1 FINAL CLINICAL STUDY PROTOCOL

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Biocon Biologics UK Limited

Protocol Title: A Randomized, Double-Blind, Parallel Group, Multicenter, Phase 3 Study to Compare the Efficacy and Safety of Bmab 1200 and Stelara® in Patients with Moderate to Severe Chronic Plaque Psoriasis

Protocol Number: BM12H-PSO-03-G-02

STELLAR-2: Study to Test Efficacy and safety of biosimiLar ustekinumab to steLARa

IND Number:	153118
EudraCT Number:	2021-006668-25
Name of Investigational Product:	Bmab 1200
Phase of Development:	Phase 3
Indication:	Plaque Psoriasis
Sponsor:	[redacted]
Sponsor Contact	[redacted]
Protocol Version:	Version 3.0; Amendment 02
Protocol Date:	12-Jan-2023

PROTOCOL APPROVAL SIGNATURES

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This study will be conducted in compliance with the clinical study protocol, International Council for Harmonisation (ICH) guidelines for current Good Clinical Practice (GCP), and applicable regulatory requirements.

INVESTIGATOR SIGNATURE PAGE

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Confidentiality and Current Good Clinical Practice (GCP)/E6(R2)/Compliance Statement

- I, the undersigned, have reviewed this protocol, including appendices, and I will conduct the study as described in compliance with this protocol, GCP, and relevant International Council for Harmonisation (ICH) guidelines.
- I am thoroughly familiar with the appropriate use of the study drug, as described in this protocol and any other information provided by Biocon Biologics UK Limited including, but not limited to, the current investigator's brochure.
- Once the protocol has been approved by the independent ethics committee (IEC)/institutional review board (IRB), I will not modify this protocol without obtaining prior approval of Biocon Biologics UK Limited and of the IEC/IRB. I will submit the protocol amendments and/or any informed consent form modifications to Biocon Biologics UK Limited and the IEC/IRB, and approval will be obtained before any amendments are implemented.
- I ensure that all persons or party assisting me with the study are adequately qualified and informed about the Biocon Biologics UK Limited study drug and of their delegated study-related duties and functions as described in the protocol.
- I ensure that source documents and trial records that include all pertinent observations on each of the site's trial patients will be attributable, legible, contemporaneous, original, accurate, and complete.
- I understand that all information obtained during the conduct of the study with regard to the patients' state of health will be regarded as confidential. No patients' names will be disclosed. All patients will be identified by assigned numbers on all case report forms, laboratory samples, or source documents forwarded to the Sponsor. Clinical information may be reviewed by the Sponsor or its agents or regulatory agencies. Agreement must be obtained from the patient before disclosure of patient information to a third party.
- Information developed in this clinical study may be disclosed by Biocon Biologics UK Limited to other clinical investigators, regulatory agencies, or other health authority or government agencies as required.

<Name>

<Title>

<Institution>

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Investigator Signature

_____

Date (DD-Mmm-YYYY)

2 SYNOPSIS

Title of Study:	A Randomized, Double-Blind, Parallel Group, Multicenter, Phase 3 Study to Compare the Efficacy and Safety of Bmab 1200 and Stelara® in Patients with Moderate to Severe Chronic Plaque Psoriasis
Protocol Number:	BM12H-PSO-03-G-02
Investigators/Study Sites:	The study is planned to be conducted in Europe and North America across approximately 42 sites in 6 countries.
Phase of Development:	Phase 3
Objectives:	Primary Objective: • To demonstrate equivalent efficacy between Bmab 1200 and Stelara® in patients with moderate to severe chronic plaque psoriasis. Secondary Objectives: • To assess the efficacy of Bmab 1200 based on other efficacy parameters and timepoints over the study period as compared with Stelara®. • To assess the safety and tolerability of Bmab 1200 as compared with Stelara® over the study period. • To assess the immunogenicity of Bmab 1200 as compared with Stelara® over the study period. • To assess the PK of Bmab 1200 as compared with Stelara®. • To assess the safety and immunogenicity after switching from Stelara® to Bmab 1200.
Study Endpoints:	Primary Endpoint: • Percentage change from baseline in the Psoriasis Area and Severity Index (PASI) score at Week 12 (Time Frame: Baseline [Day 1] to Week 12). Secondary Endpoints: Efficacy Endpoints: • Percentage change from baseline in the PASI score at Weeks 4, 8, 16, 20, 28, 40, and 52 (Time Frame: Baseline [Day 1] through Weeks 28 and 52). • PASI improvement of ≥50% relative to baseline (PASI 50), PASI improvement of ≥75% relative to baseline (PASI 75), and PASI improvement of ≥90% relative to baseline (PASI 90) at Weeks 4, 8, 12, 16, 20, 28, 40, and 52 (Time Frame: Baseline [Day 1] through Weeks 28 and 52). • Static Physician's Global Assessment (sPGA) response of cleared or almost clear/minimal (PGA of 0 or 1) at Weeks 4, 8, 12, 16, 20, 28, 40, and 52 (Time Frame: Baseline [Day 1] through Weeks 28 and 52). • Area under effect curves (AUECs) of PASI score from baseline to Week 12 (Time Frame: Baseline [Day 1] through Week 12). • Raw PASI scores at Weeks 4, 8, 12, 16, 20, 28, 40, and 52 (Time Frame: Baseline [Day 1] through Weeks 28 and 52). • Change from baseline in affected body surface area (BSA) at Weeks 4, 8, 12, 16, 20, 28, 40, and 52 (Time Frame: Baseline [Day 1] through Weeks 28 and 52). • Change from baseline in quality of life (QoL) as measured by Dermatology Life Quality Index (DLQI) scores at Weeks 4, 8, 12, 16, 20, 28, 40, and 52 (Time Frame: Baseline [Day 1] through Weeks 28 and 52). Safety Endpoints: • Treatment-emergent adverse events (TEAEs) including adverse events of special interest (AESIs) and adverse reactions (ADRs) during the treatment periods (Time Frame: Baseline [Day 1] through Weeks 28 and 52).

	• Injection site reactions and hypersensitivity at Day 1, Week 4, Week 16, Week 28, Week 40, and throughout the study (Time Frame: Baseline [Day 1] through Weeks 28 and 52).
	• Other safety endpoints as follows (Time Frame: Baseline [Day 1] through Weeks 28 and 52):
	  ○ Absolute values and changes from baseline in
	  ▪ Clinical laboratory assessments (hematology, clinical chemistry, and urinalysis)
	  ▪ Vital sign parameters (systolic and diastolic blood pressure, pulse rate, respiratory rate, and body temperature)
	  ▪ 12-lead electrocardiogram (ECG)
	  ○ Physical examination
	Immunogenicity Endpoints:
	• Proportion of patients developing antidrug antibodies (ADAs) and neutralizing antibodies (NAbs) during treatment period 1 (TP1) (Time Frame: Baseline [Day 1] through Week 16).
	• Proportion of patients developing ADAs and NAbs during treatment period 2 (TP2) (Time Frame: post rerandomization/dosing on Week 16 through Week 28 predosing).
	• Proportion of patients developing ADAs and NAbs during treatment period 3 (TP3) (Time Frame: postdosing on Week 28 through Week 52).
	Pharmacokinetic (PK) Endpoints:
	• Serum concentrations of ustekinumab during TP1 (Time Frame: Baseline [Day 1] through Week 16).
	• Serum concentrations of ustekinumab during TP2 (Time Frame: post rerandomization/dosing on Week 16 through Week 28 predosing).
	• Serum concentrations of ustekinumab during TP3 (Time Frame: postdosing on Week 28 through Week 52).

Study Design:	This is a randomized, double-blind, active-controlled, parallel group, multicenter study designed to compare efficacy, safety, immunogenicity, and PK of Bmab 1200 with Stelara® in adult patients with moderate to severe chronic plaque psoriasis. The study is planned to be conducted in Europe and North America across approximately 42 sites in 6 countries. The study will be conducted in an outpatient setting, and the participation for each patient will consist of a screening period (up to 4 weeks/28 days) and a double-blind, active-controlled treatment period (52 weeks) with a rerandomization step for switching therapy before Week 16 dosing. The total duration of the study (excluding the screening period) will be 52 weeks. **Screening Period.** A suitable number of patients will be screened to enroll a total of 384 patients with moderate to severe chronic plaque psoriasis who are deemed eligible for receiving systemic therapy or phototherapy and are naïve to ustekinumab. **Double-Blind, Active-Controlled Treatment Period.** TP1 - From baseline visit to Week 16 (predosing): Eligible patients will be randomly assigned in a 1:1 ratio to receive Bmab 1200 or Stelara® based on predefined stratification factors of [redacted] [redacted] i s w l r ve s u y r at he bas i s , We Week 16. Patients weighing ≤100 kg will receive a subcutaneous dose of 45 mg of either drug at each of the above visits, while patients weighing >100 kg will receive a subcutaneous dose of 90 mg (45 mg × 2). TP2 - From Week 16 dosing to Week 28 (predosing):

	All continuing patients who receive study treatment at the baseline visit and Week 4 and achieve at least PASI 50 response by Week 12 will be rerandomized before receiving study treatment at Week 16. Before dosing at Week 16, patients in the Stelara® arm will be randomly assigned in a 1:1 ratio to receive either Bmab 1200 or Stelara® at Week 16. This is done to obtain data after a single switch in patients who have been treated with Stelara®. To maintain the study blinding, the patients in the original Bmab 1200 group will also go through the rerandomization procedure; however, they will be assigned and continue to receive Bmab 1200. The rerandomization will take place using the original strata used for the randomization at baseline. TP3 - From Week 28 dosing to Week 52: All continuing patients who complete TP2 (receive study treatment at the baseline visit and Weeks 4 and 16) and achieve at least PASI 75 response at Week 28 will be offered to enter TP3 of the study to continue the same treatment they were rerandomized to receive during TP2 (Bmab 1200 or Stelara®) in a blinded manner. For patients not eligible to enter the TP3, the end of study visit will occur at Week 28. During the double-blind, active-controlled treatment period, all randomized patients will be evaluated for efficacy, safety, tolerability, PK, and immunogenicity at scheduled visits per the Schedule of Assessments (Table 1). All assessments except for those related to the occurrence of injection site and hypersensitivity reactions will take place before the administration of study treatment at the baseline visit and Weeks 4, 16, 28, and 40. Efficacy assessments will include the clinician's assessments of PASI, sPGA, BSA, and patient's reported QoL measured by DLQI (see Table 1 for all the scheduled visits). Refer to Section 11 for more details on efficacy assessments. Safety and tolerability will be assessed by monitoring adverse events (AEs), injection site reactions and hypersensitivity, vital signs, physical examination, 12 -lead ECG, and safety laboratory tests (hematology, chemistry, and urinalysis) at scheduled visits (see Table 1 for all the scheduled visits). Complete details on the safety and tolerability assessments are provided in Section 12. For the PK and immunogenicity assessments, blood samples will be collected at the Baseline visit (predose), Week 2, Week 4 (predose), Week 8, Week 12, Week 16 (predose), Week 20, Week 28 (predose), Week 40 (predose), and Week 52. Serum levels of ustekinumab, as well as the presence and titer of ADAs and NAbs, will be evaluated for both the Bmab 1200 and Stelara® arms. All patients will have an end of study (EOS) visit at Week 52 for efficacy, safety, PK, and immunogenicity assessments as per the Schedule of Assessments (Table 1). Patients who discontinue study treatment before the end of Week 16 will be followed up for efficacy to the Week 16 scheduled assessment. However, the primary endpoint analysis will be done at Week 12 only. Patients who discontinue study treatment on or after Week 16 dosing and before the Week 28 dosing will be followed up for efficacy to the Week 28 scheduled assessment. Any patient that discontinues study treatment during TP1 or TP2 will be followed up for safety and immunogenicity to Week 28 and will then be discontinued from the study. Patients who discontinue study treatment on or after Week 28 dosing (ie, during TP3) will be followed up for efficacy, safety and immunogenicity to the EOS at Week 52. Every reasonable effort will be made to contact early discontinued patients who are lost to follow-up to obtain further safety information. Details regarding follow-up efforts are to be documented in the patient's medical records/source documentation.
Selection of Patients:	Inclusion Criteria: Individuals must meet all of the following criteria to be included in the study:

1. Patient is willing and able to provide informed consent form (ICF), able to follow study instructions, and comply with the protocol requirements as per the investigator's opinion.
2. Patient is aged 18 to 80 years, both inclusive, and weighing <130 kg at the time of the screening visit.
3. Patient has a diagnosis of chronic plaque psoriasis for at least 6 months and is a candidate for systemic therapy or phototherapy at the time of the screening visit.
4. Patient with moderate to severe chronic plaque psoriasis as defined by BSA involvement ≥10%, PASI score ≥12, and sPGA ≥3 at the screening and baseline visits.
5. Patient has stable disease for at least 2 months before the baseline visit (ie, without clinically significant changes in the investigator's opinion).
6. Patient has adequate renal and hepatic function at the screening as defined by the following clinical chemistry results:
   a) Serum creatinine ≤1.5 × upper limit of normal (ULN)
   b) Serum alanine aminotransferase (ALT) and aspartate aminotransferase (AST) ≤2 × ULN
   c) Serum total bilirubin ≤1.5 × ULN, unless there is a documented history of Gilbert syndrome
7. Patient has the following hematology laboratory test results at screening:
   a) Hemoglobin ≥10.0 g/dL
   b) Absolute neutrophil count ≥1500/μL (SI units: ≥1.5 × 10^9 cells/L)
   c) Platelet count ≥100 000/μL (SI units: ≥100 × 10^9 cells/L)
8. Patient has had a previous failure, inadequate response, intolerance, or contraindication to at least one antipsoriatic systemic therapy.
9. Women of childbearing potential must have a negative serum pregnancy test during screening and a negative urine pregnancy test at baseline. A female patient is considered not of childbearing potential when postmenopausal (at least 12 consecutive months without menses without an alternative medical cause) or surgically sterilized (hysterectomy, bilateral salpingectomy, and bilateral oophorectomy).
10. Women of childbearing potential and male patients with a female partner of childbearing potential must be willing to use highly effective contraceptive precautions which are consistent with local regulations regarding the use of birth control methods for patients participating in clinical studies throughout the study period and continuing for at least 15 weeks after the last dose of study drug. See APPENDIX 1 for acceptable highly effective contraceptive methods. Abstinence from heterosexual intercourse is accepted when this is the usual lifestyle of the patient and must be continued for at least 15 weeks after the last dose of study drug.

Exclusion Criteria:

Individuals meeting any of the following criteria at the screening or baseline are ineligible to participate in this study:

1. Patient has nonplaque psoriasis, such as erythrodermic psoriasis, pustular psoriasis, guttate psoriasis, medication-induced psoriasis, other skin conditions (eg, eczema), other current or chronic systemic autoimmune or inflammatory disease at the time of screening visit that would interfere with the evaluation of the effect of the study treatment of psoriasis. Patients with concurrent psoriatic arthritis will be allowed to participate.
2. Patient who has a current or past history of any of the following infections:

	a) Current or past history of congenital or acquired immunodeficiency or patient is positive for the human immunodeficiency virus (HIV) antibodies (HIV-1 or HIV-2) at screening. b) Patient has current infection with hepatitis B virus (HBV) or hepatitis C virus (HCV) as per serological tests at screening. ○ For HBV, patients who test positive to hepatitis B surface antigen (HBsAg) will be excluded. Patients who test positive to hepatitis B core antibody (HBcAb) only (HBsAg negative), may be enrolled if they also test positive to hepatitis B surface antibody (HBsAb). ○ For HCV, patient who test positive to HCV antibody will be excluded unless they test negative for HCV RNA. c) Presence of active infection at screening or history of infection requiring intravenous antibiotics and/or hospitalization ≤8 weeks before baseline visit, or oral/intramuscular antibiotics ≤4 weeks before baseline visit, or topical antibiotics ≤2 weeks before baseline visit. Minor localized fungal infections or topical antibiotics for facial acne may be allowed. d) Any recurrent bacterial, fungal, opportunistic or viral infection including recurrent/disseminated herpes zoster that, based on the investigator´s clinical assessment, causes a safety risk and makes the patient unsuitable for the study. Note: Recurrent infections are defined as 2 or more severe infections in 1 year, 3 or more respiratory infections (eg, sinusitis, otitis, bronchitis) in 1 year, or the need for antibiotics for 2 months/year. e) History of invasive/systemic fungal infection (eg, histoplasmosis) or nontubercular mycobacterial infection. 3. Patient meeting any of the following tuberculosis (TB)-related conditions: a) Patient who has current or history of active TB. b) Patient who has signs or symptoms suggestive of active TB upon medical history or physical examination including chest radiography at screening. If a chest radiography performed within the past 3 months before screening is available, it does not need to be repeated at screening. c) Patients with current latent TB (defined as a positive result of interferon-γ release assay [IGRA] with a negative examination of chest radiography [posterior-anterior and lateral views, or per country regulations where applicable] and absence of symptoms). Patients with positive IGRA may be enrolled if they have documentation of completed appropriate country-specific TB prophylaxis within the past 5 years or have received at least 1 month of country-specific TB prophylaxis before the baseline visit and are willing to complete its entire course, and do not have other risk factors, radiologic findings, or physical evidence supporting latent or active TB. It is the responsibility of the investigator to verify the adequacy of previous anti-TB treatment and provide appropriate documentation. If a patient's initial IGRA test result is indeterminate, the test can be repeated once. If the test result is again indeterminate, the patient will be excluded from the study. d) Patient who has had exposure to a person with active TB, such as first-degree family members or coworkers within 16 weeks before the baseline visit.

	4. Patient has an underlying condition (including, but not limited to metabolic, hematologic, renal, hepatic, pulmonary, neurologic including central nervous system demyelinating disease, endocrine, cardiac, infection, or gastrointestinal) which, in the opinion of the investigator, significantly immune-compromises the patient and/or places the patient at unacceptable risk for receiving an immunomodulatory therapy. 5. Patient had a major surgical intervention within 12 weeks of the baseline or planned major surgery during the study period. 6. Patient who has prior exposure to more than 1 biologic agent for the treatment of psoriasis or psoriatic arthritis. 7. Patient who has received or plans to receive any of the following prohibited medications or treatment that could affect psoriasis: a) Topical therapies for the treatment of psoriasis (including, but not limited to, corticosteroids, vitamin D analogs, calcineurin inhibitors or retinoids) within 2 weeks before the baseline visit. However, restricted use of rescue topical treatment may be allowed as per Section 9.8. b) Ultraviolet A phototherapy (with or without oral psoralen) or ultraviolet B phototherapy for the treatment of psoriasis within 4 weeks before the baseline visit. c) Systemic steroids within 4 weeks before the baseline visit. d) Any nonbiologic systemic therapies for the treatment of psoriasis or psoriatic arthritis within 4 weeks before the baseline visit. e) Any biologic systemic therapy with a mechanism of action that could impact the course of psoriasis/psoriatic arthritis or its evaluations, within 5 half-lives or 90 days, whichever is longer, before the baseline visit. f) Any monoclonal antibody (mAb) within 5 half-lives or 90 days, whichever is longer, before the baseline visit. g) Any drug that directly targets interleukin (IL)-12, IL-17, or IL-23 including ustekinumab either investigational or approved. h) Any investigational drug other than study treatment within 4 weeks or 5 half-lives (whichever is longer) before the baseline visit. i) Any other drug that may impact psoriasis (eg, beta-blockers, lithium, antimalarials) within 4 weeks before the baseline visit. Note: However, patients on stable doses of beta-blockers for 3 months before the baseline visit are allowed. j) Herbal or any nonpharmaceutical medicine to treat psoriasis within 2 weeks before the baseline visit. 8. Patient has received a live or live-attenuated vaccine within 4 weeks before the baseline visit. Patient must agree not to receive a live or live-attenuated vaccine during the study and up to 15 weeks after the last dose of the study treatment. 9. Patient who has had Bacillus Calmette-Guérin (BCG) vaccination within 1 year before the baseline visit. Patients must agree not to receive a BCG vaccination during the study and at least 1 year after the last dose of the study treatment. 10. Patient who had confirmed coronavirus disease 2019 (COVID-19) infection and was hospitalized requiring oxygen in the last 8 weeks prior to screening. In case of asymptomatic/mildly symptomatic patient with confirmed COVID-19 infection during the last 4 weeks prior to screening, and who have not recovered from COVID-19 as per site and/ local regulatory guidelines at screening, would also be excluded from the study.

	11. Patient who has received or is planning to receive COVID-19 vaccination within 2 weeks before or after the baseline visit. However, COVID-19 vaccination >2 weeks before or after the baseline visit is permitted. 12. Patient has a history of hypersensitivity to any biologic systemic therapy or any of the excipients of Stelara®. 13. Patient who is not willing to limit ultraviolet light exposure (eg, excessive sun exposure and/or the use of tanning devices) during the study. 14. Patient is pregnant or breastfeeding (lactating) at the time of screening or baseline visit. 15. Patient has history of malignancy within 5 years except adequately treated cutaneous squamous or basal cell carcinoma, in situ cervical cancer, or in situ breast ductal carcinoma. 16. Have a transplanted organ/tissue or stem cell transplantation. 17. Evidence (as assessed by the investigator using good clinical judgment) of alcohol or drug abuse or dependency in the last 3 years before screening. 18. Patient has a severe progressive or uncontrolled, clinically significant disease that in the judgment of the investigator renders the patient unsuitable for the study. [redacted]
Withdrawal Criteria:	**Study Treatment Discontinuation Reasons:** 1. Patient does not comply with the protocol and has an important protocol deviation(s) in the investigator's opinion. 2. Patient receives prohibited medication(s). 3. Patient has serious or any other AEs, or any medical, physical, or psychiatric condition(s) that, in the investigator's opinion, would pose a significant risk to the patient or interfere with interpretation of study data. 4. Patient does not achieve PASI 50 response at Week 12. 5. Patient becomes pregnant. 6. Patient withdraws consent for study treatment, or the investigator or Sponsor decides to discontinue study treatment. **Study Discontinuation Reasons:** 1. Patient is lost to follow-up. 2. Patient withdraws consent from study participation. 3. Death. 4. Patient withdrawn at investigator's discretion because of medical (eg, condition as assessed by the investigator as requiring therapy/intervention that will interfere with the patient's subsequent study visits) or administrative (eg, persistent noncompliance, inability to comply with the study schedule) reasons. 5. Study or site terminated by Sponsor 6. Patient does not achieve at least PASI 75 response at Week 28.

