enable review for completeness and acceptability. Any correction to the data entered into the eCRF must be carried out by the Investigator or a designated member of staff. These changes may be made either on the initiative of the investigational staff or in response to monitoring or data queries. Any changes or corrections to the CRF should not obscure the original entry (i.e., an audit trail should be maintained). Monitors and clinical data managers will review the eCRF for accuracy and can generate queries to the investigational staff for resolution. Corrections will be recorded in an audit trail that records the old information, the new information, and identification of the person making the changes, date of correction made, and reason for change. The Investigator must sign and date the eCRF pages as indicated.

Medical/surgical history and underlying diseases and AEs will be coded using the MedDRA.

Concomitant medications will be coded using the World Health Organization-Drug Dictionary. The versions of coding dictionaries used will be stated in the clinical study report.

10.6. Quality Control and Quality Assurance

During the conduct of the study, the Sponsor or its agent will conduct periodic monitoring visits to ensure that the protocol and ICH-GCP are being followed. The monitors may review source documents to confirm that the data recorded are accurate. The Investigator and institution will allow the domestic and foreign regulatory authorities and the authorised representative of the Sponsor including monitors and auditors' direct or remote access to source documents to perform this verification without violating the confidentiality of the subject, to the extent permitted by the applicable laws and regulations. The investigational site may be subject to review by the IRB/IEC, to quality assurance audits and/or quality control visits performed by the Sponsor, and/or to inspection by appropriate regulatory authorities. It is important that the Investigators and their relevant personnel are available during the monitoring visit, possible audits, and/or regulatory inspection(s) and that sufficient time is devoted to the process.

10.7. Protocol Deviation

PDs will be pre-defined prior to subject enrolment and documented separately named as Protocol Deviation Definition List which includes category (e.g., violation of inclusion/exclusion criteria, use of prohibited medication, non-compliance with treatment), deviation description, severity (major or minor), time point for each PD. Major PDs are defined as those deviations from the protocol likely to have an impact on the perceived efficacy and/or safety of study treatments.

PDs will be reviewed and confirmed prior to database lock to decide which subjects and/or subject data will be excluded from certain analyses. Decisions regarding the exclusion of subjects and/or subject data from analyses will be documented and approved prior to database lock.

PDs related to COVID-19 will be listed separately, if needed.

11. Ethics Considerations and Administrative Procedures

11.1. Institutional Review Boards and Independent Ethics Committees

The Investigator and the Sponsor will follow all local laws and regulations relating to contact with and approvals from the IRB/IEC.

The Investigator must provide the Sponsor with documentation of IRB/IEC approval of the protocol and informed consent before the study may begin at the Investigator site. The Investigator will supply documentation to the Sponsor relating to the annual renewal of the protocol, if applicable, from the IRB/IEC and any approvals of revisions to the ICF or amendments to the protocol.

The Investigator will report promptly to the IRB/IEC any new information that may adversely affect the safety of subjects or the conduct of the study. Similarly, the Investigator will submit written summaries of the study status to the IRB/IEC on a regular basis and in accordance with the timelines required locally. Upon completion of the study, the Investigator will provide the ethics committee with a report on the outcome of the study if required by local regulations.

11.2. Ethical Conduct of the Study

This study will be conducted and informed consent will be obtained from each subject according to the ethical principles stated in the Declaration of Helsinki (2013), the ICH-GCP and the applicable drug and data protection laws and regulations of the countries where the study will be conducted.

11.3. Subject Information and Informed Consent

The ICF will be used to explain the risks and benefits of study participation to the subject in simple terms before the subject enters into the study. The ICF contains a statement that the consent is freely given, that the subject is aware of the risks and benefits of entering the study, and that the subject is free to withdraw from the study at any time. Written consent must be given by the subject and/or legal representative, after the receipt of detailed information on the study.

