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Statistical Analysis Plan for Interventional Studies

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Sponsor Name: Biocon Biologics UK Limited.

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

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.

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[redacted]

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Revision History

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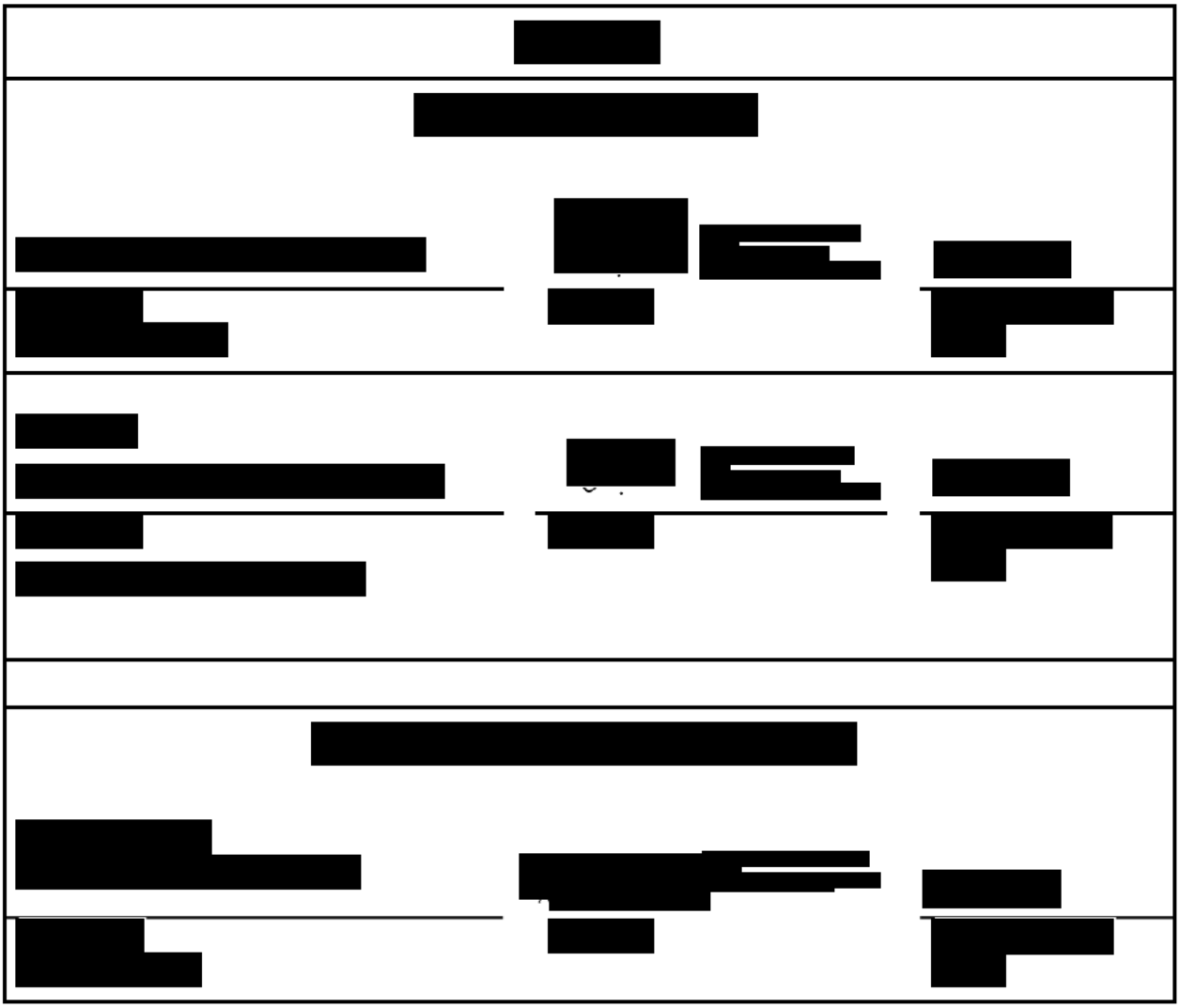

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1. Glossary of Abbreviations