Planned Sample Size:	Approximately 384 patients with moderate to severe plaque psoriasis will be enrolled and randomly assigned to one of the 2 treatment groups in a 1:1 ratio (192 patients in the Bmab 1200 group and 192 patients in the Stelara® group).
Investigational Therapy:	Patients will receive Bmab 1200 by subcutaneous injection via prefilled syringe (PFS) at the baseline visit, Week 4, Week 16, Week 28, and Week 40 based on the patient's baseline body weight as follows: • Patients who weigh ≤100 kg: Bmab 1200 45 mg (1 injection of 45 mg PFS) • Patients who weigh >100 kg: Bmab 1200 90 mg (2 injections of 45 mg PFS)
Reference Therapy:	Patients will receive Stelara® by subcutaneous injection via PFS at the baseline visit, Week 4, Week 16, Week 28, and Week 40 based on the patient's baseline body weight as follow: • Patients who weigh ≤100 kg: Stelara® 45 mg (1 injection of 45 mg PFS) • Patients who weigh >100 kg: Stelara® 90 mg (2 injections of 45 mg PFS)
Treatment Duration:	The total duration of the study (excluding the screening period) will be 52 weeks.
Efficacy Evaluations:	Efficacy assessments include assessment of PASI score, sPGA, BSA, and DLQI.
Safety Evaluations:	Safety assessments include AE monitoring, injection site reactions and hypersensitivity, vital signs, physical examinations (complete and/or abbreviated), 12-lead ECGs, laboratory results (routine hematology, chemistry, and urinalysis).
Pharmacokinetics:	For all patients, PK blood samples for the determination of serum concentration of ustekinumab will be collected at the time points specified in the schedule of events (Table 1). On the days of study treatment administration, blood samples must be taken before the treatment. Details of blood sample collection, processing, storage, and shipping procedures are provided in a separate laboratory manual. The PK of ustekinumab will be assessed using a validated bioanalytical method for serum concentration at a central laboratory. An additional blood sample of 5 mL will be collected from all patients before the first dose administration for PK method validation.
Immunogenicity Evaluations:	The immunogenicity of Bmab 1200 and Stelara® will be assessed by ADA and NAb tests using a validated immunoassay. It will be specified in a separate method validation report. Serum samples for immunogenicity testing will be collected at the time points specified in the schedule of events (Table 1). The ADA serum samples will be stored frozen before shipment to a central laboratory for evaluation. Details of blood sample collection, processing, storage, and shipping procedures are described in the central laboratory manual. In case of positive results in the ADA evaluation, the ADA titer will be evaluated, and evaluation of NAb levels will be conducted. An additional blood sample of 10 mL will be collected from all patients before the first dose administration for immunogenicity assay validation. Additional blood samples for immunogenicity for patients with hypersensitivity reactions considered as possibly, probably, or definitely related to study treatment will be obtained as soon as possible after the onset of the reaction whenever this is feasible.
Determination of Sample Size:	The sample size calculation is based on the primary endpoint, percentage change from baseline in the PASI score at Week 12. Equivalence will be established if the 90% confidence interval (CI) of the difference between the treatments (Bmab 1200, Stelara®) in the percentage change in the PASI score from baseline to Week 12 is within the equivalence margin of ±10%. Assuming that the treatments are equally effective and that the common standard deviation (SD) of the percentage change from baseline in the PASI score at Week 12 is 30%, a total sample size of 384

	patients including a dropout rate of 10% patients ensures a power of 85% with a two one-sided 5% level of significance.
Statistical Methods and Planned Analyses:	Statistical analysis will be performed using SAS software Version 9.4 or later (SAS Institute, Cary, NC). Unless otherwise specified, continuous variables will be summarized using the mean, SD, median, minimum value, and maximum value, by treatment group. Categorical variables will be summarized using frequency counts and percentages by treatment group. Data will be listed in data listings. All CIs presented, except for the primary endpoint (percentage change from baseline in the PASI score) will be two-sided 95% CIs, unless otherwise specified. For the primary efficacy endpoint, a 90% CI will be presented, and equivalence will be established if the 90% CI falls entirely within the predefined margin of ±10%; this approach is equivalent to two one-sided tests (TOST) at the 5% significance level. Unless otherwise specified, analyses for TP1 will be presented by treatment group (Bmab 1200, Stelara®) up to predose Week 16. However, the primary endpoint analysis will be done at Week 12 only. Analyses for TP2 and TP3 will be presented by the treatment regimen (Bmab 1200-Bmab 1200, Stelara®-Bmab 1200, Stelara®-Stelara®). <u>Analysis Sets:</u> Full Analysis Set (FAS): The FAS will consist of all patients who sign the ICF and are randomized into TP1. The FAS will be used for the primary analyses of efficacy. Per-Protocol Set (PPS): The PPS will consist of all patients in the FAS, who receive at least 2 study treatment administrations (Baseline and Week 4), and do not experience any important protocol deviations affecting primary efficacy at Week 12. The PPS will be used for supportive analyses of efficacy. Safety Set (SAF): The SAF will consist of all patients who receive at least one study treatment administration. The SAF will be used for analyzing safety and immunogenicity data during the treatment period. The SAF will be used for all analyses of safety and immunogenicity. PK Set (PKS): The PKS will consist of all patients who receive at least one full dose of study treatment and have at least 1 post-treatment PK result before Week 16, excluding observations after relevant intercurrent events (ICEs) that may impact PK evaluations (eg, missing a dose, errors or deviations in dosing or receipt of other therapies which also contain ustekinumab). The PKS will be used for analyses of PK. Further analysis sets are proposed for the analyses of TP2 and TP3. See Section 15.2. <u>Efficacy Analysis:</u> The statistical hypothesis associated with the primary efficacy analysis of the percentage change from baseline in the PASI score at Week 12 is: • H_0: ($\mu_{Bmab\ 1200}$ - $\mu_{Stelara} \leqslant$ -10%) or ($\mu_{Bmab\ 1200}$ - $\mu_{Stelara} \geqslant$ +10%) • H_1: -10% < $\mu_{Bmab\ 1200}$ - $\mu_{Stelara}$ < +10% where $\mu_{Bmab\ 1200}$ and $\mu_{Stelara}$ denote the true mean percentage change from baseline in the PASI score at Week 12 for Bmab 1200 and Stelara®, respectively. The estimand framework will be applied for the primary efficacy endpoint, per International Council for Harmonisation (ICH) E9 addendum. ICEs are described in Section 15.5.1.2. The primary estimand is aligned with a treatment policy approach for all ICEs except death. The estimate of the treatment effect in this instance will be influenced by any effects of prohibited medication that are used to treat psoriasis, missing or early/late treatment, and/or premature discontinuation where a poor outcome may not be expected.

	Additional complementary secondary and tertiary estimands are proposed to study the effects of the defined ICEs. Equivalence testing will be conducted using the primary estimand. For the main analyses of the primary, secondary and tertiary estimands of the primary efficacy endpoint, data obtained from remote visits (for example, due to patient not being able to attend the site due to regional lockdown) will not be considered and will instead be imputed based on the handling of the ICE will be discussed in the statistical analysis plan (SAP). Sensitivity analyses, considering such data, may be added as appropriate. Missing data, and data handled under hypothetical strategies will be multiple imputed using composite, missing-at-random (MAR) and missing not at random (MNAR) approaches, per Section 15.9. The primary, secondary, and tertiary estimands will be analyzed using an analysis of covariance (ANCOVA) model to fit the percentage change from baseline in the PASI score at Week 12 on the FAS in each imputed dataset. The ANCOVA will include the stratification factors [redacted] The mean difference between treatment groups will be estimated based on the least squares means in the ANCOVA model. The estimated treatment differences and the associated SDs resulted from each multiply imputed dataset will be combined using the Rubin's rule as a single estimate of treatment difference presented with a 90% CI. A tipping point analysis on the primary estimand, and a mixed effect model for repeated measures will be implemented as sensitivity analysis to the above. Supportive analyses on the primary, secondary and tertiary estimands will be conducted on the PPS. Secondary efficacy endpoints will implement the same estimands framework for endpoints related to PASI score and sPGA. For the secondary efficacy endpoints related to BSA and DLQI, a single primary estimand handling all ICEs with a treatment policy strategy will be applied. For this estimand, available data occurring on or after the ICE will be analyzed as observed (except remote visits, similar to the primary efficacy endpoint). No margins of equivalence are applied to secondary efficacy endpoints. Continuous secondary efficacy endpoints related to PASI will implement the same analysis method as that for the primary efficacy endpoint. Continuous secondary efficacy endpoints related to BSA and DLQI will be analyzed using mixed effect model for repeated measures (MMRM), similar to the sensitivity analysis of the primary efficacy endpoint. Binary secondary efficacy endpoints will be analyzed using a Cochran-Mantel-Haenszel (CMH) test, adjusted for the randomization strata (region, body weight at baseline category, baseline psoriatic arthritis status, and previous biologic use). The estimate of the risk difference, with corresponding CMH adjusted 2 sided 95% CI, will be presented. The validity of the CMH test, in particular with respect to the size of strata combination, will be reviewed. If small strata combinations cast doubt on the use of the CMH test, strata may be pooled, or a nonstratified test will be used. For analyses using multiple imputation, the analysis will be conducted on the complete dataset, for each imputation separately. Modelled results will be combined using Rubin's rule (PROC MIANALYZE) for tabulation. Additionally, supportive analyses will be conducted for the endpoints related to PASI and sPGA for the primary, secondary, and tertiary estimands on the PPS. All inferential analyses of the primary efficacy endpoint, including multiple imputation approaches will be conducted during TP1 only (ie, up to and including Week 16). However, primary analysis will be done at Week 12 only. During TP2 (Week 16 post rerandomization through Week 28 predosing) and TP3 (Week 28 postdosing through Week 52), only descriptive analyses will be performed for

	efficacy. The handling of estimands as detailed above will also only apply up to and including Week 16. After this point, data will only be analyzed as observed. Safety Analysis: Safety data reported during TP1, TP2, and TP3 will be separately analyzed by treatment group on the SAF or by treatment regimen on the SAF for TP2 and/or TP3, respectively. AEs will be classified according to the time of onset of the AE into pretreatment AEs, TEAEs and post-treatment-emergent AEs. All reported AEs will be coded using the most recent version of the Medical Dictionary for Regulatory Activities (MedDRA) coding dictionary. An overall summary of incidence will be presented for TEAEs, treatment-emergent serious adverse events (SAEs), study treatment-related TEAEs and treatment-emergent SAEs, TEAEs leading to study discontinuation, TEAEs leading to discontinuation of study treatment (Bmab 1200 or Stelara®), and AESIs by treatment period and treatment/regimen. Additional summaries of these AEs will be presented by MedDRA system organ class (SOC) and preferred term (PT), by treatment period and treatment/regimen. The clinical safety laboratory test values, vital signs, ECG parameter values, and physical examinations will be summarized by treatment period and treatment/regimen. For laboratory parameters and vital signs, original results and change from baseline will be summarized at each visit. Potentially clinically significant values will be flagged and summarized. PK Analysis: Serum concentrations of Bmab 1200 and Stelara® will be listed and descriptively summarized by treatment (Bmab 1200, Stelara®) and visit for TP1 and by treatment regimen (Bmab 1200-Bmab 1200, Stelara®-Bmab 1200, Stelara®-Stelara®) and visit for TP2 and TP3. Descriptive statistics will include arithmetic and geometric mean, SD, coefficient of variation and geometric coefficient of variation, minimum, maximum, and median, plus percentage of concentration values below the lower limit of quantification. Additional subgroup analyses of PK data by treatment and ADA status will be presented. Immunogenicity Analysis: Incidence of ADAs to Bmab 1200 and Stelara® including titer and NAbs will be descriptively summarized at each time point and cumulative up to the time point by treatment (Bmab 1200, Stelara®) for TP1 and by treatment regimen (Bmab 1200 Bmab 1200, Stelara®-Bmab 1200, Stelara®-Stelara®) for TP2 and TP3. The titer values for positive ADA will be descriptively summarized.

3 TABLE OF CONTENTS

3.1 List of In-text Tables

3.2 List of In-text Figures

4 LIST OF ABBREVIATIONS

Abbreviation	Definition
ADA	antidrug antibody
ADR	adverse reaction
AE	adverse event
AESI	adverse event of special interest
ANCOVA	analysis of covariance
AUEC	area under effect curve
BCG	Bacillus Calmette-Guérin
BDRM	Blinded Data Review Meeting
BSA	body surface area
CI	confidence interval
CMH	Cochran-Mantel-Haenszel
COVID-19	coronavirus disease 2019
CSR	clinical study report
CTCAE	Common Terminology Criteria for Adverse Events
DLQI	Dermatology Life Quality Index
ECG	electrocardiogram
eCRF	electronic case report form
EOS	end of study
EU	European Union
FAS	Full Analysis Set
FAS2	Full Analysis Set for treatment period 2
FDA	Food and Drug Administration
HBcAb	hepatitis B core antibody
HBsAb	hepatitis B surface antibody
HBsAg	hepatitis B surface antigen
HBV	hepatitis B virus
HCV	hepatitis C virus
HIV	human immunodeficiency virus
HRT	hormone replacement therapy
IB	Investigator's Brochure
ICE	intercurrent event
ICF	informed consent form
ICH	International Council for Harmonisation
IEC	independent ethics committee
IGRA	interferon-γ release assay
IL	interleukin
IRB	institutional review board
mAb	monoclonal antibody
MAR	missing-at-random

Abbreviation	Definition
MedDRA	Medical Dictionary for Regulatory Activities
MI	multiple imputation
MNAR	missing-not-at-random
NAb	neutralizing antibody
PASI	Psoriasis Area and Severity Index
PASI 50/75/90/100	Psoriasis Area and Severity Index improvement of ≥50%/75%/90%/100% relative to baseline
PFS	prefilled syringe
PGA	Physician's Global Assessment
PK	pharmacokinetic(s)
PKS	Pharmacokinetic Set
PKS2	Pharmacokinetic Set for treatment period 2
PMDA	Pharmaceuticals and Medical Devices Agency
PPS	Per-Protocol Set
PRES	posterior reversible encephalopathy syndrome
PT	preferred term
QoL	quality of life
RNA	ribonucleic acid
RTSM	Randomization and Trial Supply Management
SAE	serious adverse event
SAF	Safety Set
SAF2	Safety Set for treatment period 2
SAP	statistical analysis plan
SD	standard deviation
SOC	system organ class
sPGA	static Physician's Global Assessment
SUSAR	suspected unexpected serious adverse reaction
TB	tuberculosis
TEAE	treatment-emergent adverse event
TOST	two one-sided tests
TP1	treatment period 1
TP2	treatment period 2
TP3	treatment period 3
UK	United Kingdom
US	United States
ULN	upper limit of normal
WHO	World Health Organization

5 INTRODUCTION

5.1 Background on Plaque Psoriasis

Psoriasis is a chronic, immune-mediated, inflammatory condition that affects more than 8 million people in the United States and approximately 125 million people (2% to 3% of the total population) worldwide.[1] In Europe, the prevalence of psoriasis among adults varies geographically. In Southern and North Eastern Europe, 3% to 5% of the population are affected, compared to just over 1% of the population in the United Kingdom (UK).[2] Psoriasis is characterized by scaly, erythematous papules, and plaques that are often pruritic. There are many types of psoriasis, including guttate psoriasis, pustular psoriasis, plaque psoriasis, inverse psoriasis, and erythrodermic psoriasis. The most common type is plaque psoriasis, affecting 80% to 90% of patients. In individuals with lighter skin complexion, plaque psoriasis typically appears as raised, red patches covered with a silvery white buildup of dead skin cells or scale. On skin of color, the discoloration is darker and thicker, and more of a purple or grayish color or darker brown. These patches or plaques most often appear on the scalp, knees, elbows and lower back, and their size can range between 1 and >10 cm in diameter.[3,4] Psoriasis may reduce physical and mental functioning, affects psychosocial functions, and also significantly affects health- related quality of life (QoL).[5,6,7]

Treatment options for psoriasis include topical treatments for milder disease, and systemic treatments for moderate to severe disease that does not respond sufficiently to topical treatments. Topical treatments include corticosteroids, anthralin, synthetic vitamin D3, and vitamin A. Systemic therapies include phototherapy including psoralen and ultraviolet A, acitretin, cyclosporine, methotrexate, apremilast, and various systemic biologic products. Biologic products work by interfering with specific components of the autoimmune response, including tumor necrosis factor alpha (TNFα) or various interleukin (IL) inhibitors.

5.2 Background on Study Treatments

5.2.1 Background on Bmab 1200

Bmab 1200 is a fully human immunoglobulin G subunit 1 kappa (IgG1κ) monoclonal antibody (mAb) that is being developed as a proposed biosimilar medicinal product to the reference product, Stelara® (ustekinumab) marketed by Janssen Biotech Inc. Stelara® was originally approved in the European Union (EU) in January 2009 and in the United States in September 2009. Stelara® is indicated for the following conditions: moderate to severe plaque psoriasis, active psoriatic arthritis, and moderately to severely active Crohn's disease and ulcerative colitis.[8,9]

Bmab 1200 is of approximate molecular weight of 148 600 Daltons and composed of 1326 amino acid residues with 2 identical heavy and light chains linked by covalent disulfide bonds and noncovalent heavy-heavy and heavy-light chain interactions. All cysteine residues are involved in disulphide bonds resulting in a total of 16 disulphide bonds.

Physicochemical/analytical comparability evaluations have been done to show that Bmab 1200 is of similar quality profile as that of Stelara®. Details are provided in the Investigator's Brochure (IB).[10]

5.2.1.1 Nonclinical Studies

Nonclinical Pharmacology

The primary pharmacodynamic studies conducted with Bmab 1200 included multiple assays for measuring Fab and Fc functionality such as p40 binding potency, neutralization of IL-12 induced Signal Transducer and Activator of Transcription (STAT)-4 activation, IL-12 and IL-23 binding, neutralization of IL-23 induced STAT-3 activation, neutralization of IL-12 induced IFNγ production, binding kinetics of FcγRIa, FcγRIIa, FcγRIIIa-V158, FcγRIIIa-F158, FcRn, FcγRIIb, FcγRIIIb, and C1q.

These assays demonstrated that Bmab 1200 had potency comparable to US-Licensed Stelara® and EU-Approved Stelara® for the various batches analyzed.

Toxicology

No pharmacokinetic (PK), toxicokinetic (TK), antidrug antibody (ADA) evaluation and toxicology have been performed yet for Bmab 1200.

Based on appropriate Food and Drug Administration (FDA) and EMEA guidelines as well as the feedback received from FDA type 2 meeting (Reference ID: 4796456) and EMA Scientific Advice (EMEA/H/SA/4410/1/2020/III) in vivo studies are deemed not necessary for the establishment of biosimilarity, as functional assays performed as a part of primary pharmacodynamics are highly sensitive in detecting differences between Bmab 1200, US-Licensed Stelara® and EU-Approved Stelara®.

A detailed description of nonclinical studies is provided in the IB.[10]

5.2.1.2 Clinical Studies

To date, 2 clinical studies have been initiated with Bmab 1200. As part of the biosimilar development program and in accordance with the applicable biosimilar guidelines, the following clinical studies with Bmab 1200 have been initiated:

- Study BM12H-NHV-01-G-01: A randomized, double-blind, 3-arm, parallel design study in healthy volunteers to evaluate the PK, safety, tolerability, and immunogenicity of Bmab 1200 after single subcutaneous injection (45 mg) in comparison with EU-approved Stelara® and US-licensed Stelara®.
- Study BM12H-PSO-03-G-02 (present study): A randomized, double-blind, parallel group, multicenter, Phase 3 study to compare the efficacy and safety of Bmab 1200 and Stelara® in patients with moderate to severe chronic plaque psoriasis.

Information from clinical studies conducted with Stelara® in psoriasis is summarized in Section 5.2.2.

5.2.2 Background on reference product Stelara® (ustekinumab)

Ustekinumab is a recombinant, fully human immunoglobulin G subunit 1 kappa (IgG1κ) mAb that binds with specificity to the shared p40 protein subunit of human cytokines IL-12 and IL-23. These are naturally occurring proteins that regulate the immune system and immune-mediated inflammatory disorders. Ustekinumab inhibits the bioactivity of human IL-12 and IL-23 by preventing p40 from binding to the IL-12Rβ1 receptor protein expressed on the surface of immune cells. Ustekinumab cannot bind to IL-12 or IL-23 that is already bound to IL-12Rβ1 cell surface receptors. Thus, ustekinumab is not likely to contribute to complement- or antibody-mediated cytotoxicity of cells with IL-12 and/or IL-23 receptors. IL-12 and IL-23 are heterodimeric cytokines secreted by activated antigen presenting cells, such as macrophages and dendritic cells, and both cytokines participate in immune functions. IL-12 stimulates natural killer (NK) cells and drives the differentiation of CD4+ T cells toward the T helper 1 cell (Th1) phenotype, IL-23 induces the T helper 17 cell (Th17) pathway. However, abnormal regulation of IL-12 and IL-23 has been associated with immune-mediated diseases, such as psoriasis and psoriatic arthritis. By binding the shared p40 subunit of IL-12 and IL-23, ustekinumab may exert its clinical effects in psoriasis and psoriatic arthritis through interruption of the Th1 and Th17 cytokine pathways, which are central to the pathology of these diseases.[8,9]

In adult patients with plaque psoriasis, Stelara® is administered subcutaneously at an initial dose of 45 mg, followed by a dose of 45 mg after 4 weeks, and then every 12 weeks thereafter. For patients with a body weight of >100 kg, an initial dose of 90 mg is recommended because of better efficacy, followed by a dose of 90 mg after 4 weeks, and then every 12 weeks thereafter.

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

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

At Week 12, PASI 75 was achieved by 171 (67.1%) patients who received ustekinumab 45 mg and 170 (66.4%) patients who received ustekinumab 90 mg, as compared with 8 (3.1%) patients who received placebo (difference in response rate versus placebo 63.9%, 95% confidence interval [CI] 57.8-70.1, P <0.0001 for 45 mg and 63.3%, 57.1-69.4, P <0.0001 for 90 mg). At Week 40, long-term response had been achieved by 150 patients in the 45 mg group and 172 patients in the 90 mg group. Of these, 162 patients were randomly assigned to maintenance

ustekinumab and 160 to withdrawal. PASI 75 response was better maintained to at least 1 year in those receiving maintenance ustekinumab than in those withdrawn from treatment at Week 40 (P <0.0001 by log-rank test).[11]

In a long-term study, initial clinical responses were generally maintained through Week 244 (PASI 75: 63.4% and 72.0%; PASI improvement of ≥90% relative to baseline [PASI 90]: 39.7% and 49.0%; PASI improvement of ≥100% relative to baseline [PASI 100]: 21.6% and 26.4%) for patients receiving 45 mg and 90 mg, respectively. Similarly, PASI 75 responses were generally maintained among initial responders (79.1% [45 mg] and 80.8% [90 mg]) and partial responders (57.6% [45 mg] and 55.1% [90 mg]).[12]

Psoriasis Study 2 (PHOENIX 2) evaluated 1230 patients. Patients randomized to ustekinumab received 45 or 90 mg doses at Weeks 0 and 4 followed by an additional dose at Week 12. All patients were followed for up to Week 52 after first administration of study treatment.