The Investigator is responsible for ensuring that informed consent is obtained from each subject or legal representative and for obtaining the appropriate signatures and dates on the ICF prior to the performance of any protocol procedures and prior to the administration of IP. The Investigator will provide each subject with a copy of the signed and dated ICF and this will be documented in the subject's source notes.

11.4. Investigator Information

11.4.1. Investigator Obligations

This study will be conducted in accordance with the ICH-GCP (2016), the ethical principles that have their origin in the Declaration of Helsinki (2013) and local laws and regulations.

The Investigator is responsible for ensuring that the study is conducted according to the signed Investigator statement, the study protocol and applicable regulations; for protecting the rights, safety and welfare of subjects under the Investigator's care; and for the control of drugs under investigation. The Investigator must obtain the informed consent of each subject to whom IP is administered.

11.4.2. Coordinating Investigator

The Sponsor will designate the Coordinating Investigator who will have the responsibility for the coordination of the Investigators in a multicentre clinical study.

11.4.3. Training of Investigator Site Personnel

Before the first subject is enrolled into the study, a Sponsor representative will review and discuss the requirements of the clinical study protocol and related documents with the investigational staff and will also train them in any study-specific procedures.

The Investigator will ensure that appropriate training relevant to the study is given to all investigational staff and that any new information relevant to the performance of this study is forwarded to the investigational staff involved.

The Investigator will maintain a record of all individuals involved in the study (medical, nursing, and other investigational staff).

11.4.4. Protocol Signatures

The Investigator must sign the Investigator Signature Page of this protocol prior to starting recruitment for the study. By signing the protocol, the Investigator confirms in writing that he/she has read, understands and will strictly adhere to the study protocol and will conduct the study in accordance with ICH-GCP and applicable regulatory requirements.

11.4.5. Financing and Insurance

Samsung Bioepis is the Sponsor of this study and will be providing the finances to cover the operation of the study. Details of financial agreements are provided in the Clinical Study Agreements with the

Investigator sites and in contracts with other companies involved in the running of the study.

The Sponsor has obtained suitable insurance for this study. A copy of the insurance details will be provided to each Investigator who will be responsible for providing the IRB/IEC with these details according to local requirements.

12. Publication Policy

The Sponsor supports the efforts of health authorities to increase the transparency of medical research conducted in human subjects. The Sponsor will register and maintain the information of clinical studies on a public registry program. The Sponsor is committed to the public disclosure of the results from clinical studies through posting on public clinical study data banks. The Sponsor will comply with the guidelines of regulatory authorities with regards to public registration and disclosure of clinical study data.

The clinical study data collected during the study are confidential and proprietary to the Sponsor. Sponsor shall have the right to delete any confidential or proprietary information contained in any proposed abstract or presentation.

Any publications from this study should be approved by the Sponsor prior to publication or presentation. The rights of the Investigator with regard to publication of this study are described in the Clinical Study Agreement.

13. References

1. Global report on Psoriasis. WHO. (2016). Retrieved Feb 18, 2020 from https://apps.who.int/iris/bitstream/handle/10665/204417/9789241565189_eng.pdf

2. Menter A, Gottlieb A, Feldman SR, et al. Guidelines of care for the management of psoriasis and psoriatic arthritis. *J Am Acad Dermatol*. 2008; 56 (5): 826-850.

3. Product Information of Stelara®. EMA. (Jan 29, 2021). Retrieved Feb 15, 2021 from https://www.ema.europa.eu/en/documents/product-information/stelara-epar-product-information_en.pdf

4. European Public Assessment Report (EPAR) of Stelara®. EMA. (Feb 09, 2009). Retrieved Feb 18, 2020 from https://www.ema.europa.eu/en/documents/assessment-report/stelara-epar-public-assessment-report_en.pdf

5. Griffiths CE, Strober BE, van de Kerkhof P, et al. Comparison of ustekinumab and etanercept for moderate-to-severe psoriasis. *N Engl J Med*. 2010; 362 (2): 118-28.