Abbreviation	Description
ADA	Anti-drug Antibody
ADaM	Analysis Data Model
AE	Adverse Event
AESI	Adverse Event of Special Interest
ALT	Alanine Aminotransferase
ANCOVA	Analysis of Covariance
aPTT	activated Partial Thromboplastin Time
ARDS	Acute Respiratory Distress Syndrome
AST	Aspartate Aminotransferase
ATC	Anatomical Therapeutic Chemical
BSA	Body Surface Area
CI	Confidence Interval
CNS	Central Nervous System
CRO	Contract Research Organization
CTCAE	Common Terminology Criteria for Adverse Events
CS	Clinically Significant
CSR	Clinical Study Report
DLQI	Dermatology Life Quality Index
ECG	Electrocardiogram
ECMO	Extracorporeal Membrane Oxygenation
EDC	Electronic Data Capture
EW	Early Withdrawal
eCRF	electronic Case Report Form
FAS	Full Analysis Set
FAS2	Full Analysis Set for TP2
FAS3	Full Analysis Set for TP3
FDA	Food and Drug Administration
hs-CRP	high-sensitivity C-reactive protein
ICE	Intercurrent Event

Abbreviation	Description
ICH	International Conference on Harmonization
IGRA	Interferon-γ release assay
LDH	Lactate Dehydrogenase
mAb	Monoclonal Antibody
MAR	Missing-at-Random
Max	Maximum
MedDRA	Medical Dictionary for Regulatory Activities
MI	Multiple Imputation
Min	Minimum
MMRM	Mixed Model for Repeated Measures
MNAR	Missing-not-at-random
NAb	Neutralizing Antibody
NCS	Not Clinically Significant
PASI	Psoriasis Area and Severity Index
PASI 50/75/90/100	PASI improvement of ≥50%/75%/90%/100% relative to baseline
PFS	Prefilled Syringe
PGA	Physician's Global Assessment
PK	Pharmacokinetic
PKS	Pharmacokinetic Set
PKS2	Pharmacokinetic Set for TP2
PKS3	Pharmacokinetic Set for TP3
PPS	Per-Protocol Set
PR	PR Interval (time from the beginning of the P wave until the beginning of the QRS complex)
PRES	Posterior Reversible Encephalopathy Syndrome
PT	Preferred Term
QD	Quaque Die
QoL	Quality of Life
QRS	QRS Complex (the combination of three of the graphical deflections seen on a typical electrocardiogram)
QT	QT Interval (time between the start of the Q wave and the end of the T wave in the heart's electrical cycle)

Abbreviation	Description
QTc	Corrected QT Interval
QTcF	QTc by Fridericia's correction formula
SAE	Serious Adverse Event
SAF	Safety Set
SAF2	Safety Set for TP2
SAF3	Safety Set for TP3
SAP	Statistical Analysis Plan
SAS®	Statistical Analysis Software
SD	Standard Deviation
SOC	System Organ Class
SOP	Standard Operating Procedure
sPGA	static Physician's Global Assessment
TEAE	Treatment-Emergent Adverse Event
TFL	Table, Figure, and Listing
TP1	Treatment Period 1
TP2	Treatment Period 2
TP3	Treatment Period 3
ULN	Upper Limit of Normal
WHO	World Health Organization
WHO-DD	WHO Drug Dictionary
WOCBP	Women of Childbearing Potential

2. Purpose

The purpose of this Statistical Analysis Plan (SAP) is to ensure that the data listings, summary tables and figures which will be produced, and the statistical methodologies which will be used, are complete and appropriate to allow valid conclusions regarding the study objectives.

2.1. Responsibilities

[redacted] will perform the statistical analyses and is responsible for the production and quality control of all Tables, Figures, and Listings (TFLs).

2.2. Timings of Analyses

Two database locks (DBLs) are planned for the trial. The first DBL is planned after all patients complete scheduled Week 28 assessments or early terminate the study and the second DBL is planned after all eligible patients complete Week 52 scheduled assessments.

The primary analysis of efficacy, safety, immunogenicity, and pharmacokinetics for FDA submission is planned after all patients complete the Week 28 (TP1 + TP2) scheduled assessments or terminate early from the study. For all patients who are eligible for participating in TP3, the additional analysis of efficacy, safety, immunogenicity, and pharmacokinetics is planned after all eligible patients complete Week 52 scheduled assessments or terminate early from the trial.

3. Study Objectives

3.1. Primary Objective

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

3.2. 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.

4. Study Details/Design

4.1. Brief Description

This is a randomized, double-blind, active-controlled, parallel group, multicenter study designed to compare efficacy, safety, immunogenicity, and PK of Bmab 1200 and 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.