At Week 12, PASI 75 was achieved by 273 (66.7%) patients who received ustekinumab 45 mg and 311 (75.7%) patients who received ustekinumab 90 mg, as compared with 15 (3.7%) patients who received placebo (difference in response rate 63.1%, 95% CI 58.2-68.0, P <0.0001 for the 45 mg group versus placebo and 72.0%, 67.5-76.5, P <0.0001 for the 90 mg group versus placebo). More partial responders at Week 28 who received ustekinumab 90 mg every 8 weeks achieved PASI 75 at Week 52 than did those who continued to receive the same dose every 12 weeks (22 [68.8%] versus 11 [33.3%]; difference in response rate 35.4%, 95% CI 12.7-58.1, P =0.004).[13]

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

At Week 12, PASI 75 was achieved by 67.5% of patients who received 45 mg of ustekinumab and 73.8% of patients who received 90 mg, as compared with 56.8% of those who received etanercept (P =0.01 and P <0.001, respectively). Similarly, 65.1% of patients who received 45 mg of ustekinumab and 70.6% of patients who received 90 mg of ustekinumab had cleared or minimal disease according to the Physician's Global Assessment (PGA), as compared with 49.0% of those who received etanercept (P <0.001 for both comparisons).[14]

The most common adverse reactions (ADRs) (>5% of patients) of Stelara® reported in clinical trials were nasopharyngitis and headache, which were mild in severity and did not necessitate treatment discontinuation. The most common serious ADR was hypersensitivity including anaphylaxis.[8,9] Stelara® may increase the risk of infections and reactivation of latent infections including tuberculosis (TB). Approximately 6% to 12.4% of patients treated with Stelara® in psoriasis and psoriatic arthritis clinical studies developed antibodies to ustekinumab, which were

generally low titer. In psoriasis studies, the majority of patients who were positive for antibodies to ustekinumab had neutralizing antibodies (NAbs).[15]

5.3 Clinical Risks/Benefits of Bmab 1200

In this study, the therapeutic equivalence of Bmab 1200 versus Stelara® in patients with moderate to severe plaque psoriasis will be assessed. The nonclinical characterization of Bmab 1200 that supports its biosimilarity to Stelara® is the basis to also expect clinical comparability in terms of safety and efficacy of Bmab 1200 and Stelara®.

The Bmab 1200 drug product will have the same pharmaceutical form and strength as Stelara® (45 mg/0.5 mL). The proposed dosing regimen is in line with the label of Stelara®.[8,9]

The proposed safety monitoring is deemed to be sufficient to monitor potential risks of Bmab 1200 administration. Patients deemed at a higher risk of developing serious ADRs to Stelara® or Bmab 1200, such as those with a prior history of cancer, active TB, or anaphylactic reactions will not be allowed to participate in the study as per eligibility criteria of current protocol and in agreement with the Warnings and Precautions of the reference product label. Patients with latent TB can enter the study only if they have completed or are receiving antibiotic prophylactic therapy for TB, and all enrolled patients will be closely monitored all along the study for potential signs and symptoms of TB.

Use of topical medication, even if with some restrictions, is allowed in the course of the trial.

This trial does not include a placebo arm, 50% of enrolled patients will receive Stelara® while 50% will receive Bmab 1200 for which there is an expectation of favorable efficacy and safety, even if not yet demonstrated. However, patients not responding to treatment at Week 12 (ie, not achieving PASI improvement of ≥50% relative to baseline [PASI 50] response) will not receive any further dosing with study treatment thus avoiding any further exposure to an ineffective drug as per psoriasis management guidelines. Based upon the clinical evidence as well as the proven safety profile of Stelara® and the above main aspects of the study design, the benefits of the conduct of the proposed clinical study outweigh the associated risks. Detailed information about the known and expected benefits and risks and reasonably expected adverse events (AEs) of Bmab 1200 and Stelara® is provided in the Bmab 1200 IB.[10]

Given the current worldwide coronavirus disease 2019 (COVID-19) pandemic and the potential risk for COVID-19 viral infection at the time and in the countries of this study, measures are implemented in this protocol to enable identification of patients who are likely to be infected to exclude them from enrollment or from subsequent study drug administration. Enrolled patients are required to comply with recommendation for individual protection from COVID-19 infection for the duration of the study. In addition, their condition will be closely monitored so that, in case of suspected infection, administration of study drug can be withhold and further examinations conducted as deemed appropriate by the Investigator. Such measures may need to be modified or implemented in accordance with the pandemic status, availability of a vaccine, relevant national guidelines, or recommendations from medical associations at the time of trial execution.

5.4 Study Rationale

Bmab 1200 is currently being developed as a proposed biosimilar to Stelara®. For the approval of a biosimilar, it must be shown that there are no clinically meaningful differences between the 2 products. The stepwise "totality of evidence" approach adopted by regulatory authorities for biosimilars means that the type of clinical studies required varies on a case-by-case basis. However, equivalence between biosimilar and reference product- in both PK and efficacy are usually required, as is a demonstration of acceptable safety and immunogenicity. Therefore, the PK profile of Bmab 1200, the EU-approved Stelara®, and the US-licensed Stelara® is being compared to demonstrate PK equivalence in a Phase 1 study in healthy volunteers (Study BM12H-NHV-01-G-01). An additional assessment of the similarity with regards to efficacy, PK, safety, and immunogenicity will be carried out in this proposed comparative clinical study (Study BM12H-PSO-03-G-02) in patients with moderate to severe chronic plaque psoriasis. The sponsor considers that the proposed clinical development program will be sufficient to demonstrate PK equivalence (PK similarity healthy volunteer study) and therapeutic equivalence and safety (Study BM12H-PSO-03-G02 comparative clinical similarity) of Bmab 1200 to the reference product. In accordance with regulatory guidance (EMA/CHMP/BMWP/403543/2010; FDA 2015; World Health Organization [WHO] 2009), safety, including immunogenicity, should be investigated in the patient population that carries the highest risk of an immune response. Based on previous data summarized in Stelara® product labeling,[8,9] approximately 6% to 12.4% of patients treated with Stelara® in psoriasis and psoriatic arthritis clinical studies developed antibodies to ustekinumab, which were generally low titer. In Crohn's disease and ulcerative colitis clinical studies, 2.9% to 4.6% of patients treated with Stelara® for approximately 1 year developed antibodies to ustekinumab.

As Stelara® is given as monotherapy in psoriasis, it allows for a much clearer approach for a demonstration of biosimilarity compared with psoriatic arthritis, Crohn's disease, and ulcerative colitis, where other immunosuppressive agents would be given concomitantly. Consequently, psoriasis has been selected as the indication for this Phase 3 clinical study because of the relatively high magnitude of the treatment effect and immunogenicity rates observed in the Stelara® clinical studies in this indication; thus, facilitating the detection of potential differences between Bmab 1200 and Stelara®.

Because the proposed study will be multicountry, patients will be stratified by region to maintain the balance between both arms with regard to treatment practices. As patients will be receiving either 45 mg or 90 mg depending on body weight (≤100 kg or >100 kg, respectively) per the approved label of Stelara®, [redacted] is considered as a stratification factor to have a comparable number of patients with 45 mg or 90 mg between the 2 treatment groups. Further, study will also be stratified based on [redacted] (Yes or No) and [redacted] (Yes or No), as both conditions may affect response to study treatment.

A single switch is included in the study through rerandomization as Week 16 for demonstration of comparable immunogenicity and safety (descriptive statistics) after switching from original biologic to the biosimilar.

6 STUDY OBJECTIVES AND ENDPOINTS

6.1 Study Objectives

6.1.1 Primary Objective

- To demonstrate equivalent efficacy between Bmab 1200 and Stelara® in patients with moderate to severe chronic plaque psoriasis.

6.1.2 Secondary Objectives

The secondary objectives are as follows:

- To assess the efficacy of Bmab 1200 based on other efficacy parameters and timepoints over the study period as compared with Stelara®.
- To assess the safety and tolerability of Bmab 1200 as compared with Stelara® over the study period.
- To assess the immunogenicity of Bmab 1200 as compared with Stelara® over the study period.
- To assess the PK of Bmab 1200 as compared with Stelara®.
- To assess the safety and immunogenicity after switching from Stelara® to Bmab 1200.

6.2 Study Endpoints

6.2.1 Primary Endpoint

- Percentage change from baseline in the PASI score at Week 12 (Time Frame: Baseline [Day 1] to Week 12).

6.2.2 Secondary Endpoints

6.2.2.1 Efficacy Endpoints

The secondary efficacy endpoints are as follows:

- Percentage change from baseline in the PASI score at Weeks 4, 8, 16, 20, 28, 40, and 52 (Time Frame: Baseline [Day 1] through Weeks 28 and 52).
- PASI 50, PASI 75, and PASI 90 at Weeks 4, 8, 12, 16, 20, 28, 40, and 52 (Time Frame: Baseline [Day 1] through Weeks 28 and 52).
- Static Physician's Global Assessment (sPGA) response of cleared or almost clear/minimal (PGA score of 0 or 1) at Weeks 4, 8, 12, 16, 20, 28, 40, and 52 (Time Frame: Baseline [Day 1] through Weeks 28 and 52).
- Area under effect curves (AUECs) of PASI score from baseline to Week 12 (Time Frame: Baseline [Day 1] through Week 12).
- Raw PASI scores at Weeks 4, 8, 12, 16, 20, 28, 40, and 52 (Time Frame: Baseline [Day 1] through Weeks 28 and 52).

- Change from baseline in affected body surface area (BSA) at Weeks 4, 8, 12, 16, 20, 28, 40, and 52 (Time Frame: Baseline [Day 1] through Weeks 28 and 52).
- Change from baseline in QoL as measured by Dermatology Life Quality Index (DLQI) scores at Weeks 4, 8, 12, 16, 20, 28, 40, and 52 (Time Frame: Baseline [Day 1] through Weeks 28 and 52).

6.2.2.2 Safety Endpoints

The safety endpoints of this study are as follows:

- Treatment-emergent adverse events (TEAEs) including adverse events of special interest (AESIs) and ADRs during the treatment periods (Time Frame: Baseline [Day 1] through Weeks 28 and 52).
- Injection site reactions and hypersensitivity at Day 1, Week 4, Week 16, Week 28, Week 40, and throughout the study (Time Frame: Baseline [Day 1] through Weeks 28 and 52).
- Other safety endpoints as follows (Time Frame: Baseline [Day 1] through Weeks 28 and 52):
  - Absolute values and changes from baseline in
    - Clinical laboratory assessments (hematology, clinical chemistry, and urinalysis)
    - Vital sign parameters (systolic and diastolic blood pressure, pulse rate, respiratory rate, and body temperature)
    - 12-lead electrocardiogram (ECG)
  - Physical examination

6.2.3 Immunogenicity Endpoints

- Proportion of patients developing ADAs and NAbs during treatment period 1 (TP1) (Time Frame: Baseline [Day 1] through Week 16).
- Proportion of patients developing ADAs and NAbs during treatment period 2 (TP2) (Time Frame: post rerandomization/dosing on Week 16 through Week 28 predosing).
- Proportion of patients developing ADAs and NAbs during treatment period 3 (TP3) (Time Frame: postdosing on Week 28 through Week 52).

6.2.4 Pharmacokinetic Endpoints

- Serum concentrations of ustekinumab during TP1 (Time Frame: Baseline [Day 1] through Week 16).
- Serum concentrations of ustekinumab during TP2 (Time Frame: post rerandomization/dosing on Week 16 through Week 28 predosing).
- Serum concentrations of ustekinumab during TP3 (Time Frame: postdosing on Week 28 through Week 52).

7 INVESTIGATIONAL PLAN

7.1 Description of Overall Study Design and Plan

This is a randomized, double-blind, active-controlled, parallel group, multicenter study designed to compare efficacy, safety, immunogenicity, and PK of Bmab 1200 with Stelara® in adult patients with moderate to severe chronic plaque psoriasis. The study is planned to be conducted in Europe and North America across approximately 42 sites in 6 countries. The study will be conducted in an outpatient setting, and the participation for each patient will consist of a screening period (up to 4 weeks/28 days) and a double-blind, active-controlled treatment period (52 weeks) with a rerandomization step for switching therapy before Week 16 dosing. The total duration of the study (excluding the screening period) will be 52 weeks.

Screening Period

A suitable number of patients will be screened to enroll a total of 384 patients with moderate to severe chronic plaque psoriasis who are deemed eligible for receiving systemic therapy or phototherapy and are naïve to ustekinumab.

Double-Blind, Active-Controlled Treatment Period

TP1 - From baseline visit to Week 16 (predosing):

Eligible patients will be randomly assigned in a 1:1 ratio to receive Bmab 1200 or Stelara® based o fi d s r t f c ti ct o [redacted] i s l ve s udy t e t the baseline visit, Week 4, and Week 16. Patients weighing ≤100 kg will receive a subcutaneous dose of 45 mg of either drug at each of the above visits, while patients weighing >100 kg will receive a subcutaneous dose of 90 mg (45 mg × 2).

TP2 - From Week 16 dosing to Week 28 (predosing):

All continuing patients who receive study treatment at the baseline visit and Week 4 and achieve at least PASI 50 response by Week 12 will be rerandomized before receiving study treatment at Week 16. Before dosing at Week 16, patients in the Stelara® arm will be randomly assigned in a 1:1 ratio to receive either Bmab 1200 or Stelara® at Week 16. This is done to obtain data after a single switch in patients who have been treated with Stelara®. To maintain the study blinding, the patients in the original Bmab 1200 group will also go through the rerandomization procedure; however, they will be assigned and continue to receive Bmab 1200. The rerandomization will take place using the original strata used for the randomization at baseline.

TP3 - From Week 28 dosing to Week 52:

All continuing patients who complete TP2 (receive study treatment at the baseline visit and Weeks 4 and 16) and achieve at least PASI 75 response at Week 28 will be offered to enter TP3

of the study to continue the same treatment they were rerandomized to receive during TP2 (Bmab 1200 or Stelara®) in a blinded manner.

For patients not eligible to enter the TP3, the end of study visit will occur at Week 28.

During the double-blind, active-controlled treatment period, all randomized patients will be evaluated for efficacy, safety, tolerability, PK, and immunogenicity at scheduled visits per the Schedule of Assessments (Table 1). All assessments except for those related to occurrence of injection site and hypersensitivity reactions will take place before the administration of study treatment at the baseline visit and Weeks 4, 16, 28, and 40.

Efficacy assessments will include the clinician's assessments of PASI, sPGA, BSA, and patient's reported QoL measured by DLQI (see Table 1 for all the scheduled visits). Refer to Section 11 for more details on efficacy assessments.

Safety and tolerability will be assessed by monitoring AEs, injection site reactions and hypersensitivity, vital signs, physical examination, 12-lead ECG, and safety laboratory tests (hematology, chemistry, and urinalysis) at scheduled visits (see Table 1 for all the scheduled visits). Complete details on the safety and tolerability assessments are provided in Section 12.

For the PK and immunogenicity assessments, blood samples will be collected at the baseline visit (predose), Week 2, Week 4 (predose), Week 8, Week 12, Week 16 (predose), Week 20, Week 28 (predose), Week 40 (predose), and Week 52. Serum levels of ustekinumab, as well as the presence and titer of ADAs and NAbs, will be evaluated for both the Bmab 1200 and Stelara® arms.

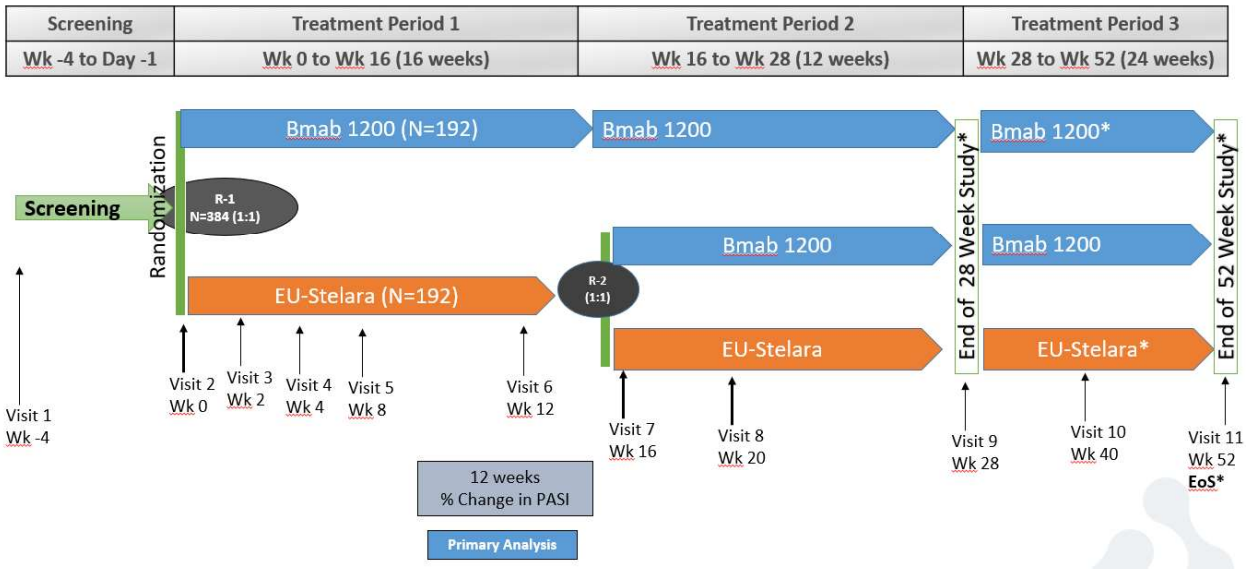
All patients will have an end of study (EOS) visit at Week 52 for efficacy, safety, PK, and immunogenicity assessments as per the Schedule of Assessments (Table 1).

Patients who discontinue study treatment before the end of Week 16 will be followed up for efficacy to the Week 16 scheduled assessment. However, the primary endpoint analysis will be done at Week 12 only. Patients who discontinue study treatment on or after Week 16 dosing and before the Week 28 dosing will be followed up for efficacy to the Week 28 scheduled assessment. Any patient that discontinues study treatment during TP1 or TP2 will be followed up for safety and immunogenicity to Week 28 and will then be discontinued from the study. Patients who discontinue study treatment on or after Week 28 dosing (ie, during TP3) will be followed up for efficacy to the EOS at Week 52.

Every reasonable effort will be made to contact early discontinued patients who are lost to follow-up to obtain further safety information. Details regarding follow-up efforts are to be documented in the patient's medical records/source documentation.

An overview of the study design is shown in Figure 1.

Figure 1. Study Design Schematic



*US FDA has agreed to 28 Week study while extended study to fulfill PMDA requirement will continue and end at Week 52.
Abbreviations: EU, European Union; PASI, Psoriasis Area and Severity Index; R1, randomization-; R-2, rerandomization; Wk, Week.
Note: Study treatment will be administered at a dose of 45 mg or 90 mg (based on body weight category) at baseline visit, Week 4, Week 16, Week 28, and Week 40.
To maintain the study blinding, the patients in the original Bmab 1200 group will also go through the rerandomization procedure; however, they will be assigned and continue to receive Bmab 1200.

7.2 Discussion of Study Design

This study has been designed in accordance with guidelines for the development of biosimilars, that require a double-blind, parallel arm, active-controlled confirmatory clinical study comparing the clinical efficacy, safety, and immunogenicity of the biosimilar product (Bmab 1200) with those of the reference product (Stelara®). The study design accommodates for a single switch design, which allows for the assessment of any safety and immunogenicity or efficacy effects of a single transition from the reference product Stelara® to Bmab 1200 as required by the FDA in therapeutic equivalence trials of biosimilar products.

The doses of 45 mg and 90 mg ustekinumab based on patient's body weight at enrollment have been selected for this study in accordance with the approved dosing recommendations of Stelara®.

The primary efficacy endpoint of the study is the percent improvement from baseline in the PASI score at Week 12. PASI score is a tool that has been widely used in the psoriasis clinical trials to determine the severity of disease and its improvement or worsening in the course of treatment. Although percent change of PASI from baseline was not the primary endpoint of the pivotal

studies of Stelara® in psoriasis, it was a key secondary endpoint, and is deemed as a more sensitive and adequate endpoint for a therapeutic equivalence study. Percent improvement from baseline in PASI score will be assessed throughout the study to adequately monitor and compare the time course of the response to study treatment and its effects on the clinical signs and symptoms of plaque psoriasis. The additional efficacy end points (sPGA, BSA, DLQI) are those more commonly used in psoriasis clinical trials and also represent the main efficacy end points of the pivotal Stelara® studies. The physician global assessment chosen for this study is the same 6-point sPGA that was employed in the Stelara® pivotal trials.

Patients not achieving a minimal clinically significant response (PASI 50) after receiving 2 doses of study treatment (baseline visit and Week 4) will be withdrawn from the study treatment to be directed to different and more effective therapeutic options and to avoid exposing them to the risks of receiving further doses of ustekinumab without clinical benefit.

Patients not achieving at least PASI 75 response after 3 doses of study treatment (baseline visit, Week 4, and Week 16), as measured at Week 28 visit, will not be offered to proceed with TP3 and will not be dosed further nor continue until Week 52. Their end of study visit will be at Week 28.

The potential immunogenic effects of Bmab 1200 in comparison with Stelara® will be evaluated over a 52-week period in parallel with measurement of ustekinumab serum concentration to be able to observe any potential relationship between ADA production, ustekinumab plasma drug levels, and efficacy measures.

The study design, evaluations, and duration are considered adequate to support the objectives of the study, which is to assess similarity of efficacy, safety, and immunogenicity between Bmab 1200 and the reference product. Justification for the equivalence margins for percent PASI improvement is provided in Section 15.1.

7.3 End of Study

A patient will have fulfilled the requirements for study completion if/when the patient has completed all study periods, including the visit at Week 52, as indicated in the Schedule of Assessments (Table 1). For patients not entering the TP3, the end of study visit will occur at Week 28.

The end of the study or study completion will be the last patient's last visit for any protocol related activity.

8 SELECTION OF STUDY POPULATION

Section 7.1 provides information regarding number of patients planned to be enrolled.