6. Biosimilar medicines: Overview. EMA. Retrieved Mar 09, 2020 from https://www.ema.europa.eu/en/human-regulatory/overview/biosimilar-medicines-overview

7. Guidance on the management of clinical trials during the COVID-19 (Coronavirus) pandemic. EMA. (Mar 2020, Version 4.0 on Feb 04, 2021). Retrieved Feb 15, 2021 from https://ec.europa.eu/health/sites/health/files/files/eudralex/vol-10/guidanceclinicaltrials_covid19_en.pdf

8. Guidance on conduct of clinical trials of medical products during COVID-19 public health emergency. FDA. (Mar 2020, updated on Jan 27, 2021). Retrieved Feb 15, 2021 from https://www.fda.gov/regulatory-information/search-fda-guidance-documents/fda-guidance-conduct-clinical-trials-medical-products-during-covid-19-public-health-emergency

9. Prescribing Information of Stelara®. FDA. (Dec 11, 2020). Retrieved Feb 15, 2021 from https://www.accessdata.fda.gov/drugsatfda_docs/label/2020/761044s008lbl.pdf

10. Guideline on similar biological medicinal products containing biotechnology-derived protein as active substance: non-clinical and clinical issues. EMA. (Jul 01, 2015). Retrieved Feb 18, 2020 from https://www.ema.europa.eu/en/documents/scientific-guideline/guideline-similar-biological-medicinal-products-containing-biotechnology-derived-proteins-active_en-2.pdf

11. Leonardi CL, Kimball AB, Papp KA, et al. Efficacy and safety of ustekinumab, a human interleukin-12/23 monoclonal antibody, in patients with psoriasis: 76-week results from a randomised, double-blind, placebo-controlled trial (PHOENIX 1). *Lancet*. 2008; 371 (9625): 1665-74.

12. Papp KA, Langley RG, Lebwohl M, et al. Efficacy and safety of ustekinumab, a human interleukin-12/23 monoclonal antibody, in patients with psoriasis: 52-week results from a randomised, double-blind, placebo-controlled trial (PHOENIX 2). *Lancet*. 2008; 371 (96251675-84.

13. Fiorentino D, Ho V, Lebwohl MG, et al. Risk of malignancy with systemic psoriasis treatment in the Psoriasis Longitudinal Assessment Registry. *J Am Acad Dermatol*. 2017; 77(5): 845-854.e5

14. Guidance for industry: Scientific considerations in demonstrating biosimilarity to a reference product. FDA. (Apr 2015). Retrieved Feb 18, 2020 from

https://www.fda.gov/media/82647/download

15. Guideline on similar biological medicinal products containing biotechnology-derived proteins as active substance: quality issues (revision 1). EMA. (Dec 01, 2014). Retrieved Feb 18, 2020 https://www.ema.europa.eu/en/documents/scientific-guideline/guideline-similar-biological-medicinal-products-containing-biotechnology-derived-proteins-active_en-0.pdf

16. Finlay AY, Khan GK. Dermatology Life Quality Index (DLQI) -- a simple practical measure for routine clinical use. *Clin Exp Dermatol*. 1994; 19 (3), 210-06.

17. Tsai TF, Ho JC, Song M, et al. Efficacy and safety of ustekinumab for the treatment of moderate-to-severe psoriasis: a phase III, randomized, placebo-controlled trial in Taiwanese and Korean patients (PEARL). *J Dermatol Sci*. 2011; 63 (3): 154-63.

18. Zhu X, Zheng M, Song M, et al. Efficacy and safety of ustekinumab in Chinese patients with moderate to severe plaque-type psoriasis: results from a phase 3 clinical trial (LOTUS). *J Drugs Dermatol*. 2013; 12 (2): 166-74.

19. Igarashi A, Kato T, Kato M, et al. Efficacy and safety of ustekinumab in Japanese patients with moderate-to-severe plaque-type psoriasis: long-term results from a phase 2/3 clinical trial. *J Dermatol*. 2012; 39 (3): 242-52.