8.1 Inclusion Criteria

Individuals must meet all of the following criteria to be included in the study:

1. Patient is willing and able to provide informed consent form (ICF), able to follow study instructions, and comply with the protocol requirements as per the investigator's opinion.
2. Patient is aged 18 to 80 years, both inclusive, and weighing <130 kg at the time of the screening visit.
3. Patient has a diagnosis of chronic plaque psoriasis for at least 6 months and is a candidate for systemic therapy or phototherapy at the time of the screening visit.
4. Patient with moderate to severe chronic plaque psoriasis as defined by BSA involvement ≥10%, PASI score ≥12, and sPGA ≥3 at the screening and baseline visits.
5. Patient has stable disease for at least 2 months before the baseline visit (ie, without clinically significant changes in the investigator's opinion).
6. Patient has adequate renal and hepatic function at the screening as defined by the following clinical chemistry results:
   a) Serum creatinine ≤1.5 × upper limit of normal (ULN)
   b) Serum alanine aminotransferase (ALT) and aspartate aminotransferase (AST) ≤2 × ULN
   c) Serum total bilirubin ≤1.5 × ULN, unless there is a documented history of Gilbert syndrome
7. Patient has the following hematology laboratory test results at screening:
   a) Hemoglobin ≥10.0 g/dL
   b) Absolute neutrophil count ≥1500/µL (SI units: ≥1.5 × 10^9 cells/L)
   c) Platelet count ≥100 000/µL (SI units: ≥100 × 10^9 cells/L)
8. Patient has had a previous failure, inadequate response, intolerance, or contraindication to at least one antipsoriatic systemic therapy.
9. Women of childbearing potential must have a negative serum pregnancy test during screening and a negative urine pregnancy test at baseline. A female patient is considered not of childbearing potential when postmenopausal (at least 12 consecutive months without menses without an alternative medical cause) or surgically sterilized (hysterectomy, bilateral salpingectomy, and bilateral oophorectomy).

10. Women of childbearing potential and male patients with a female partner of childbearing potential must be willing to use highly effective contraceptive precautions which are consistent with local regulations regarding the use of birth control methods for patients participating in clinical studies throughout the study period and continuing for at least 15 weeks after the last dose of study drug. See APPENDIX 1 for acceptable highly effective contraceptive methods. Abstinence from heterosexual intercourse is accepted when this is the usual lifestyle of the patient and must be continued for at least 15 weeks after the last dose of study drug.

8.2 Exclusion Criteria

Individuals meeting any of the following criteria at the screening or baseline are ineligible to participate in this study:

1. Patient has nonplaque psoriasis, such as erythrodermic psoriasis, pustular psoriasis, guttate psoriasis, medication-induced psoriasis, other skin conditions (eg, eczema), other current or chronic systemic autoimmune or inflammatory disease at the time of screening visit that would interfere with the evaluation of the effect of the study treatment of psoriasis. Patients with concurrent psoriatic arthritis will be allowed to participate.
2. Patient who has a current or past history of any of the following infections:
   a) Current or past history of congenital or acquired immunodeficiency or patient is positive for the human immunodeficiency virus (HIV) antibodies (HIV-1 or HIV-2) at screening.
   b) Patient has current infection with hepatitis B virus (HBV) or hepatitis C virus (HCV) as per serological tests at screening.
      - For HBV, patients who test positive to hepatitis B surface antigen (HBsAg) will be excluded. Patients who test positive to hepatitis B core antibody (HBcAb) only (HBsAg negative), may be enrolled if they also test positive to hepatitis B surface antibody (HBsAb).
      - For HCV, patient who test positive to HCV antibody will be excluded unless they test negative for HCV RNA.
   c) Presence of active infection at screening or history of infection requiring intravenous antibiotics and/or hospitalization ≤8 weeks before baseline visit, or oral/intramuscular antibiotics ≤4 weeks before baseline visit, or topical antibiotics ≤2 weeks before baseline visit. Minor localized fungal infections or topical antibiotics for facial acne may be allowed.
   d) Any recurrent bacterial, fungal, opportunistic, or viral infection including recurrent/disseminated herpes zoster that, based on the investigator´s clinical assessment, causes a safety risk and makes the patient unsuitable for the study.

Note: Recurrent infections are defined as 2 or more severe infections in 1 year, 3 or more respiratory infections (eg, sinusitis, otitis, bronchitis) in 1 year, or the need for antibiotics for 2 months/year.

e) History of invasive/systemic fungal infection (eg, histoplasmosis) or nontubercular mycobacterial infection.

3. Patient meeting any of the following TB-related conditions:

   a) Patient who has current or history of active TB.

   b) Patient who has signs or symptoms suggestive of active TB upon medical history or physical examination including chest radiography at screening. If a chest radiography performed within the past 3 months before screening is available, it does not need to be repeated at screening.

   c) Patients with current latent TB (defined as a positive result of interferon-γ release assay [IGRA] with a negative examination of chest radiography [posterior-anterior and lateral views, or per country regulations where applicable] and absence of symptoms). Patients with positive IGRA may be enrolled if they have documentation of completed appropriate country-specific TB prophylaxis within the past 5 years or have received at least 1 month of country-specific TB prophylaxis before the baseline visit and are willing to complete its entire course, and do not have other risk factors, radiologic findings, or physical evidence supporting latent or active TB. It is the responsibility of the investigator to verify the adequacy of previous anti-TB treatment and provide appropriate documentation. If a patient's initial IGRA test result is indeterminate, the test can be repeated once. If the test result is again indeterminate, the patient will be excluded from the study.

   d) Patient who has had exposure to a person with active TB, such as first-degree family members or coworkers within 16 weeks before the baseline visit.

4. Patient has an underlying condition (including, but not limited to metabolic, hematologic, renal, hepatic, pulmonary, neurologic including central nervous system demyelinating disease, endocrine, cardiac, infection, or gastrointestinal) which, in the opinion of the investigator, significantly immune compromises the patient and/or places the patient at unacceptable risk for receiving an immunomodulatory therapy.

5. Patient had a major surgical intervention within 12 weeks of the baseline or planned major surgery during the study period.

6. Patient who has prior exposure to more than 1 biologic agent for the treatment of psoriasis or psoriatic arthritis.

7. Patient who has received or plans to receive any of the following prohibited medications or treatment that could affect psoriasis:
   a) Topical therapies for the treatment of psoriasis (including, but not limited to, corticosteroids, vitamin D analogs, calcineurin inhibitors or retinoids) within 2 weeks before the baseline visit. However, restricted use of rescue topical treatment may be allowed as per Section 9.8.
   b) Ultraviolet A phototherapy (with or without oral psoralen) or ultraviolet B phototherapy for the treatment of psoriasis within 4 weeks before the baseline visit.
   c) Systemic steroids within 4 weeks before the baseline visit.
   d) Any nonbiologic systemic therapies for the treatment of psoriasis or psoriatic arthritis within 4 weeks before the baseline visit.
   e) Any biologic systemic therapy with a mechanism of action that could impact the course of psoriasis/psoriatic arthritis or its evaluations, within 5 half-lives or 90 days, whichever is longer, before the baseline visit.
   f) Any mAb within 5 half-lives or 90 days, whichever is longer, before the baseline visit.
   g) Any drug that directly targets IL-12, IL-17, or IL-23 including ustekinumab either investigational or approved.
   h) Any investigational drug other than study treatment within 4 weeks or 5 half-lives (whichever is longer) before the baseline visit.
   i) Any other drug that may impact psoriasis (eg, beta-blockers, lithium, antimalarials) within 4 weeks before the baseline visit.
      Note: However, patients on stable doses of beta-blockers for 3 months before the baseline visit are allowed.
   j) Herbal or any nonpharmaceutical medicine to treat psoriasis within 2 weeks before the baseline visit.
8. Patient has received a live or live-attenuated vaccine within 4 weeks before the baseline visit. Patient must agree not to receive a live or live-attenuated vaccine during the study and up to 15 weeks after the last dose of the study treatment.
9. Patient who has had Bacillus Calmette-Guérin (BCG) vaccination within 1 year before the baseline visit. Patients must agree not to receive a BCG vaccination during the study and at least 1 year after the last dose of the study treatment.

10. Patient who had confirmed COVID-19 infection and was hospitalized requiring oxygen in the last 8 weeks prior to screening. In case of asymptomatic/mildly symptomatic patient with confirmed COVID-19 infection during the last 4 weeks prior to screening, and who have not recovered from COVID-19 as per site and/ local regulatory guidelines at screening, would also be excluded from the study.
11. Patient who has received or is planning to receive COVID-19 vaccination within 2 weeks before or after the baseline visit. However, COVID-19 vaccination >2 weeks before or after the baseline visit is permitted.
12. Patient has a history of hypersensitivity to any biologic systemic therapy or any of the excipients of Stelara®.
13. Patient who is not willing to limit ultraviolet light exposure (eg, excessive sun exposure and/or the use of tanning devices) during the study.
14. Patient is pregnant or breastfeeding (lactating) at the time of screening or baseline visit.
15. Patient has history of malignancy within 5 years except adequately treated cutaneous squamous or basal cell carcinoma, in situ cervical cancer, or in situ breast ductal carcinoma.
16. Have a transplanted organ/tissue or stem cell transplantation.
17. Evidence (as assessed by the investigator using good clinical judgment) of alcohol or drug abuse or dependency in the last 3 years before screening.
18. Patient has a severe progressive or uncontrolled, clinically significant disease that in the judgment of the investigator renders the patient unsuitable for the study.

Treatment Period 3 (TP3) specific enrollment criteria:

- Patient is willing and able to provide revised informed consent form (ICF), able to follow study instructions, and comply with the protocol requirements as per the investigator's opinion.
- Patient has not developed any condition/ or met study discontinuation or treatment discontinuation criteria which precludes his/her participation in the TP3.

Note: For patients not meeting TP3 specific enrollment criteria, the end of study visit will occur at Week 28.

8.3 Rescreening/Retesting

Individuals who sign the ICF to participate in the study but who do not subsequently meet all the requirements as outlined in the inclusion and exclusion criteria and therefore do not enroll (screen failures) may be rescreened depending on the criteria that were not met. Such individuals may be allowed to rescreen up to 1 time upon discussion and agreement with the medical monitor and/or Sponsor.

Repeating an exclusionary laboratory test such as alanine aminotransferase (ALT), aspartate aminotransferase (AST), or bilirubin within the same screening procedure may be allowed only once, upon agreement with the medical monitor, if the abnormal result was not associated with a pathology or was considered incidental by the investigator. Retesting should not prolong the screening duration beyond the allowed 4 weeks. Serology or TB tests cannot be repeated.

8.4 Study Withdrawal, Removal, and Replacement of Patients

Patients may withdraw from the study at any time and for any reason without prejudice to their future medical care by the investigator or at the study site. The investigator may also discontinue the study treatment in the interest of patient safety.

Study Treatment Discontinuation Reasons:

1. Patient does not comply with the protocol and has an important protocol deviation(s) in the investigator's opinion.
2. Patient receives prohibited medication(s).
3. Patient has serious or any other AEs, or any medical, physical, or psychiatric condition(s) that, in the investigator's opinion, would pose a significant risk to the patient or interfere with interpretation of study data.
4. Patient does not achieve PASI 50 response at Week 12.
5. Patient becomes pregnant.
6. Patient withdraws consent for study treatment, or the investigator or Sponsor decides to discontinue study treatment.

Study Discontinuation Reasons:

1. Patient is lost to follow-up.
2. Patient withdraws consent from study participation.
3. Death.
4. Patient withdrawn at investigator’s discretion because of medical (eg, condition as assessed by the investigator as requiring therapy/intervention that will interfere with the patient’s subsequent study visits) or administrative (eg, persistent noncompliance, inability to comply with the study schedule) reasons.
5. Study or site terminated by Sponsor
6. Patient does not achieve at least PASI 75 response at Week 28.

Additionally, the Sponsor may stop the study at any time for safety, regulatory, legal, or other reasons aligned with good clinical practice (GCP). The Sponsor should promptly inform the investigators and the regulatory authority of the termination or suspension and the reason(s) for the termination or suspension. This study may be terminated at the discretion of the Sponsor or

any regulatory agency. An investigator may elect to discontinue or stop the study at his or her study site for any reason, including safety or low enrollment.

Patients who discontinue study treatment before the end of Week 16 will be followed up for efficacy to the Week 16 scheduled assessment. Patients who discontinue study treatment on or after Week 16 dosing and before Week 28 dosing will be followed up for efficacy to the Week 28 scheduled assessment. All patients that discontinue study treatment during TP1 and TP2 will be required to attend the scheduled visits for safety and immunogenicity to Week 28, at which point they will be discontinued from the study. Patients who discontinue study treatment after entering TP3 at Week 28 will be required to attend the scheduled visits for efficacy, safety, and immunogenicity to the EOS at Week 52.

Every reasonable effort will be made to contact early discontinued patients who are lost to follow-up to obtain further safety information. Details regarding follow-up efforts are to be documented in the patient's medical records/source documentation.

If a patient terminates participation in the study and does not return for the completion/termination visit, their last recorded assessments shall remain recorded with their last visit. The reason for discontinuation will be recorded. In accordance with applicable regulatory guidance, de-identified data that have already been collected and incorporated in study database will continue to be used and/analyzed (and any identifiable data will be destroyed).

Patients who receive study treatment and withdraw from the study before its completion will not be replaced.

8.4.1 Pregnancy

Patients will be instructed that known or suspected pregnancy occurring during the study should be confirmed and reported to the investigator. If a patient becomes pregnant, the investigator must withdraw the patient from the study without delay. The patient must not receive any further doses of the study drug. The investigator should also be notified of pregnancy occurring during the study but confirmed after completion of the study. In the event that a female patient or female partner of a male patient is subsequently found to be pregnant after inclusion in the study, any pregnancy will be followed up to term or as per the applicable local guidelines for follow-up, and the status of mother and child will be reported to the Sponsor after delivery. A separate consent will be obtained from the pregnant partner before collecting any information pertaining to the pregnancy. See Section 12.8.5 for further reporting and monitoring details.

The investigator should notify the Sponsor on a Pregnancy Reporting form within 24 hours of knowledge of the pregnancy. Full details of the pregnancy will be recorded on the withdrawal page (exit form) of the electronic case report form (eCRF). Pregnancy is not to be considered an AE; however, spontaneous miscarriages, congenital abnormalities, and any premature termination of pregnancy will be reported as serious adverse event (SAEs) as described in Section 12.8.5.

8.4.2 Completion of the Study or Lost to Follow-up

The study will be completed when all patients have completed their study-related procedures in accordance with the protocol including the follow-up period and EOS visit.

The following actions must be taken if a patient fails to return to the clinic for a required study visit:

- The site must attempt to contact the patient and reschedule the missed visit as soon as possible and counsel the patient on the importance of maintaining the assigned visit schedule and ascertain whether the patient wishes to and/or should continue in the study.
- Before a patient is deemed lost to follow-up, the investigator or designee must make every effort to regain contact with the patient (where possible, 3 telephone calls and, if necessary, a certified letter to the patient's last known mailing address or local equivalent methods). These contact attempts should be documented in the patient's medical record.

If the patient continues to be unreachable, he/she will be considered to have withdrawn from the study because of reason of lost to follow-up.

9 TREATMENTS

9.1 Details of Study Treatments

9.1.1 Identity of Study Treatments

Bmab 1200 is a mAb that is being developed by Biocon Biologics UK Limited as a proposed biosimilar to Stelara®. The International Nonproprietary Name of the commercially available reference material (Stelara®) is ustekinumab.

The reference product, EU-approved Stelara®, is supplied as a sterile, preservative-free solution of ustekinumab at a concentration of 45 mg/0.5 mL in a single-use prefilled syringe (PFS) with passive safety needle guard for subcutaneous administration. The solution is clear to slightly opalescent, colorless to light yellow and may contain a few small translucent or white particles of protein. Each 0.5 mL PFS delivers 45 mg ustekinumab, L-histidine, L-histidine-monohydrochloride monohydrate, Polysorbate 80, sucrose, and water for injections.[9]

Bmab 1200 will be supplied as a [redacted] for subcutaneous administration. Each [redacted]

Dosing instructions to be followed are described in the Pharmacy Manual.

The Sponsor will provide adequate supplies of Bmab 1200 and Stelara® for distribution to the study sites.

The following drug supplies will be used in the study:

Product	Supplied as:
Bmab 1200	[redacted]
EU-approved Stelara®	PFS containing 45 mg/0.5 mL of ustekinumab

a. Abbreviation: EU, European U on; FS, pr e s nge.
b. Note: Bmab 1200 [redacted] whereas Stelara® PFS will come with a passive safety needle guard.

9.1.2 Packaging and Storage

The Sponsor will provide the investigator and study sites with adequate quantities of Bmab 1200 and EU-approved Stelara®. Bmab 1200 will be manufactured and packaged in accordance with Good Manufacturing Practice (GMP) for medicinal products for use in human clinical trials and provided with a certificate of analysis. All study treatments will be labeled in accordance with GMP and local regulatory requirements.

Bmab 1200 and EU-approved Stelara® must be kept in a secured area at a controlled refrigerated temperature between 2 °C and 8 °C and must not be frozen. Individual PFS may be stored at room temperature up to 30 °C for a maximum single period of up to 30 days in the original

carton to protect from light. Once a syringe has been stored at room temperature (up to 30 °C), it should not be returned to the refrigerator. The recommended storage conditions, and expiry date where required, are stated on the product label approved by each regulatory authority.

9.1.3 Study Drug Retention, Return and Destruction

Study drug must be retained at sites until completion or termination of the study, and written authorization from the Sponsor has been received. All unused and used study drug must be destroyed at the site or returned, as specified by Sponsor. It is the investigator's responsibility to ensure that appropriate records of the disposal are documented and maintained. No used or unused study drug may be disposed until fully accounted for by the study monitor. Retention samples will be stored in compliance with the current applicable regulatory guidance at the clinical trial depot or warehouse.

9.2 Method of Administration of Study Treatments

Patients will receive either Bmab 1200 or Stelara® by subcutaneous injection via PFS at the baseline visit, Week 4, Week 16, Week 28, and Week 40 based on the patient's baseline body weight as follows:

- Patients who weigh ≤100 kg: Bmab 1200 or Stelara® 45 mg (1 injection of 45 mg PFS)
- Patients who weigh >100 kg: Bmab 1200 or Stelara® 90 mg (2 injections of 45 mg PFS)

Injection sites include upper arms, thighs, and abdomen. For patients who receive two 45 mg PFSs for a 90-mg dose, the 2 injections will be one right after the other at different injection sites. If possible, areas of the skin that show psoriasis lesions should be avoided as injection sites. The actual injection site(s) should be documented.

Detailed administration instructions will be provided in the Pharmacy Manual.

9.3 Measures to Minimize Bias: Study Treatment Assignment and Blinding

9.3.1 Method of Study Treatment Assignment

At screening RAVE EDC will assign a unique patient identification number to the patient known as the patient number. This number will be associated with the patient throughout the study. Every patient who signs an ICF must be entered into the RAVE EDC regardless of eligibility to obtain a patient number. This 8-digit number will consist of a 3-digit country-specific code, followed by a 2-digit site identification and a 3-digit number assigned sequentially within each site to each patient, starting at 001.

At the baseline visit patients will be randomly assigned to receive Bmab 1200 (test product) or Stelara® (reference product) in a 1:1 allocation ratio (using a permuted block design), stratified by the factors described below. A separate unblinded Biostatistical team will generate the randomization schedule using SAS software Version 9.4 or later (SAS Institute Inc, Cary, North Carolina) for RAVE EDC, which will link sequential patient randomization numbers to treatment codes. Based on the randomization schedule, each patient will be assigned a unique

number (randomization number) that encodes the patient's assignment to one of the 2 treatment groups of the study.

The first randomization to treatment assignment (at baseline visit) will be stratified by the following:

- Geographic region where the patient was enrolled (United States versus Europe),
- Body weight (≤100 kg versus >100 kg),
- Prior exposure to biologic therapies for psoriasis or psoriatic arthritis (Yes versus No),
- Concomitant psoriatic arthritis (Yes versus No).

When randomized, the patient will be assigned a randomization number through the RAVE EDC in accordance with the randomization code generated by the authorized personnel at the contract research organization (CRO). At the study site, the randomization schedule will only be accessible to authorized unblinded pharmacy personnel or designee. Once a randomization number is allocated to one patient, it may not be assigned to another patient even if the former discontinued the study.

All continuing patients who receive study treatment at Weeks 0 and 4 and achieve at least PASI 50 response by Week 12 will be rerandomized before receiving study treatment at Week 16. Before dosing at Week 16, patients in the Stelara® arm will be randomly assigned in a 1:1 ratio to receive either Bmab 1200 or Stelara® at Week 16. To maintain the study blinding, the patients in the original Bmab 1200 group will also go through the rerandomization procedure; however, they will be assigned and continue to receive Bmab 1200. The re-randomization will take place using the original strata as recorded at baseline (under which the original randomization occurred). For patients continuing into TP3, the patients will continue with the same treatment as randomized during TP2 in a blinded manner.

9.3.2 Blinding

This study will be double-blind (ie, the patient and the investigator will be blinded to the study treatment assignment), during the whole study period.

A RAVE EDC and Randomization and Trial Supply Management (RTSM) will be used for patient randomization and a randomization number will be assigned automatically. According to the randomization schedule as indicated in the Schedule of Assessments (Table 1) and in accordance with the Pharmacy Manual, the investigator or designee will obtain the study drug number from the RAVE EDC for the patient, and the number will be provided to the unblinded pharmacist or other unblinded site staff who delegated to the study at the study center who is responsible for dispensing of study treatments.

Bmab 1200 will be supplied as a [redacted] e biosimilar ustekinumab) for injection, whereas EU-approved Stelara® will be supplied as a PFS with passive needle safety guard with ustekinumab for injection. Thus,

blinding from the primary packaging will not be feasible, but blinding will be maintained at the secondary packaging level with similar packaging for both the products. Therefore, 2 different teams, ie, blinded and unblinded team will be assigned to maintain the blinding and handle the study treatment administration. The designated, unblinded site staff will administer the study medication injections in such a manner that the participant remains blinded (eg, by eye coverings at the time of the injection). Blinded staff/any other personnel must not be involved in any activities pertaining to the receipt, handling, or administration of study medication. All study medication documentation (ie, shipping receipts, accountability logs, and RTSM randomization materials) must be maintained only by unblinded site staff. Designated, unblinded personnel must be appropriately trained and certified (per country guidelines) to administer injections. Unblinded site staff should not share any treatment assignment information with others.

No other study site personnel, patients, Sponsor personnel, or Sponsor designees will be unblinded to treatment assignment throughout the duration of the study unless unblinding is required. If an investigator becomes unblinded to a given patient's study treatment, that patient will be discontinued from the study unless there are ethical reasons for that patient not to be discontinued; approval from the Sponsor's medical monitor must be obtained in such instances.

In the event that emergency unblinding is required for a given patient because of AEs or concerns for the patient's safety or wellbeing, the investigator may break the randomization code for the patient via RAVE RTSM, by which system the unblinding will be captured. The investigator should try every effort to discuss with medical monitor before the code break and the investigator is responsible for notifying the medical monitor and/or Sponsor of such an event as soon as possible. The unblinding and its cause will also be documented in the eCRF.

In the event of drug-related, serious, unexpected AE (suspected unexpected serious adverse reaction [SUSAR]), Pharmacovigilance Group will be provided with the treatment assignment for the patient for the purpose of regulatory reporting. Details of the process are outlined in separate Safety Management Plan.

Two database locks are planned for this study: one at the time of the Week 28 analysis and the other at the time of the Week 52 analysis. The study team will continue to remain blinded to the study treatments until the final analysis; a separate analysis team and reporting team will conduct the unblinded analyses for the Week 28 clinical study report (CSR) which will be described in detail in a separate document for the study.

9.4 Dosage Modification

No dose adjustment is permitted for this study.

9.5 Treatment Accountability and Compliance

The unblinded pharmacist or other designated unblinded site staff will maintain records of study treatment delivered to the study site, the inventory at the study site, the distribution to each patient, and the return of materials to the Sponsor or designee for storage or disposal. These

records should include dates, quantities, batch/serial numbers, expiration dates, in-clinic temperature log, and unique code numbers assigned to the product and study patients.

Only patients enrolled in the study may receive the study treatment and only authorized site personnel may supply or administer the study treatment. Reasons for departure from the expected dispensing regimen must also be recorded. At the completion of the study, to satisfy regulatory requirements regarding drug accountability, all study treatments will be reconciled and retained or destroyed according to applicable regulations. Further guidance and information for the final disposition of unused study treatment are provided in the Study Reference Manual.

Treatment compliance will be evaluated by comparing the number of doses expected with the number of doses administered and comparing the amount of the total dose planned with the amount of total dose administered.

A dose visit window of ±3 days is recommended for Week 4 dosing and ±7 days for the Week 16 and Week 40 dosing. For Week 28, a dose visit window is recommended to be ±7 days, however, a longer visit window may be considered only in cases where needed to ensure that the eligible patients are given opportunity to participate in TP3 (but dosing is not to be postponed to more than 4 weeks). Data handling for analysis of scheduled assessments performed outside of the allotted time window will be discussed and agreed on a by-patient basis in the Blinded Data Review Meetings (BDRMs), with the report finalized before each database lock.

9.6 Prior and Concomitant Therapy

Restricted prior therapies are provided in Section 8.2, and a complete list of prohibited medications is provided in Section 9.7.

Patients are recommended to continue maintaining their usual lifestyle during the study and refrain from initiating a diet to lose weight unless medically indicated for their safety.

All medications and other treatments taken by the patient during the study must be recorded on the eCRF. The entry must include the dose, regimen, route, indication, and dates of use. This will include all prescription drugs, herbal products, vitamins, minerals, and over-the-counter medications. Any changes in concomitant medications also will be recorded in the patient's eCRF.

Any concomitant medication deemed necessary for the welfare of the patient during the study may be given at the discretion of the investigator. However, it is the responsibility of the investigator to ensure that details regarding the medication are recorded in full in the eCRF.

9.7 Prohibited Therapies

Medications taken by or administered to the patient for the period before screening will be recorded in the eCRF.

The following therapies are prohibited during the study period. Patients who have received these prohibited therapies (see Section 8.2) or plan to receive these prohibited therapies will not be

enrolled in the study. Patient who is permanently discontinued from study treatment can be treated with alternative therapy at the investigator's discretion. Inactivated vaccines are acceptable during the study.

- Ustekinumab, either approved or investigational (other than study treatment).
- Any drug that directly targets IL-12, IL-17, IL-23.
- Any biologic systemic therapy for the treatment of psoriasis/psoriatic arthritis or one that could affect its course.
- Any nonbiologic systemic therapy that could affect psoriasis (including, but not limited to, methotrexate, cyclosporine, or systemic steroids).
- Any mAb.
- Topical therapies for the treatment of psoriasis (including, but not limited to, corticosteroids, vitamin D analogs, calcineurin inhibitors, or retinoids)
  Note: restricted use of rescue topical treatment may be allowed as stated in Section 9.8.
- Ultraviolet A phototherapy (with or without oral psoralen) or ultraviolet B phototherapy for the treatment of psoriasis.
- Any investigational drug other than study treatment.
- Initiation of any other drug that may impact psoriasis (eg, beta-blockers, lithium, antimalarials).
- Herbal or any nonpharmaceutical treatment that could affect psoriasis.
- Live or live-attenuated vaccination until at least 15 weeks after last dose of study treatment.
- BCG vaccination up to 1 year after last dose of study treatment.

9.8 Permitted Medications

Low potency topical corticosteroids, ie, least potent and mild immediately (Class VI to VII of USA 7 Group TCS Classification) on scalp, face, axillae, groin, or genitalia are allowed with the restriction NOT to use them within 24 hours before the screening and other study visits requiring PASI or sPGA measurements.

Bland moisturizers/emollients (without urea or beta or alpha hydroxy acids or any pharmaceutically active ingredients) and shampoos with salicylic acids are also allowed for treatment of psoriasis, but these should not be used in the mornings of study visits when any efficacy assessments are going to be performed.

COVID-19 vaccination >2 weeks before and after each dosing with study treatment during the study is allowed.

No other medications (for psoriasis) are permitted in this study.

9.9 Intervention After the End of the Study

After the end of the study, study treatments will not be made available to patients and their further treatment, if required, will be decided by the investigator.

10 STUDY PROCEDURES

Table 1 outlines the timing of procedures and assessments to be performed throughout the study. Section 12.5 specifies laboratory assessment samples to be obtained. See Sections 11, 12, 13, and 14 for additional details regarding efficacy, safety, PK, and immunogenicity assessments, respectively.

Table 1. Schedule of Assessments

Study Periods	Screening	Treatment Period 1					Treatment Period 2			Treatment Period 3	
Visits	**1**	**2 (Baseline)**	**3**	**4**	**5**	**6**	**7**	**8**	**9**	**10**	**11 (EOS)**
Week	**-4**	**0**	**2**	**4**	**8**	**12**	**16**	**20**	**28**	**40**	**52**
Day	**-28 to -1**	**1**	**15±3**	**29±3**	**57±5**	**85±5**	**113±7**	**141±7**	**197±7[p]**	**281±7**	**365±7**
Informed consent	X								X		
Demographic, medical history	X										
Inclusion/ Exclusion criteria	X	X[a]							X[o]		
% BSA involvement	X	X[b]		X	X	X	X	X	X	X	X
Randomization		X[b]									
Rerandomization							X[b]				
Hepatitis B, Hepatitis C and HIV-1 & -2 test[c]	X										
Serum pregnancy test[d]	X										
Urine pregnancy test[d]		X		X	X	X	X	X	X	X	X
Chest radiography[e]	X										
IGRA test[f]	X										
Study treatment (Bmab 1200 or Stelara®) administration		X		X			X		X	X	
Hypersensitivity/injection site reactions monitoring[g]		X		X			X		X	X	
PASI assessment[b]	X	X		X	X	X	X	X	X	X	X
sPGA assessment[b]	X	X		X	X	X	X	X	X	X	X
DLQI assessment[b]		X		X	X	X	X	X	X	X	X
PK sampling		X (predose)	X	X (predose)	X	X	X (predose)	X	X	X	X

Study Periods	**Screening**	**Treatment Period 1**					**Treatment Period 2**			**Treatment Period 3**	
Visits	**1**	**2 (Baseline)**	**3**	**4**	**5**	**6**	**7**	**8**	**9**	**10**	**11 (EOS)**
Week	**-4**	**0**	**2**	**4**	**8**	**12**	**16**	**20**	**28**	**40**	**52**
Day	**-28 to -1**	**1**	**15±3**	**29±3**	**57±5**	**85±5**	**113±7**	**141±7**	**197±7[p]**	**281±7**	**365±7**
									(predose)	(predose)	
Immunogenicity sampling		X (predose)	X	X (predose)	X	X	X (predose)	X	X (predose)	X (predose)	X
Blood sample for method validations		X[h]									
Clinical Laboratory Evaluations (Hematology, clinical chemistry, and urinalysis)[i]	X	X		X	X	X	X	X	X	X	X
Physical examination[j]	X	X		X	X	X	X	X	X	X	X
Vital signs[k]	X	X		X	X	X	X	X	X	X	X
Body weight, height[l]	X	X		X			X		X	X	
12-lead ECG[m]	X	X					X		X	X	X
Prior and concomitant medications	X	X	X	X	X	X	X	X	X	X	X
TB clinical monitoring[n]	X	X	X	X	X	X	X	X	X	X	X
Adverse events	X	X	X	X	X	X	X	X	X	X	X

Abbreviations: BSA, body surface area; DLQI, Dermatology Life Quality Index; ECG, electrocardiogram; EOS, end of study; HBcAb, hepatitis B core antibody; HBsAb, hepatitis B surface antibody; HBsAg, hepatitis B surface antigen; HCV, hepatitis C virus; HIV, human immunodeficiency virus; IGRA, interferon-γ release assay; PASI, Psoriasis Area and Severity Index; PK, pharmacokinetic; sPGA, static Physician's Global Assessment; TB, tuberculosis; V, Visit; Wk, Week.

EOS, End of Study visit: for patients not entering the TP3, EOS will occur at Week 28. Otherwise, EOS will occur at Week 52.

Note: For all patients who discontinue study treatment early, every effort should be made to complete regularly scheduled study visits as recommended in Section 7.1. Patients who discontinue study treatment before the end of Week 16 will be followed up for efficacy to the Week 16 scheduled assessment. However, the primary endpoint analysis will be done at Week 12 only. Patients who discontinue study treatment on or after Week 16 dosing and before Week 28 dosing will be followed up for efficacy to the Week 28 scheduled assessment. Any patient that discontinues study treatment during TP1 or TP2 will be followed up for safety and immunogenicity to Week 28 and will then be discontinued from the study. Patients who discontinue study treatment on or after Week 28 dosing (ie, during TP3) will be followed up for efficacy to the EOS at Week 52. Every reasonable effort will be made to contact early discontinued patients who are lost to follow-up to obtain further safety information. If a patient terminates participation in the study and does not return for the completion/termination visit, their last recorded assessments shall remain recorded with their last visit. Details regarding follow-up efforts are to be documented in the patient's medical records/source documentation.

a. Confirmation of eligibility (per applicable inclusion/exclusion criteria).

b. For study treatment administration visits, procedures will be performed before the study treatment administration.

c. At screening, if the HBsAg test result is positive, the patient will be excluded from the study. If a patient has HBsAg negative and HBcAb positive, the patient will be excluded from the study if testing HBsAb negative while may be enrolled if HBsAb positive. At screening, hepatitis C antibody and HIV will be assessed in all patients. If the HCV test results is positive, HCV RNA will be performed at screening. If the HCV RNA test result is negative, the patient can be included in the study at the investigator's discretion. If the HIV test result is positive, the patient must be excluded from the study. See Section 12.5.2 for details.

d. Pregnancy test is only required for woman of childbearing potential. Urine pregnancy test can be performed more frequently if required by country-specific legislation.

e. A chest radiography (both posterior-anterior and lateral views) is not required at screening if a chest radiography within 12 weeks before screening is available unless it is required by the investigator.

f. The IGRA analysis will be performed at the central laboratory. No further IGRA testing is required during the treatment period for patients who have at least 1 positive IGRA result and have completed the country-specific TB prophylaxis. For patients who discontinued early from the study treatment, IGRA test is unnecessary after the discontinuation.

g. Additional vital signs including blood pressure, pulse and respiratory rates, and body temperature (prior to the beginning of the study treatment administration and at least 1 hour after the end of the study treatment administration) will be monitored for possible hypersensitivity reactions. In addition, hypersensitivity will be monitored by routine continuous clinical monitoring, including patient-reported signs and symptoms. In case of hypersensitivity, emergency equipment, such as adrenaline, antihistamines, corticosteroids, and respiratory support including inhalational therapy, oxygen, and artificial ventilation must be available; in addition, any types of ECG can be performed. Hypersensitivity that may occur after the administration of the study treatment will be monitored. If the patient experiences any hypersensitivity signs and symptoms outside study site, the patient can visit the study site for further assessment. Injection site reactions will be assessed at least 1 hour after the end of the study treatment administration. After the study visits, all patients will be instructed to report hypersensitivity or injection site reactions promptly to the study site; see Section 10.2.

h. Blood sample will be collected from all patients, 5 mL blood will be collected before the first dose administration for PK method validations, additional 10 mL blood will be collected before the first dose administration for immunogenicity method validations.

i. See Section 12.5 for the list of clinical laboratory tests.

j. Full physical examination will be done at screening. Abbreviated, ie, sign/symptom-directed examination will be done at subsequent time points.

k. Vital signs include systolic and diastolic blood pressure, pulse rate, body temperature, and respiratory rate. On the dosing day visits, vital signs will be assessed within 2 hours before dosing. Vital sign measurements are to be taken before blood collection for laboratory tests.

l. Height will be measured only at screening.

m. All scheduled 12-lead ECGs must be performed at the study site after the patient has rested quietly for at least 5 minutes in the supine position. Regardless of the 12-lead ECG result, further cardiological evaluation can be conducted at the investigator's discretion.

n. Throughout the study, patients will be monitored for the clinical signs and symptoms of TB. An additional IGRA or chest radiography can be performed at the investigator's discretion based on the judgment per the signs and symptoms of TB monitoring. The investigator will confirm the absence of active TB prior to the subsequent dose administration.

o. Confirmation of eligibility for TP3 (per applicable inclusion/exclusion criteria).

p. Visit window for Week 28 may be extended only in cases where needed to ensure that the eligible patients are given opportunity to participate in TP3 (but dosing is not to be postponed to more than 4 weeks). Prior discussion with the Sponsor and/or delegate is needed.

10.1 Informed Consent

ICFs must be approved for use by the reviewing independent ethics committee (IEC)/institutional review board (IRB). Before performing any study-related procedures, the investigator (or designee) will obtain written ICF from the patient.

In the event that rescreening occurs, the individual is required to sign a new ICF and must be assigned a new identification number.

All patients who are eligible and are willing to enter the TP3 are required to be re-consented as outlined in the Schedule of Assessments (Table 1).

10.2 Study Procedures

Assessments and their timing are to be performed as outlined in the Schedule of Assessments (Table 1). Section 12.5 specifies laboratory assessment samples to be obtained.

Assessments and procedures scheduled at a visit where study drug is administered should be performed before administration of treatment unless otherwise indicated in the Schedule of Assessments (Table 1).

Efficacy assessments are described in Section 11 and include assessment of PASI score, sPGA, BSA, and DLQI.

Safety assessments are described in Section 12 and include AE monitoring, injection site reactions and hypersensitivity, vital signs, physical examinations (complete and/or abbreviated), 12-lead ECGs, laboratory results (routine hematology, chemistry, and urinalysis).

PK and immunogenicity assessments are described in Sections 13 and 14, respectively.

DLQI should be administered before any other procedures of the visit. Blood sampling for safety laboratory, PK or immunogenicity should be performed after vital signs and ECG measurements. Study drug injection and monitoring for hypersensitivity reactions should be the last procedures of the visit.

The investigator may, at his/her discretion, arrange for a patient to have an unscheduled assessment, especially in the case of AEs that require follow-up or are considered by the investigator to be possibly related to the use of study drug. The unscheduled visit page in the eCRF must be completed.

All patients will be required to remain at the study site for at least 1 hour after study treatment administration to monitor them for potential hypersensitivity reactions. Injection site will also be inspected for potential injection site reactions. Patients will be advised to promptly report to the study site any symptoms occurring within 24 hours after the study treatment that may be suggestive of hypersensitivity reaction.

If social distancing rules are in effect because of the pandemic situations such as COVID-19, sites will have the option to perform the scheduled site visits (per Table 1) either at the patient's home or remotely at the investigator's discretion and according to local regulations even if limited study assessments could be performed. During this time, where access to study site is restricted, the study drug injections except the first dose, may be administered at the patient's home by qualified unblinded site staff. All patients will be instructed to promptly report any hypersensitivity or injection site reactions to the study site.

If a patient tests positive for COVID-19 during the study, he/she may be quarantined as needed and any affected scheduled visits can be arranged or skipped at the discretion of the investigator upon discussing with the medical monitor. Compliance with the permitted visit window should be applied at the best possibility. If the patient requires hospitalization, an SAE should be reported and the patient should be followed up as outlined in Section 12.8.3.

During the COVID-19 pandemic, any potential measures or changes will be handled according to local regulations. If the COVID-19 pandemic wanes off, there is no need to amend the protocol in terms of any specific information relating to COVID-19, including whether some tests/procedures are no longer required.

11 EFFICACY ASSESSMENTS

The Schedule of Assessments (Table 1) outlines the efficacy assessments to be performed throughout the study and their timing.

11.1 Psoriasis Area Severity Index

The PASI is a quantitative rating score for measuring the severity of psoriatic lesions based on area coverage and plaque appearance and their response to therapy.[16] For the PASI assessment, the body is divided into 4 regions: the head, upper limbs, trunk, and lower limbs (APPENDIX 2). Each of these areas is assessed separately for erythema, induration/thickness, and scaling, which are each rated on a scale of 0 to 4 based on severity of the lesion. Degree of involvement on each of the 4 anatomic regions is scored on a scale of 0 (no involvement) to 6 (90% to 100% involvement). The total qualitative score (sum of erythema, thickness, and scaling scores) is multiplied by the degree of involvement for each body region and then multiplied by a constant. The sum of all lesion scores can range from 0 (no disease) to 72 (maximal disease), with the higher score indicating more severe disease. PASI scores are treated as a continuous score with 0.1 increments and if any individual score is missing, the PASI score will not be calculated. PASI scores are used to calculate the PASI response rate (eg, PASI 50 means ≥50% reduction from baseline in the PASI score).

11.2 Static Physician's Global Assessment

The sPGA is a quantitative rating score of the patient's psoriasis based on physician's assessment at a given time point according to the following categories: induration, erythema, and scaling (APPENDIX 3). The sPGA is a 6-point scale and patient's psoriasis is graded as clear (0), minimal (1), mild (2), moderate (3), marked (4), severe (5). The sum of the scores for induration, erythema, and scaling will be divided by 3 to obtain a final sPGA score.

11.3 Body Surface Area

Total % BSA afflicted by psoriasis will be estimated using a handprint of the patient at each visit as outlined in the schedule of events (Table 1). The entire palmar surface of the patient's handprint is assumed to correspond to approximately 1% of total BSA.[17,18]

11.4 Dermatology Life Quality Index

The DLQI is a dermatology specific QoL instrument designed to assess the impact of the disease on a patient's QoL (APPENDIX 4).[19] It is a 10-item patient-reported outcome questionnaire that, in addition to evaluating overall QoL, can be used to assess 6 different aspects that may affect QoL: symptoms and feelings, daily activities, leisure, work or school performance, personal relationships, and treatment. Nine of the 10 questions have response categories including "not relevant" (score of 0), "not at all" (score of 0), "a little" (score of 1), "a lot" (score of 2) and "very much" (score of 3); Question 7 is a "yes"/ "no" question where "yes" is scored as 3. Eight items also have a "Not relevant" option scored "0," which indicates no problems. Total scores

range from 0 to 30 (less to more impairment) and a 5-point change from baseline is considered a clinically important difference. If the answer to one question in a domain is missing, that domain is treated as missing. If 2 or more questions are left unanswered (missing), DLQI total score is treated as missing.

12 SAFETY ASSESSMENTS

12.1 Medical History

Medical history will be recorded at screening. Investigators should document the occurrence, signs, and symptoms of the patient's pre-existing conditions, including all prior significant illnesses before screening. Additional pre-existing conditions present at the time when ICF is given and up to the time of first dosing are to be regarded as concomitant. Medical history will include alcohol consumption and smoking history, if applicable.

Illnesses first occurring or detected during the study and/or worsening of a concomitant illness during the study are to be documented as AEs on the eCRF in accordance with Section 12.8. All changes not present at baseline or described in the past medical history and identified as clinically noteworthy must be recorded as AEs.

Additionally, demographic data will be collected for all patients and include date of birth or age according to applicable regulations, sex, race, and ethnicity. The demographic details will be recorded in the eCRF.

12.2 Vital Signs

Systolic and diastolic blood pressure, pulse rate, respiratory rate, and body temperature will be assessed. Blood pressure and pulse measurements will be assessed in a semisupine position, preferably with a completely automated device. Blood pressure and pulse measurements should be preceded by at least 5 minutes of rest for the patient in a quiet setting without distractions (eg, television, cell phones). Vital sign measurements are to be taken before blood collection for laboratory tests. On the dosing day visits, vital signs will be assessed within 2 hours before dosing.

Vital signs will be measured at scheduled visits as indicated in the schedule of events (Table 1). Out-of-range blood pressure, respiratory rate, or heart rate measurements will be repeated at the investigator's discretion. Any confirmed, clinically significant vital sign measurements must be recorded as AEs.

12.3 Physical Examination

A complete physical examination will include, at a minimum, assessments of the cardiovascular, respiratory, gastrointestinal, musculoskeletal, and neurological systems. Height and weight will also be measured and recorded. The complete physical examination will be performed at screening only. Abbreviated, ie, sign/symptom-directed examination including weight will be performed at subsequent time points as specified in the schedule of events (Table 1). Investigators should pay special attention to clinical signs related to previous serious illnesses.

12.4 Electrocardiograms

All scheduled 12-lead ECGs will be performed at the study site after the patient has rested quietly for at least 5 minutes in a supine position. A 12-lead ECG will be performed at the time points specified in the schedule of events (Table 1); additional ECG recordings can be performed during study treatment administration or the 1-hour monitoring for hypersensitivity reactions at the investigator's discretion. If following the ECG review by the investigator, there are any ECG findings that would indicate any clinically significant cardiac abnormalities, the patient will be referred to a cardiologist for further evaluation. The investigator will then report the event in the source documents and the eCRF. Regardless of the 12-lead ECG result, further evaluation with a cardiologist can be done at the investigator's discretion.

12.5 Laboratory Assessments

Laboratory assessment samples (Table 2) are to be obtained at designated visits as detailed in the Schedule of Assessments (Table 1).

Table 2. Laboratory assessment

Clinical chemistry	total protein, serum bilirubin (total, direct), alanine aminotransferase, aspartate aminotransferase, alkaline phosphatase, gamma-glutamyl transferase, blood urea nitrogen, creatinine, albumin, sodium, potassium, calcium, chloride, inorganic phosphorus, glucose, lactate dehydrogenase, total cholesterol, triglyceride, high-density lipoprotein cholesterol, C-reactive protein (CRP), estimated glomerular filtration rate (eGFR), and uric acid
Hematology	red blood cells, total and differential white blood cell count, absolute neutrophil count, platelet count, hemoglobin, and hematocrit
Urinalysis	bilirubin, blood, glucose, ketones, leukocytes, nitrite, pH, protein, specific gravity, and urobilinogen
Viral serology	Hepatitis B, hepatitis C and human immunodeficiency virus (HIV) tests (see Section 12.5.2 for details)

Blood and urine samples will be analyzed at a central laboratory facility. Any abnormal laboratory test results (hematology, clinical chemistry, or urinalysis) including those that worsen from baseline and are clinically significant in the medical and scientific judgment of the investigator are to be recorded as AEs or SAEs. For urine sample analysis, if there are any clinically significant abnormalities, a microscopic analysis will be performed.

However, any clinically significant safety assessments that are associated with the underlying disease, unless judged by the investigator to be more severe than expected for the patient's condition, are not to be reported as AEs or SAEs.