APPENDIX I. Dermatology Life Quality Index Questionnaire

Hospital No: Date: **DLQI**

Name:

Address: Diagnosis: Score:

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.

Protocol Signature Pages

SIGNATURE PAGE

Declaration of Sponsor Representative

Protocol Title: A Phase III, Randomised, Double-blind, Multicentre Clinical Study to Evaluate the Efficacy, Safety, Tolerability, Pharmacokinetics, and Immunogenicity of SB17 (proposed ustekinumab biosimilar) Compared to Stelara® in Subjects with Moderate to Severe Plaque Psoriasis

This clinical study protocol was subjected to critical review. The information it contains is consistent with current knowledge of the risks and benefits of the investigational medicinal product, as well as with the moral, ethical, and scientific principles governing clinical research as set out in the Declaration of Helsinki, 2013 and the guidelines on Good Clinical Practice applicable to this clinical study.

Sponsor Representative

Name: PPD

Institution: Samsung Bioepis Co., Ltd.

Signature: PPD Date: PPD
(MMM DD, YYYY)

SIGNATURE PAGE

Declaration of the Principal Investigator

Protocol Title: A Phase III, Randomised, Double-blind, Multicentre Clinical Study to Evaluate the Efficacy, Safety, Tolerability, Pharmacokinetics, and Immunogenicity of SB17 (proposed ustekinumab biosimilar) Compared to Stelara® in Subjects with Moderate to Severe Plaque Psoriasis

This clinical study protocol was subjected to critical review. The information it contains is consistent with current knowledge of the risks and benefits of the investigational medicinal product, as well as with the moral, ethical, and scientific principles governing clinical research as set out in the Declaration of Helsinki, 2013 and the guidelines on Good Clinical Practice applicable to this clinical study.

Principal Investigator

Name: _____

Institution: _____

Signature: _____ Date: _____
(MMM DD, YYYY)

CHANGE HISTORY OF PROTOCOL AMENDMENT

Amendment 1: Version 2.0, Feb 15, 2021

Section Affected	Original Content	Amended/New Content	Rationale
SYNOPSIS Eligibility Criteria for Main Period	Exclusion Criteria (…) 14. Have active or latent tuberculosis (TB) at Screening, by known history or any of the following: a. Positive QuantiFERON®-Gold Plus test. b. Positive chest X-ray findings (radiographs taken within 3 months prior to Randomisation with radiologist confirmation will be accepted) determined by a qualified radiologist, including active TB, untreated or inadequately treated old, inactive or healed TB. c. By any other positive findings determined by TB specialist, including suggestive signs or symptoms of TB or recent close contact with active TB patients. (…)	Exclusion Criteria (…) 14. Have active or latent tuberculosis (TB) at Screening, by known history or any of the following: a. Positive QuantiFERON®-Gold Plus test. b. Positive chest X-ray findings (radiographs taken within 3 months prior to Randomisation with radiologist confirmation will be accepted) determined by a qualified **physician such as** radiologist **or pulmonologist**, including active TB, untreated or inadequately treated old, inactive or healed TB. c. By any other positive findings determined by TB specialist, including suggestive signs or symptoms of TB or recent close contact with active TB patients. (…)	To clarify the reviewer
LIST OF STUDY STAFF	**SPONSOR:** **Samsung Bioepis Co., Ltd.** 107, Cheomdan-daero, Yeonsu-gu, Incheon, 21987 Republic of Korea	**SPONSOR:** **Samsung Bioepis Co., Ltd.** ~~**107, Cheomdan-daero,**~~ **76, Songdogyoyuk-ro,** Yeonsu-gu, Incheon, 21987 Republic of Korea	Administrative Change

Section Affected	Original Content	Amended/New Content	Rationale
	Clinical Project Manager PPD Clinical Development Lead PPD Clinical Research Scientist PPD Statistician PPD Safety Physician PPD Project Safety Lead PPD	Clinical Project Manager PPD Clinical Development Lead PPD Clinical Research Scientist PPD Statistician PPD Safety Physician PPD	