The investigator must review the laboratory reports, document this review, and record any clinically relevant changes occurring during the study. If the laboratory reports are not transferred electronically, the values must be filed with the source information (including reference ranges). In most cases, clinically significant abnormal laboratory findings are those that

are not associated with the underlying disease, unless judged by the investigator to be more severe than expected for the patient's condition.

All laboratory tests with values considered clinically significantly abnormal during participation in the study should be repeated until the values return to normal or baseline or are no longer considered clinically significant by the investigator or medical monitor.

All protocol-required laboratory assessments must be conducted in accordance with the laboratory manual and the schedule of events (Table 1). If laboratory values from non-protocol specified laboratory assessments performed at the institution's local laboratory require a change in patient management or are considered clinically significant by the investigator (eg, SAE or AE or dose modification), then the results must be recorded in the eCRF.

12.5.1 Laboratory Assessments at Screening

IGRA, HBV, HCV, HIV, and pregnancy (serum at screening and urine during the study, only for women of childbearing potential) tests will be performed at screening. Clinical laboratory tests details are presented in Section 12.5 above.

12.5.2 Viral Serology Tests

All virology tests will be performed at the central laboratory.

At screening, HBsAg, HBsAb, and HBcAb will be assessed as specified in Table 3.

Table 3. Eligibility Based on Serologic Markers for Hepatitis B Infection

Test Results			Eligibility
HBsAg	HBsAb	HBcAb	
+	+/–	+/–	Not eligible
–	–	+	Not eligible
–	+	+	Eligible
–	–	–	Eligible

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

If the HBsAg test result is positive, the patient will be excluded from the study. If a patient has HBsAg negative and HBcAb positive, the patient will be excluded from the study if testing HBsAb negative while may be enrolled if HBsAb positive.

At screening, hepatitis C antibody and HIV will be assessed in all patients. If the HCV test results is positive, HCV RNA will be performed at screening. If the HCV RNA test result is negative, the patient can be included in the study at the investigator's discretion. If the HIV test result is positive, the patient must be excluded from the study.

12.5.3 Interferon-γ Release Assay Test

A blood IGRA test will be performed at screening on all patients to test for latent TB. Patients will be enrolled or excluded from the study as described in Section 8.2. Additional IGRA test can be conducted during the study at the investigator's discretion if there a suspicion of TB infection.

12.6 Injection Site Reaction Monitoring

Patients will be assessed for injection site reactions for at least 1 hour after the end of each dosing, as specified in the schedule of events (Table 1). Severity of injection site reactions will be based on Common Terminology Criteria for Adverse Events (CTCAE) criteria.

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

12.7 Hypersensitivity Monitoring

Patients will be assessed for hypersensitivity reactions for at least 1 hour after the end of the study treatment administration, as specified in the schedule of events (Table 1) Emergency medication and equipment, such as adrenaline, antihistamines, corticosteroids, and respiratory support including inhalational therapy, oxygen, and artificial ventilation must be available at the study site and any additional procedures like ECG recording as required can be performed. If patients have signs and symptoms of hypersensitivity/allergic reactions at home (hives, difficulty breathing, or swelling of face, eyes, lips, or mouth or any symptoms of cardiac origin), patients or caregivers should be advised to call the study site or get immediate help.

For patients who experience or develop life-threatening treatment-related anaphylactic reactions, study treatment administration must be stopped and permanently discontinued.

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

12.8 Adverse Events

12.8.1 Adverse Events

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

An AE is any untoward medical occurrence in a patient or clinical investigation patient administered a pharmaceutical product and which does not necessarily have to have a causal relationship with this treatment.

An AE can therefore be any unfavorable and unintended sign (including an abnormal laboratory finding, for example), symptom, or disease temporally associated with the use of a medicinal product, whether or not considered related to the medicinal product. Patients will be instructed to contact the investigator at any time after randomization if any symptoms develop.

A TEAE is defined as any event absent before exposure to the study treatment that emerges after first exposure to study treatment, or any event already present that worsens in either intensity or frequency after exposure to the study treatment.

An ADR is defined as any noxious and unintended responses to an investigational medicinal product related to any dose administered.

Anticipated day-to-day fluctuations of pre-existing diseases or conditions present or detected at the start of the study that do not worsen would not be considered AEs. Situations where an untoward medical occurrence has not occurred (eg, hospitalization for elective surgery, social and/or convenience admissions) would not be considered AEs. Laboratory results of the disease being studied, medical/surgical procedures are not an AE but rather the condition/event that leads to it are defined as an AE, details please refer to Sections 12.2 and 12.5.

12.8.1.1 Eliciting and Documenting Adverse Events

AEs will be assessed from the time the patient signs the ICF until the end of the study.

If the investigator learns of any SAE, including a death, at any time after the end of the study, and he/she considers the event to be reasonably related to the study treatment or study participation, the investigator must promptly notify the Sponsor/Sponsor representative.

At every study visit, patients will be asked a standard nonleading question to elicit any medically related changes in their wellbeing.

In addition to patient observations, AEs identified from any study data (eg, laboratory values, physical examination findings, ECG changes) or identified from review of other documents that are relevant to patient safety will be documented on the AE page in the eCRF. The investigator can follow-up AEs by unscheduled clinic visits or telephone calls with the patients at their discretion. Either unscheduled visits or follow-up calls need to be documented in the patient's medical records and in the eCRF as appropriate.

AEs will be recorded in the patient's medical records in accordance with the investigator's normal clinical practice and on the AE page of the eCRF. SAEs that occur during the study must be documented in the patient's medical record, on the AE/SAE page of the eCRF.

The investigator should attempt to establish a diagnosis of the event based on the signs, symptoms and/or other clinical information. In such cases, the diagnosis should be documented as the AE (and SAE if serious) and not the individual signs/symptoms. If a clinically significant abnormal laboratory finding or other abnormal assessment meets the definition of an AE (and SAE if serious), then the AE/SAE page of the eCRF page must be completed as appropriate. A diagnosis, or clinical signs or symptoms if the diagnosis is unknown, rather than the clinically significant laboratory finding or abnormal assessment, should be used to complete the AE/SAE page. As additional information becomes available and a diagnosis is achieved, the signs/symptoms or abnormal finding verbatim should be updated on the eCRF.

If no diagnosis is known and clinical signs or symptoms are not present, then the abnormal finding should be recorded on the AE/SAE page.

12.8.1.1.1 Assessment of Severity

The severity of an AE refers to the extent to which an AE affects the patient's daily activities. The severity of the AE will be graded based on the CTCAE v5.0, based on the following general guidelines (a semicolon indicates "or" within each description). Any AEs not covered by the CTCAE criteria will be assessed and classified as per the same guidelines below:

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

Abbreviation: AE, adverse event.

* Instrumental activities of daily living refer to preparing meals, shopping for groceries or clothes, using the telephone, managing money, etc.

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

Changes in the severity of an AE should be documented to allow an assessment of the duration of the event at each level of intensity. AEs characterized as intermittent do not require documentation of onset and duration of each episode.

The SAE will not be closed out if it is of changing severity during the course. It will be reported with changes in the severity as it upgrades in follow-up reports such that each upgraded sequela will not be recorded as a new SAE but continuation of same SAE and the serious and unexpected ADRs will be reported to the local regulatory authority/IEC within the stipulated timeline. Only the highest grade of severity will be considered for analysis purpose.

12.8.1.1.2 Assessment of Causality

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

The investigator's causality assessment should consider the potential etiologies for the observed AE. An AE may be related to study treatment, other concomitant medications, the underlying disease pathology, intercurrent illness, a procedure performed in the course of the study, or another reason. Among the potential etiologies, the investigator should decide based on the most likely causal relationship. When a causality assessment is provided for an SAE, it is important to include a rationale for the assessment so that a better understanding of the reported event can be compiled. The rationale should be accompanied by all available supporting evidence, including

relevant laboratory tests, histopathology evaluations, and the results of other diagnostic procedures.

The relationship or association of the study treatment in causing or contributing to the AE will be characterized using the following:

- UNRELATED: There is no temporal association between the investigational product and the reported event and event is clearly due to other causes (eg, concomitant medication, underlying disease etc).
- UNLIKELY: Time to drug intake makes a relationship improbable. Another explanation is more likely such as disease, environment, or other medication.
- POSSIBLY: Treatment with the study drug caused or contributed to the AE, ie, the event follows a reasonable temporal sequence from the time of drug administration or follows a known response pattern to the study drug, but could also have been produced by other factors.
- PROBABLY: A reasonable temporal sequence of the event with drug administration exists and, based upon the known pharmacological action of the drug, known or previously reported ADRs to the drug or class of drugs, or judgment based on the investigator's clinical experience, the association of the event with the investigational product seems likely. The event disappears or decreases on cessation or reduction of the dose of investigational product.
- DEFINITELY: A definite causal relationship exists between drug administration and the AE, and other conditions (concurrent illness, progression/expression of disease state, or concurrent medication reaction) do not appear to explain the event. The event reappears or worsens if the investigational product is readministered.

12.8.1.2 Action Taken with Study Treatment

Action taken for an AE associated with the study treatment:

Treatment interrupted	The treatment was temporarily interrupted, with intent to restart
Treatment withdrawn	The treatment was permanently discontinued
Unknown	Not known, not observed, not recorded, or refused
No action taken	The AE did not result in any modification of dose or frequency of dosing
Not applicable	The AE occurred before first dose or after last study dose

Abbreviation: AE, adverse event.
Note: Dose increased, or dose reduced action taken can be evaluated on case to case basis as applicable.

12.8.1.3 Outcome of Adverse Events

The outcome at the time of last observation will be classified as:

- Recovered/resolved
- Recovered/resolved with sequelae
- Recovering/resolving

- Not recovered/not resolved
- Fatal*
- Unknown

*Only select fatal as an outcome when the AE results in death. If more than one AE is possibly related to the patient's death, the fatal outcome should be indicated for the AE which is the most plausible cause of death in the opinion of the investigator. All other ongoing AE/SAEs will be recorded as not recovered/not resolved at the time of death.

Note: Although "fatal" is usually an event outcome, events such as sudden death or unexplained death should be reported as SAEs.

12.8.1.4 Adverse Event Reporting

All AEs reported or observed during the study will be recorded on the AE page in the eCRF.

AEs resulting from concurrent illnesses, reactions to concurrent illnesses, reactions to concurrent medications, or progression of disease states must also be reported. All AEs will be followed to adequate resolution. The Medical Dictionary for Regulatory Activities (MedDRA) will be used to code all AEs.

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

12.8.1.5 Follow-Up of Patients Reporting Adverse Events

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

The investigator will administer appropriate treatment for the AE/SAE resolution. The Investigator is responsible to ensure that follow-up includes any supplemental investigations as may be indicated to elucidate as completely as practical the nature and/or causality of the AE/SAE. This may include additional laboratory tests or investigations, histopathological examinations, or consultation with other health care professionals.

12.8.2 Adverse Events of Special Interest

An AESI (serious or nonserious) is defined as an AE or SAE of scientific and medical concern specific to the Sponsor's product or program, for which ongoing monitoring and rapid communication by the investigator to the Sponsor/Sponsor representative could be appropriate (International Council for Harmonisation [ICH] E2F; Council for International Organizations of Medical Sciences [CIOMS] VI).

The following events will be considered as AESIs: infections, malignancies, hypersensitivity reactions, posterior reversible encephalopathy syndrome (PRES), and noninfectious pneumonia. All AESIs must be reported to the Sponsor/Sponsor representative immediately (ie, within

24 hours) after site personnel first learn of the event. Further details on the reporting and management of AESIs are provided in the Safety Management Plan.

Infections

All AEs related to infection, including TB and sepsis, will be reported.

Malignancies

AEs related to malignancy including but not limited to cutaneous and non-cutaneous malignancies will be reported.

Hypersensitivity reactions

All AEs related to hypersensitivity reactions, including anaphylaxis and angioedema, will be reported.

Anaphylactic reactions

Anaphylaxis will be identified according to Sampson criteria.[20] Anaphylaxis is likely when any 1 of the 3 criteria are fulfilled.

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

Posterior Reversible Encephalopathy Syndrome

All AEs of PRES will be reported. Clinical presentation may include headaches, seizures, confusion, visual disturbances, and imaging changes consistent with PRES a few days to several months after ustekinumab initiation.

Noninfectious Pneumonia

All AEs of noninfectious pneumonia will be reported. Clinical presentations may include cough, dyspnea, and interstitial infiltrates.

12.8.3 Serious Adverse Events

An SAE is defined as any event that

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

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

**"Inpatient hospitalization" does not imply that the patient must have had an overnight stay in the hospital. If the patient was admitted to the hospital for less than a day for the purpose of treatment or observation, the definition of "Inpatient hospitalization" is met, provided the patient is admitted solely for treatment of the event and not admitted for any other reasons including, rehabilitation, hospice care, respite care (eg, caregiver relief), skilled nursing facilities, nursing homes, social reasons, ease of compliance, day care procedures, or for medical or hospital records (insurance reimbursement) purpose. Although, brief treatment in an outpatient clinic or emergency department does not constitute "inpatient hospitalization", depending on the intervention/treatment required for the event, it may satisfy the criteria of inpatient hospitalization to be reported as an SAE.

Events NOT to be reported as SAEs are hospitalizations for the following:

- Routine treatment or monitoring of the studied indication, not associated with any deterioration in condition
- Treatment, which was elective or preplanned, for a pre-existing condition that is unrelated to the indication under study and did not worsen
- Admission to a hospital or other institution for general care because of social or economic reasons (eg, no access to local ambulatory medical care)

12.8.3.1 Serious Adverse Events Reporting

An SAE occurring from the time informed consent is obtained to the end of the study, whether or not considered to be related to the study drug r e [redacted] nd Pharmacovigilance group and will be communicated to the Sponsor. Any such SAE due to any cause, whether or not related to the study drug, must be reported within 24 hours of the investigator becomes aware of the event. If the investigator becomes aware of an SAE with a suspected causal relationship to the study drug that occurs after the end of the clinical trial in a patient treated by him or her, the investigator shall, without undue delay, report the SAE to the [redacted] and Pharmacovigilance group and will be communicated to the Sponsor. Notification should be made using the eCRF and faxing or emailing to the [redacted] pharmacovigilance group:

[redacted]

The investigator should not wait to receive additional information to document fully the event before notification of an SAE, though additional information may be requested. If the investigator contacts the [redacted] group by telephone, then a written report must follow within 24 hours and is to include a full description of the event and sequelae in the format detailed in the SAE reporting form.

The event must also be recorded on the standard AE eCRF. Preliminary reports of SAEs must be followed up by detailed descriptions later on, including clear and anonymized photocopies of hospital case reports, consultant reports, autopsy reports, and other documents when requested and applicable. SAE reports must be made whether or not the investigator considers the event to be related to the investigational drug.

Appropriate remedial measures should be taken to treat the SAE, and the response should be recorded. Clinical, laboratory, and diagnostic measures should be employed as needed to determine the cause of the problem. The investigator must report all additional follow-up evaluations to the [redacted] group within 24 hours of becoming aware of the additional information or as soon as is practicable. All SAEs will be followed up until the investigator and Sponsor agree the event is satisfactorily resolved.

Any SAE that is not resolved by the end of the study or upon discontinuation of the patient's participation in the study is to be followed up until it either resolves, stabilizes, returns to baseline values (if a baseline value is available), the lost to follow-up, or is shown to not be attributable to the study drug or procedures.The investigator (and any designee) is required to comply with applicable regulations (including local law and guidance) regarding notification to his/her regulatory authority, IRB, IECs, institutional ethics committees, and institutions.

SUSARs, SAEs or other cases as required by the concerned competent authorities and IECs will be reported by the sponsor/representative to all concerned parties within applicable timelines. The sponsor/representative will notify the SAEs to other sites/investigators and will also submit periodic safety reports (eg, Development Safety Update Reports) as required by local and international regulations.

Additional details for SAE/SUSAR reporting including periodic safety reporting are provided in the Safety Management Plan.

Clarification in Reporting of Deaths

All patient deaths (regardless of relationship to study treatment) should be reported for patients on the study, and recorded in the eCRF. If a patient dies after signing consent but before the first dose of the study treatment, this should also be recorded in the eCRF. Death is an outcome of an AE and not an AE in itself. All reports of patient death should include an AE term (other than "Death") for the cause of the death. If an AE term is not provided, the investigator will be queried to obtain the cause of death. Only in the rare occurrence that no verbatim description of an AE can be obtained from the investigative site, will "Death-Unknown cause" be used as the event term.

12.8.4 Suspected Unexpected Serious Adverse Reactions

SUSARs are SAEs having a reasonable possibility of a causal relationship with the study drug, the nature or severity of which is not consistent with the applicable product information (eg, IB or approved product labels).

12.8.5 Pregnancy

Pregnancy is not regarded as an AE unless there is a suspicion that study treatment may have interfered with the effectiveness of a contraceptive medication. Any pregnancy that occurs during study participation must be reported by the patient or female partner of the patient to the clinical study site where the investigator will collect information related to the pregnancy and its outcome. To ensure patient safety, each pregnancy must be reported to the Sponsor/Sponsor representative within 24 hours of learning of its occurrence. The pregnancy must be followed to determine outcome (including spontaneous miscarriage, elective termination, normal birth, or congenital abnormality) and status of mother and child, even if the patient was discontinued from the study. Investigator should fill the Pregnancy Reporting Form and send to the Sponsor/Sponsor representative. Pregnancy follow-up should be recorded in the same form and

should include an assessment of the possible relationship to study drug of any pregnancy outcome. Refer Section APPENDIX 1 for details on collection of pregnancy information.

If the pregnancy is associated with an SAE (eg, if the mother is hospitalized for a medical reason), the same should be reported using the same process as for SAEs as detailed under Section 12.8.3.1 (in addition to the Pregnancy Reporting Form). Pregnancy complications and elective terminations for medical reasons must be reported as an AE or SAE. Spontaneous miscarriages must be reported as an SAE. Any SAE occurring in association with a pregnancy, brought to the investigator's attention after the patient has completed the study, and considered by the investigator as possibly related to the study treatment, must be promptly reported to the Sponsor.

12.8.6 Overdose, Underdose, and Medication Error

Because study treatments are directly administered by personnel involved in the study in a controlled manner, overdose/underdose/medication error is unlikely to occur. However, in case of overdose/underdose/medication error, the management will be as per the standard of care. In case there is overdose/underdose/ medication error, the same should be informed to the Sponsor/Sponsor representative safety team immediately (ie, within 24 hours). If overdose/underdose/medication error is associated with an AE/ SAE, AE/SAE reporting timelines (as applicable) to be followed.

In case of overdose, underdose, or medication error, it is recommended that the patient be monitored for any signs or symptoms of ADRs and appropriate symptomatic treatment be instituted immediately.

12.9 Tuberculosis Assessment

Patients with current or history of TB at screening will be excluded from the study as well as patients with latent TB as per IGRA test result who have not completed or are not receiving antibiotic prophylactic therapy as per local guidelines (see Section 8.2).

Throughout the study, patients will be monitored for the clinical signs and symptoms of TB. An additional IGRA or chest radiography may be performed at the investigator's discretion based on the judgment per the signs and symptoms of TB monitoring. Patients with active TB based on the chest radiography result and/or the clinical signs and symptoms must be permanently discontinued from study treatment.

If a patient is exposed to a person with active TB or to any condition increasing the risk of TB infection during the study period, an IGRA test will be conducted as soon as possible and prior to next administration of study treatment for those who had tested negative at screening. If the result of the IGRA is positive, patients will be referred to the clinician immediately to investigate the presence of active or latent TB based on medical history and any clinical signs and symptoms including chest radiography result. Even in the absence of clinical suspicion for active TB, study treatment will be permanently discontinued.

12.9.1 Chest Radiography

A chest radiography (posterior-anterior and lateral views, or per country regulations where applicable) should be done during screening and read by a qualified radiologist or pulmonary physician to specifically look for evidence of current or previous active or latent TB. If a chest radiography within 12 weeks prior to screening is available, it is not required at screening, and the result will be recorded in both the source documents and the eCRF.

Radiographic findings suggestive of healed TB or active TB may include but are not limited to pulmonary nodules, fibrotic scars, calcified granulomas, upper lobe infiltrates, cavitation, and pleural effusions. Any abnormal radiological changes should be discussed with the medical monitor before the baseline visit. The chest radiological examination should be available to the investigator for review before the baseline visit of the patient.

13 PHARMACOKINETICS

For all patients, PK blood samples for the determination of serum concentration of ustekinumab will be collected at the time points specified in the schedule of events (Table 1). On the days of study treatment administration, blood samples must be taken before the treatment. Details of blood sample collection, processing, storage, and shipping procedures are provided in a separate laboratory manual. The PK of ustekinumab will be assessed using a validated bioanalytical method for serum concentration at a central laboratory.

An additional blood sample of 5 mL will be collected from all patients before the first dose administration for PK method validation.

14 IMMUNOGENICITY ASSESSMENTS

The immunogenicity of Bmab 1200 and Stelara® will be assessed by ADA and NAb tests using a validated immunoassay. It will be specified in a separate method validation report.

Serum samples for immunogenicity testing will be collected at the time points specified in the schedule of events (Table 1). The ADA serum samples will be stored frozen before shipment to a central laboratory for evaluation. Details of blood sample collection, processing, storage, and shipping procedures are described in the central laboratory manual. In case of positive results in the ADA evaluation, the ADA titer will be evaluated, and evaluation of NAb levels will be conducted.

An additional blood sample of 10 mL will be collected from all patients before the first dose administration for immunogenicity assay validation.

Additional blood samples for immunogenicity for patients with hypersensitivity reactions considered as possibly, probably, or definitely related to study treatment will be obtained as soon as possible after the onset of the reaction whenever this is feasible.

15 STATISTICAL ANALYSIS

The statistical considerations summarized in this section outline the plan for data analysis in this study. Details of the statistical analyses, methods, and data conventions to be conducted will be specified in a statistical analysis plan (SAP), which will be finalized and signed-off before database lock. The SAP will serve as a complement to the protocol and supersedes it in case of differences; any changes from the analyses planned in this protocol will be documented in the SAP and discussed in the CSR.

Statistical analysis will be performed using SAS software Version 9.4 or l e [redacted] Unless otherwise specified, continuous variables will be summarized using the mean, standard deviation (SD), median, minimum value, and maximum value, by treatment group. Categorical variables will be summarized using frequency counts and percentages by treatment group. Data will be listed in data listings.

All CIs presented, except for the primary endpoint (percentage change from baseline in the PASI score) will be two-sided 95% CIs, unless otherwise specified. For the primary efficacy endpoint, a 90% CI will be presented, and equivalence will be established if the 90% CI falls entirely within the predefined margin of ±10%; this approach is equivalent to two one-sided tests (TOST) at the 5% significance level. For the Japanese Pharmaceuticals and Medical Devices Agency (PMDA), a detailed description of the analysis will be provided in the SAP.