Section Affected	Original Content	Amended/New Content	Rationale
		Project Safety Lead PPD [redacted]	
1.5.2. Known Potential Benefits	(…) The efficacy of Stelara® in PASI and PGA scores was statistically significant in plaque psoriasis after 12 weeks of treatment. The proportion of patients achieving PASI75 response at week 12 was respectively 72.2% and 65% on 45 mg and 90 mg respectively. Approximately 35 to 50% of subjects achieved a PASI90 response at Week 12. Similar efficacy was observed when efficacy was assessed using the PGA.	(…) The efficacy of Stelara® in PASI and PGA scores was statistically significant in plaque psoriasis after 12 weeks of treatment. The proportion of patients achieving PASI75 response at ~~w~~Week 12 was ~~respectively~~ 72.2% and 65% on 45 mg and 90 mg, respectively. Approximately 35 to 50% of subjects achieved a PASI90 response at Week 12. Similar efficacy was observed when efficacy was assessed using the PGA.	Editorial change
4.3. Exclusion Criteria for Main Period	Exclusion Criteria (…) 14. Have active or latent tuberculosis (TB) at Screening, by known history or any of the following: a. Positive QuantiFERON®-Gold Plus test. b. Positive chest X-ray findings (radiographs taken within 3 months prior to Randomisation with radiologist confirmation will be accepted) determined by a qualified radiologist, including active TB, untreated or inadequately treated old, inactive or healed TB. c. By any other positive findings determined by TB specialist, including suggestive signs or symptoms of TB or recent close contact with active TB patients. (…)	Exclusion Criteria (…) 14. Have active or latent tuberculosis (TB) at Screening, by known history or any of the following: a. Positive QuantiFERON®-Gold Plus test. b. Positive chest X-ray findings (radiographs taken within 3 months prior to Randomisation with radiologist confirmation will be accepted) determined by a qualified **physician such as** radiologist **or pulmonologist**, including active TB, untreated or inadequately treated old, inactive or healed TB. c. By any other positive findings determined by TB specialist, including suggestive signs or symptoms of TB or recent close contact with active TB patients. (…)	To clarify the reviewer

Section Affected	Original Content	Amended/New Content	Rationale
6.2.4. Twelve-lead Electrocardiogram	Twelve-lead electrocardiogram (ECG) measurements will be performed and reviewed by a cardiologist or qualified physician at Screening.	Twelve-lead electrocardiogram (ECG) measurements will be performed and reviewed by a cardiologist~~ or qualified physician~~**, Investigator, or designee** at Screening.	To clarify the reviewer
6.2.6 Chest X-ray	Posterior-anterior and lateral chest X-rays should be obtained at Screening and reviewed by the Investigator or designee. If chest X-rays were taken within 3 months prior to Randomisation and show no clinically significant abnormality, and there are no signs or symptoms suggestive of pulmonary disease, particularly TB or malignancy, by qualified radiologist, that would exclude the subject from the study, then a chest X-ray does not need to be repeated at Screening.	Posterior-anterior and lateral chest X-rays should be obtained **and reviewed by qualified physician such as radiologist or pulmonologist** at Screening and **the results** reviewed by the Investigator or designee. If chest X-rays were taken within 3 months prior to Randomisation and show no clinically significant abnormality, and there are no signs or symptoms suggestive of pulmonary disease, particularly TB or malignancy, by qualified ~~radiologist~~**physician review**, that would exclude the subject from the study, then a chest X-ray does not need to be repeated at Screening.	To clarify the reviewer
13. Reference	(…) 3. Product Information of Stelara®. EMA. (Feb 25, 2020). Retrieved Dec 21, 2020 from https://www.ema.europa.eu/en/documents/product-information/stelara-epar-product-information_en.pdf (…) 7. Guidance on the management of clinical trials during the COVID-19 (Coronavirus) pandemic. EMA. (Mar 2020, Version 3.0 on Apr 2020). Retrieved Oct 13, 2020 from https://ec.europa.eu/health/sites/health/files/files/eudralex/vol-10/guidanceclinicaltrials_covid19_en.pdf 8. Guidance on conduct of clinical trials of medical products during COVID-19 public health emergency. FDA. (Mar 2020, updated on Dec 2020). Retrieved Dec 21, 2020 from	(…) 3. Product Information of Stelara®. EMA. (~~Feb 25, 2020~~**Jan 29, 2021**). Retrieved ~~Dec 21, 2020~~**Feb 15, 2021** from https://www.ema.europa.eu/en/documents/product-information/stelara-epar-product-information_en.pdf (…) 7. Guidance on the management of clinical trials during the COVID-19 (Coronavirus) pandemic. EMA. (Mar 2020, ~~Version 3.0 on Apr 2020~~**Version 4.0 on Feb 04, 2021**). Retrieved ~~Oct 13, 2020~~**Feb 15, 2021** from https://ec.europa.eu/health/sites/health/files/files/eudralex/vol-10/guidanceclinicaltrials_covid19_en.pdf 8. Guidance on conduct of clinical trials of medical products during COVID-19 public health emergency. FDA. (Mar	To reflect latest version

Section Affected	Original Content	Amended/New Content	Rationale
	https://www fda.gov/regulatory-information/search-fda-guidance-documents/fda-guidance-conduct-clinical-trials-medical-products-during-covid-19-public-health-emergency 9. Prescribing Information of Stelara®. FDA. (Dec 11, 2019). Retrieved Dec 21, 2020 from https://www.accessdata.fda.gov/drugsatfda_docs/label/2019/125261s142,761044s001lbl.pdf 10. Guideline on similar biological medicinal products containing biotechnology-derived protein as active substance: non-clinical and clinical issues. EMA. (Dec 18, 2014). Retrieved Feb 18, 2020 from https://www.ema.europa.eu/en/documents/scientific-guideline/guideline-similar-biological-medicinal-products-containing-biotechnology-derived-proteins-active_en-2.pdf (…) 15. Guideline on similar biological medicinal products containing biotechnology-derived proteins as active substance: quality issues (revision 1). EMA. (May 22, 2014). Retrieved Feb 18, 2020 https://www.ema.europa.eu/en/documents/scientific-guideline/guideline-similar-biological-medicinal-products-containing-biotechnology-derived-proteins-active_en-0.pdf (…)	2020, updated on ~~Dec 2020~~**Jan 27, 2021**). Retrieved ~~Dec 21, 2020~~**Feb 15, 2021** from https://www fda.gov/regulatory-information/search-fda-guidance-documents/fda-guidance-conduct-clinical-trials-medical-products-during-covid-19-public-health-emergency 9. Prescribing Information of Stelara®. FDA. (Dec 11, ~~2019~~2020). Retrieved ~~Dec 21, 2020~~**Feb 15, 2021** from ~~https://www.accessdata.fda.gov/drugsatfda_docs/label/2019/125261s142,761044s001lbl.pdf~~**https://www.accessdata.fda.gov/drugsatfda_docs/label/2020/761044s008lbl.pdf** 10. Guideline on similar biological medicinal products containing biotechnology-derived protein as active substance: non-clinical and clinical issues. EMA. (~~Dec 18, 2014~~**Jul 01, 2015**). Retrieved Feb 18, 2020 from https://www.ema.europa.eu/en/documents/scientific-guideline/guideline-similar-biological-medicinal-products-containing-biotechnology-derived-proteins-active_en-2.pdf (…) 15. Guideline on similar biological medicinal products containing biotechnology-derived proteins as active substance: quality issues (revision 1). EMA. (~~May 22, 2014~~ **Dec 01, 2014**). Retrieved Feb 18, 2020 https://www.ema.europa.eu/en/documents/scientific-guideline/guideline-similar-biological-medicinal-products-containing-biotechnology-derived-proteins-active_en-0.pdf (…)	