Unless otherwise specified, analyses for TP1 will be presented by treatment group (Bmab 1200, Stelara®) up to predose Week 16. However, the primary endpoint analysis will be done at Week 12 only. Analyses for TP2 and TP3 will be presented by the treatment regimen (Bmab 1200-Bmab 1200, Stelara®-Bmab 1200, Stelara®-Stelara®).

15.1 Determination of Sample Size

Two randomized placebo-controlled clinical studies, ie, PHOENIX 1 and PHOENIX 2, were included in a meta-analysis to estimate the treatment effect of Stelara® in plaque psoriasis, which led to derive a similarity margin for the current Phase 3 study with the percentage change from baseline in PASI score at Week 12 as the primary endpoint. The meta-analysis (fixed effect model) yields a treatment difference of 70.66 and 95% CI (67.42, 73.89). Using a meta-analysis approach, similarity margin for %PASI improvement at Week 12 is derived as per FDA Guidance for Industry, Noninferiority Clinical Trials to Establish Effectiveness (November 2016). Margin construction is commonly designed to preserve at least 50% of the lowest treatment effect estimated from historical placebo-controlled trials and in accordance with the EMEA CHMP guideline CPMP/EWP/2158/99 on the choice of the noninferiority margin. In this case, margin could be 50% of the lower 95% CI, ie, 50% of 67.42. So, statistical methodology would set the margin at ±34%; but the margin was reduced to ±10% with ~85% preservation of lowest treatment effect for additional clinical rigor in showing no clinically meaningful differences.

The sample size calculation is based on the primary endpoint, percentage change from baseline in the PASI score at Week 12. Equivalence will be established if the 90% CI of the difference between the treatments (Bmab 1200, Stelara®) in the percentage change in the PASI score from baseline to Week 12 is within the equivalence margin of ±10%. Assuming that the treatments are equally effective and that the common SD of the percentage change from baseline in the PASI score at Week 12 is 30%, a total sample size of 384 patients including a dropout rate of 10% patients ensures a power of 85% with a two one-sided 5% level of significance.

15.2 Analysis Sets

The following analysis sets will be considered for analysis during TP1 (ie, before rerandomization at Week 16 for treatment switch) and throughout the whole study, where applicable:

Full Analysis Set (FAS): The FAS will consist of all patients who sign the ICF and are randomized into TP1. Patients in the FAS will be analyzed under the treatment as randomized. The FAS will be used for the primary analyses of efficacy.

Per-Protocol Set (PPS): The PPS will consist of all patients in the FAS, who receive at least 2 study treatment administrations (Baseline and Week 4), and do not experience any important protocol deviations affecting primary efficacy at Week 12 (see Section 15.11 for initial list of protocol deviations to be considered). Patients in the PPS will be analyzed under the treatment as randomized. The PPS will be used for supportive analyses of efficacy.

Safety Set (SAF): The SAF will consist of all patients who receive at least one study treatment administration. The SAF will be used for analyzing safety and immunogenicity data during the treatment period. Patients in the SAF will be analyzed under the treatment as actually received. The SAF will be used for all analyses of safety and immunogenicity.

PK Set (PKS): The PKS will consist of all patients who receive at least one full dose of study treatment and have at least 1 post-treatment PK result before Week 16, excluding observations after relevant intercurrent events (ICEs) that may impact PK evaluations (eg, missing a dose, errors or deviations in dosing or receipt of other therapies which also contain ustekinumab). Patients in the PKS will be analyzed under the treatment as actually received. The PKS will be used for analyses of PK.

The following analysis sets will be considered for analysis during TP2 (ie, after rerandomization at Week 16 for treatment switch up to Week 28) and TP3 (from Week 28 up to Week 52):

FAS for TP2 (FAS2): The FAS2 will consist of all patients who are rerandomized into TP2 at Week 16. Patients from the FAS2 will be analyzed under the treatment as randomized during TP2. The FAS2 will be used for the analyses of efficacy during TP2.

FAS for TP3 (FAS3): The FAS3 will consist of all patients who are re-consented and continue into TP3 at Week 28. Patients from the FAS3 will be analyzed under the treatment as randomized during TP2. The FAS3 will be used for the analyses of efficacy during TP3.

SAF for TP2 (SAF2): The SAF2 will consist of all patients who receive the rerandomized study treatment administration at Week 16 or later. Patients from the SAF2 will be analyzed under the treatment as actually received during TP2. The SAF2 will be used for the analyses of safety and immunogenicity during TP2.

SAF for TP3 (SAF3): The SAF3 will consist of all patients who continue to receive the study treatment administration at Week 28 or later. Patients from the SAF3 will be analyzed under the treatment as actually received during TP3. The SAF3 will be used for the analyses of safety and immunogenicity during TP3.

PKS for TP2 (PKS2): The PKS2 will consist of all patients who receive a full dose of rerandomized study treatment administration at Week 16 and have at least 1 PK result at Week 20 or Week 28 (predose), excluding observations after relevant events after Week 16 and up to Week 28 predose that may impact PK evaluations (eg, missing a dose, errors or deviations in dosing or receipt of other therapies which also contain ustekinumab). Patients in the PKS2 will be analyzed under the treatment as actually received during TP2. The PKS2 will be used for analyses of PK during TP2.

PKS for TP3 (PKS3): The PKS3 will consist of all patients who receive a full dose of study treatment administration at Week 28 or later and have at least 1 PK result at Week 40 or Week 52, excluding observations after relevant events after Week 28 that may impact PK evaluations (eg, missing a dose, errors or deviations in dosing or receipt of other therapies which also contain ustekinumab). Patients in the PKS3 will be analyzed under the treatment as actually received during TP3. The PKS3 will be used for analyses of PK during TP3.

Assignment to all analysis sets, including decisions made on inclusion/exclusion for the PPS and other data handling issues will be agreed on and documented in BDRM, to occur (with report finalized) before each database lock. The assignment of the PPS will be finalized during the BDRM at the time of the Week 28 database lock. As such, the PPS will not be further reviewed during the BDRM at the time of the Week 52 database lock.

15.3 Patient Disposition

Patient disposition will be summarized by treatment period and treatment/regimen and will include the number and percentage of patients achieving the following criteria: screened, screen failed, included and excluded from each analysis set (including reasons for exclusion), completed or prematurely discontinued study treatment for each period, and completed and prematurely discontinued the study, including reasons for discontinuation for both study treatment and the study.

15.4 Demographic and Baseline Characteristics

Demographic and baseline characteristics will be listed. Demographic and baseline characteristics (including, but not limited to sex, age, geographical region, race, height, body

weight, body mass index, psoriatic arthritis status, and previous biologic use for psoriasis or psoriatic arthritis) will be summarized using appropriate descriptive statistics on the FAS.

Medical history will be coded using the most recent version of the MedDRA coding dictionary. The number and percentage of patients with medical history by system organ class (SOC) and preferred term (PT) will be presented by treatment group and overall.

Details of the summaries to be produced will be included in the SAP.

15.5 Efficacy Analysis

15.5.1 Analysis of the Primary Efficacy Endpoint

The statistical hypothesis to be tested for the primary efficacy endpoint is discussed in Section 15.5.1.1. The ICEs and corresponding handling measures under the estimands framework are described in Sections 15.5.1.2 and 15.5.1.3. Additional sensitivity and supportive analyses are presented in Section 15.5.1.4.

15.5.1.1 Statistical Hypothesis

The statistical hypothesis associated with the primary efficacy analysis of the percentage change from baseline in the PASI score at Week 12 is:

- H_0: ($\mu_{Bmab\ 1200} - \mu_{Stelara} \leq -10\%$) or ($\mu_{Bmab\ 1200} - \mu_{Stelara} \geq +10\%$)
- H_1: $-10\% < \mu_{Bmab\ 1200} - \mu_{Stelara} < +10\%$

where $\mu_{Bmab\ 1200}$ and $\mu_{Stelara}$ denote the true mean percentage change from baseline in the PASI score at Week 12 for Bmab 1200 and Stelara®, respectively.

Equivalence testing will be conducted using the primary estimand.

15.5.1.2 Intercurrent Events

The relevant ICEs in this study are presented in Table 4. While the primary efficacy assessment is at Week 12, ICEs are to be considered up to and including Week 16 PASI assessment.

Table 4. Intercurrent Events

Label	ICE
ICE1 (Death)	Death due to any cause prior to PASI assessment
ICE2 (Discontinuation of study treatment due to any reason other than death)	Premature discontinuation of study treatment prior to PASI assessment, for any reason other than death
ICE3 (Prohibited therapy used for treatment of psoriasis)	Use of any prohibited therapies used for treatment of psoriasis prior to PASI assessment, per Section 9.7
ICE4 (Deviations in dosing)	Errors or deviations in study treatment dosing prior to PASI assessment, including incorrect dose received, incorrect study treatment, incorrect route, or dosing interval

Abbreviations: ICE, intercurrent event; PASI, Psoriasis Area and Severity Index.

Note that administration of study treatment with Bmab 1200 or Stelara® affects the PASI assessment at the next visit. Thus, where discontinuation of study treatment or a missed administration of study treatment occurs at a visit, the affected PASI assessment is at the next visit, scheduled to be at Baseline and Week 4 prior to Week 16 assessments. For example, in the instance of PASI at Week 12, if a study treatment administration is missed at Week 4, the PASI at Week 12 will be affected, and will thus require ICE handling.

Currently, ICEs related to the COVID-19 pandemic (such as patient being unable to attend the study site because of travel restrictions and/or the site closure for study activities per regional governance, or patient is unable to attend the site because of being in isolation) are not included. These ICEs may be added as appropriate during study conduct once the extent of effect of the pandemic on the study conduct is known. Similarly, further ICEs may be added if any patients experience emergency unblinding. The full list of ICEs will be detailed in the SAP. Note that for the main analyses of all efficacy endpoints, data obtained from remote visits (for example, due to patient not being able to attend the site due to regional lockdown) will not be included in the analysis.

The estimands for efficacy endpoints are detailed in Sections 15.5.1.3 and 15.5.2. Analyses of safety and immunogenicity will be based on data as observed regardless of the ICEs. Analyses of PK will take into account relevant ICEs that may impact PK evaluations (eg, missing a dose, errors or deviations in dosing or receipt of other therapies which also contain ustekinumab).

15.5.1.3 Estimands for the Primary Efficacy Endpoint

Primary, secondary and tertiary estimands for the primary efficacy objective "to demonstrate equivalent efficacy between Bmab 1200 and Stelara® in patients with moderate to severe chronic plaque psoriasis" are defined below.

The following estimands will apply:

Table 5. Estimands for the Primary Efficacy Endpoint

	Primary estimand	Secondary estimand	Tertiary estimand
Treatment conditions of interest	Bmab 1200 versus Stelara® Test: one injection (weight ≤100 kg) or 2 injections of Bmab 1200 (weight >100 kg) 45 mg PFS Reference: one injection (weight ≤ 100 kg) or 2 injections of Stelara® (weight > 100 kg) 45 mg PFS	Bmab 1200 versus Stelara® Test: one injection (weight ≤100 kg) or 2 injections of Bmab 1200 (weight >100 kg) 45 mg PFS Reference: one injection (weight ≤ 100 kg) or 2 injections of Stelara® (weight > 100 kg) 45 mg PFS	Bmab 1200 versus Stelara® Test: one injection (weight ≤100 kg) or 2 injections of Bmab 1200 (weight >100 kg) 45 mg PFS Reference: one injection (weight ≤ 100 kg) or 2 injections of Stelara® (weight > 100 kg) 45 mg PFS
Population	Patients with moderate to severe chronic plaque psoriasis as defined by the inclusion/exclusion criteria	Patients with moderate to severe chronic plaque psoriasis as defined by the inclusion/exclusion criteria	Patients with moderate to severe chronic plaque psoriasis as defined by the inclusion/exclusion criteria, having received all study treatment administration

	Primary estimand	Secondary estimand	Tertiary estimand
			without deviation up to Week 8 and having available PASI assessment at Week 12
Endpoint	Percentage change from baseline in the PASI score at Week 12	Percentage change from baseline in the PASI score at Week 12	Percentage change from baseline in the PASI score at Week 12
Population-level summary	Difference between treatments (Bmab 1200 minus Stelara®) in mean percentage change from baseline in PASI score at Week 12	Difference between treatments (Bmab 1200 minus Stelara®) in mean percentage change from baseline in PASI score at Week 12	Difference between treatments (Bmab 1200 minus Stelara®) in mean percentage change from baseline in PASI score at Week 12
ICEs and strategies to handle ICEs	• ICE1 (Death) *Composite variable strategy* • ICE2 (Discontinuation of study treatment due to any reason other than death) *Treatment policy strategy* • ICE3 (Prohibited therapy used for treatment of psoriasis) *Treatment policy strategy* • ICE4 (Deviations in dosing) *Treatment policy strategy*	• ICE1 (Death) *Composite variable strategy* • ICE2 (Discontinuation of study treatment due to any reason other than death) *Treatment policy strategy* • ICE3 (Prohibited therapy used for treatment of psoriasis) *Hypothetical strategy* • ICE4 (Deviations in dosing) *Hypothetical strategy*	• ICE1 (Death) *Not applicable, patient not considered in population* • ICE2 (Discontinuation of study treatment due to any reason other than death) *Not applicable, patient not considered in population* • ICE3 (Prohibited therapy used for treatment of psoriasis) *Not applicable, patient not considered in population* • ICE4 (Deviations in dosing) *Not applicable, patient not considered in population*
	ICE(s) with a composite variable strategy take priority over ICEs with other strategies.		

Abbreviations: ICE, intercurrent event; PASI, Psoriasis Area and Severity Index; PFS, prefilled syringe.

Where the strategies are described as follows in the sequence, these strategies will be applied:

- <u>For the primary estimand:</u>
  - Composite variable strategy: Death before PASI assessment up to Week 16 will be handled using a return-to-baseline multiple imputation (MI) approach (see Section 15.9).
  - Treatment policy strategy: Available data occurring on or after the ICE will be analyzed as observed. Missing PASI assessment will be imputed by a missing-at-random (MAR) application of SAS Proc MI (see Section 15.9).
  - The primary estimand is aligned with a treatment policy approach for all ICEs except death. The estimate of the treatment effect in this instance will be influenced by any effects of prohibited medication that are used to treat psoriasis, missing or early/late

treatment, and/or premature discontinuation where a poor outcome may not be expected.

- For the secondary estimand:
  - Composite variable strategy: Death before PASI assessment up to Week 16 will be handled using a return-to-baseline MI approach.
  - Treatment policy strategy: Available data occurring on or after the ICE will be analyzed as observed. Missing PASI assessment will be imputed by an MAR application of SAS Proc MI (see Section 15.9)
  - Hypothetical strategy: Available data occurring on or after the ICE will be set to missing, and multiple imputed by a missing-not-at-random (MNAR) method (see Section 15.9)
  - The approach for the secondary estimand assumes that for patients discontinuing study treatment because of any reason other than death, a nonconfounded estimate of the treatment effect is provided. For patients with deviations in study treatment dosing, or in receipt of prohibited medication used for treatment of psoriasis, this is not the case. The secondary estimand allows for the assessment of the treatment effect in an alternative, hypothetical setting where all patients take the assigned study treatment without deviation, and prohibited medications that are used for treatment of psoriasis are not available.
- For the tertiary estimand:
  - The tertiary estimand is aligned with a principal stratum strategy, whereby all patients are dosed with study treatment consistently and without deviation up to Week 4 and have an evaluable PASI assessment at the visit considered, up to and including Week 16. Because patients will not be considered in the analysis if they discontinue or experience deviation of study treatment or receive prohibited medication that is used to treat psoriasis, a comparative assessment closer to that of a PPS analysis is gained.

For the main analyses of the primary, secondary and tertiary estimands of the primary efficacy endpoint, data obtained from remote visits (for example, due to patient not being able to attend the site due to regional lockdown) will not be considered; the handling of such events as ICEs under the estimands framework will be discussed in the SAP. Sensitivity analyses, considering such data, may be added as appropriate.

The primary, secondary, and tertiary estimands will be analyzed using an analysis of covariance (ANCOVA) model to fit the percentage change from baseline in the PASI score at Week 12 on the FAS in each imputed dataset. The ANCOVA will include the stratification factors [redacted] used for the randomization at baseline as fixed factors. The mean difference between treatment

groups will be estimated based on the least squares means in the ANCOVA model. The estimated treatment differences and the associated SDs resulted from each multiply imputed dataset will be combined using the Rubin's rule as a single estimate of treatment difference presented with a 90% CI.

Equivalence will be concluded if the 90% CI at Week 12 falls within the predefined equivalence margin of ±10%. See Section 15.5.1.1 for the statistical hypotheses corresponding to the primary efficacy endpoint.

15.5.1.4 Sensitivity and Supportive Analyses of the Primary Efficacy Endpoint

The following sensitivity and supportive measures will also be conducted:

Table 6. Sensitivity and Supportive Analyses

Analysis Set	Modelling Method	Data Handling
Sensitivity Analyses Performed on Primary Estimand		
FAS	ANCOVA model including factors for treatment group (Bmab 1200 versus Stelara®, reference Stelara®), region, body weight at baseline category, baseline psoriatic arthritis status, and previous biologic use.	Tipping Point Analysis. If equivalence is observed in the primary estimand, a 2-dimensional tipping point analysis will be conducted, assessing different levels of delta shift for the imputation in each treatment group.
	MMRM including changes from baseline at Weeks 4, 8, 12, and 16 as responses. The MMRM will include treatment, week, and the stratification factors used for the randomization at baseline as fixed factors, and treatment-by-week interaction. An unstructured covariance structure will be used to model the within-patient errors. The Kenward-Roger approximation will be used to estimate denominator degrees of freedom. The mean difference between treatment groups will be estimated based on the least squares means for the treatment by-week interaction in the MMRM model. The estimates will be presented with 90% CIs.	No imputation, analyzed as observed.
Supportive Analyses Conducted on Main, Second, and Third Estimands		
PPS	ANCOVA model including factors for treatment group (Bmab 1200 versus Stelara®, reference Stelara®), region, body weight at baseline category, baseline psoriatic arthritis status, and previous biologic use.	As per primary, secondary and tertiary estimands.

Abbreviations: ANCOVA, analysis of covariance; CI, confidence interval; FAS, Full Analysis Set; MMRM, mixed effect model for repeated measures; PPS, Per-Protocol Set.

For analyses using MI, the analysis will be conducted on the complete dataset, for each imputation separately. Modelled results will be combined using Rubin's rule (PROC MIANALYZE) for tabulation.

Additional subgroup analyses based on baseline characteristics will be presented with forest plots, as will analyses of primary efficacy based on ADA and NAbs positive/negative status up to Week 12.

All inferential analyses of the primary efficacy endpoint, including MI approaches will be conducted during TP1 only (ie, up to and including Week 16). However, primary analysis will be done at Week 12 only. During TP2 (Week 16 post rerandomization through Week 28 predosing) and TP3 (Week 28 postdosing through Week 52), only descriptive analyses will be performed for efficacy. The handling of estimands as detailed above will also only apply up to and including Week 16. After this point, data will only be analyzed as observed.

15.5.2 Analysis of Secondary Efficacy Endpoints

The secondary objective of the trial with respect to efficacy is "to assess the efficacy of Bmab 1200 based on other efficacy parameters and time points over the study period as compared to Stelara®". The estimands framework will apply for the following endpoints related to the secondary efficacy objective, for all visits up to and including Week 16 (ie, during TP1, or as otherwise stated):

- PASI:
  - Percentage change from baseline in the PASI score at Weeks 4, 8, and 16
  - PASI 50, PASI 75, and PASI 90 relative to baseline at Weeks 4, 8, 12, and 16
  - Raw PASI scores at Weeks 4, 8, 12, and 16
  - AUECs of PASI score from baseline to Week 12
- sPGA response of cleared or almost clear/minimal (PGA score of 0 or 1) at Weeks 4, 8, 12, and 16.
- Change from baseline in affected BSA at Weeks 4, 8, 12, and 16.
- Change from baseline in QoL as measured by DLQI scores at Weeks 4, 8, 12, and 16.

The same estimands (primary, secondary, and tertiary) as for the primary efficacy endpoint will be applied for the secondary efficacy endpoints related to PASI and sPGA. Where ICEs relating to deviations in study treatment are assessed, dosing up to Week 4 will be considered.

For the secondary efficacy endpoints related to BSA and DLQI, a single primary estimand handling all ICEs with a treatment policy strategy will be applied. For this estimand, available data occurring on or after the ICE will be analyzed as observed (except remote visits, similar to the primary efficacy endpoint). Missing PASI assessment will be imputed by an MAR application of SAS Proc MI (see Section 15.9).

Similar to the primary efficacy analyses, for the main analyses of the secondary efficacy endpoints, data obtained from remote visits will not be considered; the handling of such events as ICEs under the estimands framework will be discussed in the SAP. Sensitivity analyses, considering such data, may be added as appropriate.

No margins of equivalence are applied to secondary efficacy endpoints.

Continuous secondary efficacy endpoints related to PASI will implement the same analysis method as that for the primary efficacy endpoint. Continuous secondary efficacy endpoints related to BSA and DLQI will be analyzed using mixed effect model for repeated measures (MMRM), similar to the sensitivity analysis of the primary efficacy endpoint. Binary secondary efficacy endpoints will be analyzed using a Cochran-Mantel-Haenszel (CMH) test, adjusted for the randomization strata (region, body weight at baseline category, baseline psoriatic arthritis status, and previous biologic use). The estimate of the risk difference, with corresponding CMH-adjusted 2-sided 95% CI, will be presented. The validity of the CMH test, in particular with respect to the size of strata combination, will be reviewed. If small strata combinations cast doubt on the use of the CMH test, strata may be pooled, or a nonstratified test will be used. For analyses using MI, the analysis will be conducted on the complete dataset, for each imputation separately. Modelled results will be combined using Rubin's rule (PROC MIANALYZE) for tabulation.

Additionally, supportive analyses will be conducted for the endpoints related to PASI and sPGA for the primary, secondary, and tertiary estimands on the PPS.

All time points up to Week 16 will also be analyzed descriptively for all efficacy measures on the FAS. For the secondary efficacy endpoints relating to TP2 (all scheduled visits after Week 16 up to Week 28 predosing) and TP3 (all scheduled visits after Week 28 postdosing to Week 52), analyses will be purely descriptive, and the estimands framework (including ICEs) will not be applied.

Subgroup analyses of secondary efficacy based on ADA status (positive versus negative up to Week 16, Week 28, and Week 52) and selected baseline characteristics may also be explored. Subgroup analyses will be conducted at least for the efficacy analyses of PASI. Further details of all analyses will be included in the SAP.

15.6 Safety Analyses

Safety data reported during TP1, TP2 and TP3 will be separately analyzed by treatment group on the SAF or by treatment regimen on the SAF2 and SAF3, respectively. No formal statistical comparisons are planned. Subgroup analyses of safety based on ADA status (positive versus negative up to Week 16, Week 28, and Week 52, or before start of AE) may also be explored for TEAEs and SAEs by MedDRA SOC and PT. Further details of all analyses will be included in the SAP.

15.6.1 Adverse Events

AEs will be classified according to the time of onset of the AE into pretreatment AEs, TEAEs and post-treatment-emergent AEs. All reported AEs will be coded using the most recent version of the MedDRA coding dictionary. An overall summary of incidence will be presented for TEAEs, treatment-emergent SAEs, study treatment-related TEAEs and treatment-emergent SAEs, TEAEs leading to study discontinuation, TEAEs leading to discontinuation of study treatment (Bmab 1200 or Stelara®), and AESIs (see Section 12.8.2) by treatment period and treatment/regimen. Additional summaries of these AEs will be presented by MedDRA SOC and PT, by treatment period and treatment/regimen. Summaries will include the total number of events with number and percentage of patients with the specified AE.

All AEs will be listed by patient, along with information regarding date of onset, duration, severity, relationship to study drug, action taken with study drug, treatment of event, and outcome.

15.6.2 Analysis of Other Safety Endpoints

The clinical safety laboratory test values, vital signs, ECG parameter values, and physical examinations will be summarized by treatment period and treatment/regimen. For laboratory parameters and vital signs, original results and change from baseline will be summarized at each visit. Potentially clinically significant values will be flagged and summarized.

Exposure in terms of number of study treatment administration and days of study treatment administration since baseline will be summarized by treatment period and treatment/regimen.

The number and percentage of patients with prior and concomitant medications will be tabulated using anatomic therapeutic classification (ATC) level of the latest version of World Health Organization Drug Dictionary (WHODrug), and PT, by treatment period and treatment/regimen. A medication's usage will be considered concomitant if it was started or continued after first administration of the study treatment. If the start date is missing, it will be assumed that the medication was used concomitantly. Details on handling partial dates (ie, year or only year and month) will be described in the SAP.

15.7 Pharmacokinetic Analysis

Serum concentrations of Bmab 1200 and Stelara® will be listed and descriptively summarized by treatment (Bmab 1200, Stelara®) and visit for TP1 and by treatment regimen (Bmab 1200-Bmab 1200, Stelara®-Bmab 1200, Stelara®-Stelara®) and visit for TP2 and TP3. Descriptive statistics will include arithmetic and geometric mean, SD, coefficient of variation and geometric coefficient of variation, minimum, maximum, and median, plus percentage of concentration values below the lower limit of quantification. Additional subgroup analyses of PK data by treatment and ADA status will be presented. Details of the PK analysis will be provided in the SAP.

15.8 Immunogenicity Analyses

Incidence of ADAs to Bmab 1200 and Stelara® including titer and NAbs will be descriptively summarized at each time point and cumulative up to the time point by treatment (Bmab 1200, Stelara®) for TP1 and by treatment regimen (Bmab 1200-Bmab 1200, Stelara®-Bmab 1200, Stelara®-Stelara®) for TP2 and TP3. The titer values for positive ADA will be descriptively summarized. A listing will be produced showing all immunogenicity results for patients with any confirmed positive result.

15.9 Handling of Missing Data

Every effort will be made to prevent patients early terminating the study and for patients who discontinue study treatment, every effort will be made to continue to collect data after discontinuation.

Where missing data exist for primary and secondary efficacy endpoints, imputation will occur where specified.

For determination of the primary efficacy endpoint analyses of percentage change in PASI score from baseline to Week 12, and other PASI related endpoints during TP1, an MI approach for missing data will be employed where appropriate. For categorical analyses related to PASI score (ie, PASI-50, PASI-75, and PASI-90), imputation of the missing PASI score data will occur, and then the category will subsequently be derived. This will also apply prior to percentage calculation.

Imputation of missing data for PASI score will occur as follows: Where a composite strategy is applied, a multiple imputed return-to-baseline approach will be implemented. The missing data will be imputed considering the stratification factors and only including the baseline PASI score. Randomized treatment group will not be considered for this imputation, as baseline response is irrespective of treatment group later assigned.

Where missing data exists that is not affected by an ICE applying either a composite or hypothetical strategy, the missing data will be imputed using an MAR approach, taking into account the treatment group as randomized, stratification factors, baseline PASI, any available PASI assessments and ICE indicators up to the visit to be imputed.

Where missing data exists that is affected by an ICE applying a hypothetical strategy, the missing data will be imputed using a MNAR approach, including available data only from patients who do not experience any ICE up to and including the visit to be imputed. Imputation under these MNAR conditions will similarly take into account the treatment group as randomized, stratification factors, baseline PASI and any available PASI assessments up to the visit to be imputed.

The number of imputations and the seed to be used, plus any further details required, will be detailed in the SAP.

A similar approach will be implemented for the secondary efficacy endpoints that are not related to PASI score, unless otherwise stated. For these analyses, the respective baseline result will be included rather than PASI score at baseline as described above.

Further to the above, a nonresponder approach will additionally be implemented for the primary estimand of binary secondary efficacy response endpoints (PASI-50, PASI-75, PASI-90, and sPGA response) as sensitivity analysis.

15.10 Interim Analysis

There is no interim analysis planned. Two database locks are planned for this study: one at the time of the Week 28 analysis and the other at the time of the Week 52 analysis. The study team will continue to remain blinded to the study treatments until the Week 52 analysis; a separate analysis team and reporting team will conduct the unblinded analyses for the Week 28 CSR which will be described in detail in a separate document for the study.

Further details will be provided in the SAP.

15.11 Protocol Deviations Leading to Exclusion from the Per-Protocol Set

Important protocol deviations leading to exclusion from the PPS may include, but are not limited to:

- Randomization criteria violations
- Inclusion/exclusion criteria violations
- Inadequate compliance with study drug, including significant deviations from the study drug administration schedule
- Prohibited medications taken
- No valid evaluation of the primary efficacy endpoint
- Other protocol deviations that could affect patients' primary efficacy outcomes

Protocol deviations affecting primary efficacy will be defined and reviewed in a standalone document during the BDRMs, to be held (with report finalized) before each database lock. The assignment of the PPS will be finalized during the BDRM at the time of the Week 28 database lock. As such, the PPS will not be further reviewed during the BDRM at the time of the Week 52 database lock.

15.12 COVID-19

Given the current COVID-19 pandemic, per regulatory guidance, a listing of patients either experiencing COVID-19 or possibly affected by COVID-19 related measures will be produced where applicable. As discussed above, the main analyses of estimands for the primary and secondary efficacy endpoints will be based on attended visits only, and remote assessment will not be considered. Details of handling of such events will be discussed in the SAP.

Further details relating to additional populations and subgroup analyses, handling of protocol deviations, handling of missing data (including use of virtual assessments and/or switches from local to centralized laboratories), and any other considerations related to COVID-19 and related measures will be detailed further in the SAP, which will be finalized and signed-off before database lock.

16 STUDY MANAGEMENT

16.1 Approval and Consent

16.1.1 Regulatory Guidelines

The investigator agrees that the study will be conducted according to the principles of ICH E6 (R2). The investigator will conduct all aspects of this study in accordance with EU General Data Protection Regulation (GDPR) directive, all national, state, and local laws or regulations. Study information from this protocol will be posted on publicly available clinical trial registers before enrollment of patients begins.

16.1.2 Confidentiality

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

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

16.1.3 Data Protection

All personal data collected related to patients, investigators, or any person involved in the study, which may be included in the Sponsor's databases, shall be treated in accordance with local data protection law.

Data collected must be adequate, relevant, and not excessive, in relation to the purposes for which they are collected. Each category of data must be properly justified and in line with the study objective.

16.1.4 Institutional Review Board/Independent Ethics Committee

Federal regulations and the ICH guidelines require that approval be obtained from an IRB/IEC before patients participate in research studies. Before study onset, the protocol, ICF, advertisements to be used for the recruitment of patients, and any other written information regarding this study to be provided to the patient or the patient's legal guardian must be approved by the IRB/IEC. Documentation of all IRB/IEC approvals and of the IRB/IEC compliance with ICH harmonized tripartite guideline E6 (R2): GCP will be maintained by the site and will be available for review by the Sponsor or its designee.

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

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

16.1.5 Patient Information and Informed Consent

A written ICF in compliance with all applicable regulatory requirements, ICH GCP, and ethical principles that have their origin in Declaration of Helsinki shall be obtained from each patient before entering the study or performing any unusual or nonroutine procedure that involves risk to the patient. An ICF template may be provided by the Sponsor to investigative sites. If any institution-specific modifications to study-related procedures are proposed or made by the site, the consent should be reviewed by the Sponsor or its designee or both before IRB/IEC submission. Once reviewed, the consent will be submitted by the investigator to his or her IRB/IEC for review and approval before the start of the study. If the ICF is revised during the course of the study, all active patients must be reconsented by signing the revised form.

Before recruitment and enrollment, each prospective patient or his or her legal guardian will be given a full explanation of the study, be allowed to read the approved ICF, and have any questions answered. Once the investigator is assured that the patient/legal guardian understands the implications of participating in the study, the patient/legal guardian will be asked to give consent to participate in the study by signing the ICF. The authorized person obtaining the ICF also signs the ICF.

The ICF will contain a separate section that addresses the use of remaining mandatory samples for optional exploratory research (if applicable) and explain/address the exploratory research portion of the study. Patient medical records need to state that written ICF was obtained.

The investigator shall retain the signed original ICF(s) and give a copy of the signed original form to the patient or legal guardian.

16.2 Data Handling/Management

As part of the responsibilities assumed by participating in the study, the investigator agrees to maintain adequate case histories for the patients treated as part of the research under this protocol. The investigator agrees to maintain accurate eCRFs and source documentation as part of the case histories. These source documents may include diary cards, laboratory reports, ECG strips, etc.

All eCRF information is to be filled in. If an item is not available or is not applicable, this fact should be indicated. Blank spaces should not be present unless otherwise directed.

Investigative site personnel will enter patient data into eCRF. The analysis data sets will be a combination of these data and data from other sources (eg, laboratory data).

Clinical data management will be performed in accordance with applicable Sponsor's standards and data cleaning procedures to ensure the integrity of the data, eg, removing errors and inconsistencies in the data. AE terms will be coded using MedDRA, an internal validated medical dictionary, and concomitant medications will be coded using World Health Organization Drug Dictionary (WHODrug).

16.3 Source Documents

Source documents are considered to be all information in original records and certified copies of original records of clinical findings, observations, data, or other activities in a clinical study necessary for the reconstruction and evaluation of the study. The investigator will provide direct access to source documents and/or source data in the facilitation of trial-related monitoring, audits, review by IECs/IRBs, and regulatory inspections.

The investigator/institution should maintain adequate and accurate source documents and trial records that include all pertinent observations on each of the site's trial patient. Source data should be attributable, legible, contemporaneous, original, accurate, and complete. Changes to source data should be traceable, not obscure the original entry, and be explained if necessary.

16.4 Record Retention

Essential documents should be retained until at least 2 years after the last approval of a marketing application in an ICH region and until there are no pending or contemplated marketing applications in an ICH region or at least 2 years have elapsed since the formal discontinuation of clinical development of the study treatment (Bmab 1200). These documents should be retained for a longer period; however, if required by the applicable regulatory requirements or by an agreement with the Sponsor. It is the responsibility of the Sponsor to inform the investigator/institution as to when these documents no longer need to be retained. No records may be transferred to another location or party without written notification to the Sponsor.

16.5 Monitoring

16.5.1 Monitoring of the Study

This study will be monitored according to an approved monitoring plan based on the objectives, purpose, design, and complexity of the study. The investigator will allocate adequate time for all monitoring visits and between visits to facilitate the requirements of the study and study timelines. The investigator will also ensure that the monitor or other compliance or quality assurance reviewer is given direct access to all study-related documents and study-related facilities (eg, pharmacy, diagnostic laboratory), phone, fax, and internet and has adequate space to conduct the monitoring visit. Site monitoring is conducted to ensure that the rights of patients are protected, that the study is implemented in accordance with the protocol and/or other operating procedures, and that the study uses high quality data collection processes. The monitor will evaluate study processes based on the Sponsor or designee standards, ICH E6, and all applicable, regulatory guidelines.

16.5.2 Inspection of Records

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

The investigator should promptly notify the Sponsor and contract research organization (CRO) of any audits scheduled by any regulatory authorities and promptly forward copies of any audit reports received to the Sponsor.

16.6 Quality Control and Quality Assurance

The Sponsor or its designee will perform the quality assurance and quality control activities of this study; however, responsibility for the accuracy, completeness, security, and reliability of the study data presented to the Sponsor lies with the investigator generating the data.

The Sponsor will arrange audits as part of the implementation of quality assurance to ensure that the study is being conducted in compliance with the protocol, standard operating procedures, GCP, and all applicable regulatory requirements. Audits will be independent of and separate from the routine monitoring and quality control functions. Quality assurance procedures will be performed at study sites and during data management to assure that safety and efficacy data are adequate and well documented.

16.7 Protocol Amendment and Protocol Deviation

16.7.1 Protocol Amendment

Any changes in the required procedures defined in this protocol, except those necessary to remove an apparent, immediate hazard to the patient, must be reviewed and approved by the Sponsor or designee. Amendments to the protocol (including emergency changes) must be submitted in writing to the investigator's IRB/IEC, along with any applicable changes to the ICF, for approval before patients can be enrolled into an amended protocol.

16.7.2 Protocol Deviations

A deviation from the protocol is an unintended or unanticipated departure from the procedures or processes approved by the Sponsor and the IRB/IEC and agreed to by the investigator. An important deviation occurs when there is nonadherence to the protocol or to local regulations or ICH GCP guidelines that may result in a significant, additional risk to the patient or impacts the integrity of study data. Should a protocol deviation occur, the Sponsor must be informed as soon as possible. Protocol deviations and the reasons they occurred will be documented in the patient's source documentation. Reporting of protocol deviations to the IEC/IRB and in accordance with applicable regulatory authority mandates is an investigator's responsibility. Protocol deviations listing will also be included in the CSR.

The protocol deviations classification and management will be defined in a standalone document and reviewed before each database lock (see also Section 15.11).

16.8 Ethical Considerations

The study will be performed in accordance with the ethical principles that have their origin in the Declaration of Helsinki, ICH GCP, and all applicable regulations.

16.9 Financing and Insurance

Before the study commences, the Sponsor (or its designee) and the investigator (or the institution, as applicable) will agree on costs necessary to perform the study. This agreement will be documented in a financial agreement that will be signed by the investigator (or the institution signatory) and the Sponsor (or its designee).

The investigator is required to have adequate current insurance to cover claims for negligence and/or malpractice. The Sponsor will provide no-exclusion insurance coverage for the clinical study as required by national regulations.

16.10 Publication Policy/Disclosure of Data and Clinical Study Reporting

After completion of the study, the data may be considered for reporting at a scientific meeting or for publication in a scientific journal. Two clinical study reports will be issued: one CSR (Week 28 CSR for FDA) with the analyses up to Week 28, and another CSR (Week 52 CSR for other agencies like PMDA) with the analyses of data up to Week 52, as described in Section 15.10. In these cases, the Sponsor will be responsible for these activities and will work with the investigators to determine how the manuscript is written and edited, the number and order of authors, the publication to which it will be submitted, and other related issues. The Sponsor has final approval authority over all such issues.

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

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

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18 APPENDICES

APPENDIX 1 describes the contraception guidelines applicable for this study.

APPENDIX 2 presents an example Psoriasis Area Severity Index worksheet.

APPENDIX 3 describes the Static Physician's Global Assessment.

APPENDIX 4 presents an example of the Dermatology Life Quality Index.

APPENDIX 5 describes calculation method for total Body Surface Area involvement.

APPENDIX 1. CONTRACEPTION GUIDELINES

Definitions:

Woman of Childbearing Potential

A woman is considered fertile following menarche and until becoming postmenopausal unless permanently sterile (see below).

If fertility is unclear (eg, amenorrhea in adolescents or athletes) and a menstrual cycle cannot be confirmed before the first dose of study treatment, additional evaluation should be considered.

Women in the following categories are not considered women of childbearing potential (WOCBP):

1. Premenarchal
2. Premenopausal female with 1 of the following:
    - Documented hysterectomy
    - Documented bilateral salpingectomy
    - Documented bilateral oophorectomy

For individuals with permanent infertility due to an alternate medical cause other than the above, (eg, Mullerian agenesis, androgen insensitivity), investigator discretion should be applied to determine study entry.

Note: Documentation can come from the site personnel's review of the patient's medical records, medical examination, or medical history interview.

3. Postmenopausal woman
    - A postmenopausal state is defined as no menses for 12 months without an alternative medical cause.
    - Women on HRT and whose menopausal status is in doubt will be required to use one of the nonestrogen hormonal highly effective contraception methods if they wish to continue their HRT during the study. Otherwise, they must discontinue HRT to allow confirmation of postmenopausal status before study enrollment.

Contraception Guidance:

Fertile men and women of childbearing potential participating in heterosexual relations must be willing to use adequate contraception (i.e., 2 effective methods, one of which must be a physical barrier method) throughout the study starting from screening and for at least 15 weeks after their last dose of study treatment; or must be sexually inactive by abstinence, which is consistent with the preferred and usual lifestyle of the patient.

Effective forms of contraception are a condom, an established form of hormonal contraception, a diaphragm or cervical/vault cap, or an intrauterine device. Periodic abstinence (eg, calendar, ovulation, symptothermal, postovulation methods) and withdrawal are not acceptable methods of contraception. Sterile men and women, postmenopausal women, and patients who have same-sex sexual relations do not have to use contraception. Sterile males and females must be surgically sterile for at least 6 months or postmenopausal (for females, amenorrhea duration for at least 1 year).

Collection of Pregnancy Information

Male Patients With Partners Who Become Pregnant

- The investigator will attempt to collect pregnancy information on any male patient's female partner who becomes pregnant while the male patient is in this study. This applies only to male patients who receive the study treatment.
- If the investigator becomes aware of a pregnancy in a female partner of a male patient, the investigator should obtain a partner pregnancy informed consent form. Consent of the pregnant partner must be obtained before any details of the pregnancy can be shared with Sponsor/Sponsor representative. If the pregnant partner provides consent to have the pregnancy followed, the investigator will record pregnancy information on the pregnancy form and submit it to the Sponsor within 24 hours of learning of the partner's pregnancy. The female partner will also be followed to determine the outcome of the pregnancy. Information on the status of the mother and child will be forwarded to the Sponsor/Sponsor representative. Follow-up of outcomes will be performed case-by-case basis if required, based on the local requirements. Any termination of the pregnancy will be reported regardless of fetal status (presence or absence of anomalies) or indication for the procedure.

Female Patients Who Become Pregnant

- The investigator will collect pregnancy information on any female patient who becomes pregnant while participating in this study. The initial information will be recorded on the appropriate form and submitted to the Sponsor/Sponsor representative within 24 hours of learning of a patient's pregnancy.
- The patient will be followed to determine the outcome of the pregnancy. The investigator will collect follow-up information on the patient and the neonate and the information will be forwarded to the Sponsor/Sponsor representative. Follow-up of outcomes will be performed case-by-case basis if required, based on the local requirements. Any termination of pregnancy will be reported, regardless of fetal status (presence or absence of anomalies) or indication for the procedure.

- While pregnancy itself is not considered to be an adverse event (AE) or serious adverse event (SAE), any pregnancy complication or elective termination of a pregnancy for medical reasons will be reported as an AE or SAE.
- A spontaneous abortion (occurring at <22 weeks gestational age) or still birth (occurring at >22 weeks gestational age) is always considered to be an SAE and will be reported as such.
- Any poststudy pregnancy-related SAE considered reasonably related to the study treatment by the investigator will be reported to the Sponsor/Sponsor representative as described in Section 12.8.3.1. While the investigator is not obligated to actively seek this information in former study patients, he or she may learn of an SAE through spontaneous reporting.
- Any female patient who becomes pregnant while participating in the study will discontinue the study treatment or may be withdrawn from the study.

APPENDIX 2. PSORIASIS AREA SEVERITY INDEX

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

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

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

PASI Score = ☐

Reference: British Association of Dermatologists. Accessed at http://www.bad.org.uk/shared/get-file.ashx?id=1654&itemtype=document. Accessed on 21 December 2021.

APPENDIX 3. STATIC PHYSICIAN'S GLOBAL ASSESSMENT

For the determination of static Physician's Global Assessment, the degree of overall lesion severity will be evaluated using the categories below:

Induration (I) (averaged over all lesions; use the National Psoriasis Foundation Reference card for measurement):

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

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

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.

Reference: https://www.accessdata.fda.gov/drugsatfda_docs/nda/2009/125261s000_StatR.pdf Accessed 21 December 2021.

APPENDIX 4. DERMATOLOGY LIFE QUALITY INDEX

DERMATOLOGY LIFE QUALITY INDEX

DLQI

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

T e a m f this [redacted] is to measure h w m ch your in problem has affected ou life OVER THE LAST WEEK. Please tick ☑ one box for each question.

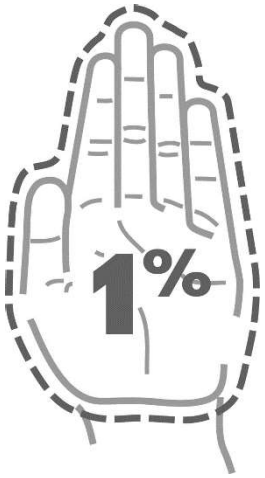
1.	Over the last week, how **itchy**, **sore**, **painful** or **stinging** has your skin been?	Very much A lot A little Not at all	❒ ❒ ❒ ❒	
2.	Over the last week, how **embarrassed** or **self conscious** have you been because of your skin?	Very much A lot A little Not at all	❒ ❒ ❒ ❒	
3.	Over the last 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 ❒

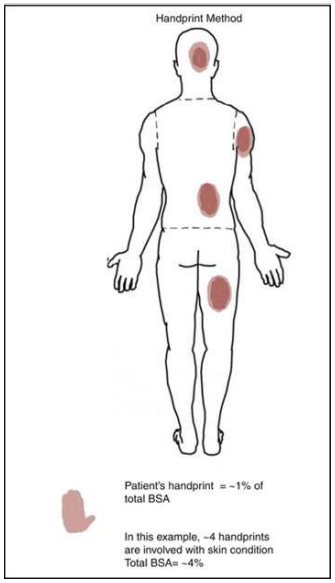
Please check you have answered EVERY question. Thank you.

APPENDIX 5. BODY SURFACE AREA INVOLVEMENT

Total % body surface area (BSA) involvement afflicted by psoriasis will be estimated using a handprint of the patient at each visit as outlined in the schedule of events (Table 1). The entire palmar surface of the patient's handprint (i.e., the patient's flat hand, thumb and fingers) is assumed to correspond to approximately 1% of total BSA.[1,2]

The investigator must **first evaluate eligibility of the inclusion criterion for the BSA involvement** before evaluating the total psoriatic involvement on the head and neck, upper extremities, trunk, and lower extremities.





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