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.

Treatment Period 1 (TP1) - From baseline visit to Week 16 (predosing):

After the Screening Period, at Day 1 eligible patients will be randomly assigned in a 1:1 ratio to receive Bmab 1200 or Stelara® based on predefined stratification factors of geographic region (US versus Europe), body weight (≤100 kg versus >100 kg), previous exposure to biologic-based therapies (Yes versus No), and concomitant psoriatic arthritis (Yes versus No). Patients will receive study treatment at 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 x 2).

Treatment Period 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 re-randomization 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.

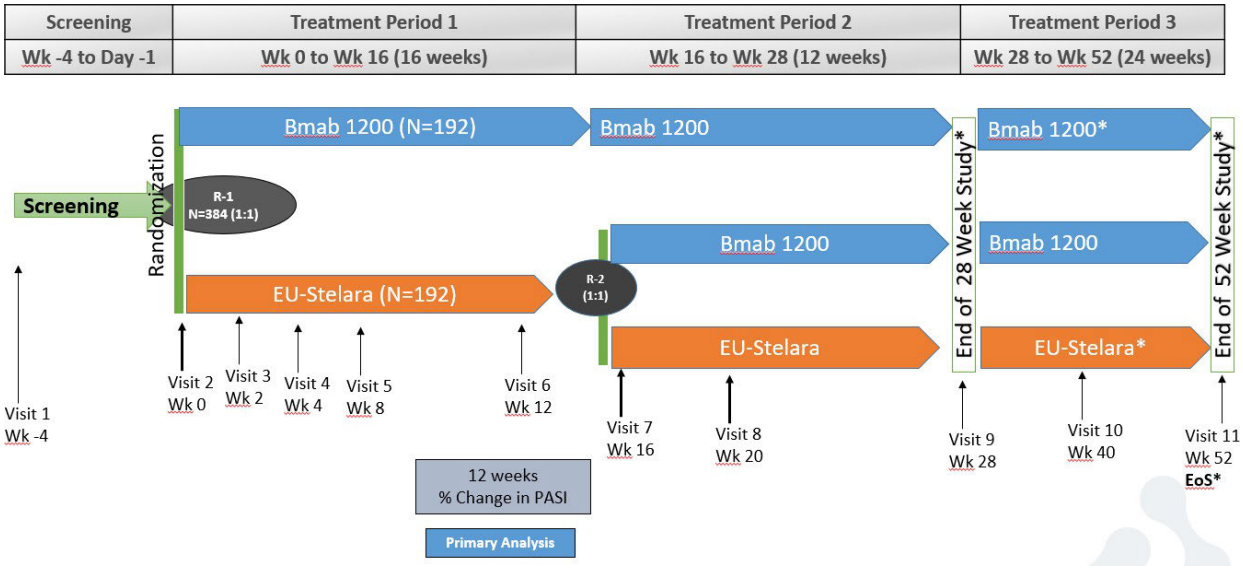
Treatment Period 3 (TP3) - From Week 28 dosing to Week 52:

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

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

The study design is illustrated in the figure below:



*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 bodyweight 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.

4.2. Patient Selection

The study will enroll patients with a diagnosis of moderate to severe chronic plaque psoriasis for at least 6 months (with BSA involvement ≥10%, PASI score ≥12, and sPGA ≥3 at screening and baseline visits), who have had a previous failure, inadequate response, intolerance or contraindication to at least one conventional anti-psoriatic systemic therapy.

4.2.1. Inclusion Criteria

Patients are eligible for the study if they meet all of the inclusion criteria specified in Section 8.1 of the study protocol.

4.2.2. Exclusion Criteria

Patients are not eligible for the study if they meet any of the exclusion criteria specified in Section 8.2 of the study protocol.

4.3. Determination of Sample Size

Two randomized placebo-controlled clinical studies, i.e., 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, Non-Inferiority 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 non-inferiority margin. In this case, margin could be 50% of the lower 95% CI, i.e., 50% of 67.42. So, statistical methodology would set the margin at ±34%; but for the FDA margin was reduced to ±10% with ~85% preservation of lowest treatment effect for additional clinical rigor in showing no clinically meaningful differences. For the PMDA, an equivalence margin of ±13% is assigned aligning with approximately 80% preservation of the lowest treatment effect, and still 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 for the FDA 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 the lowest power of 85% with a two one-sided 5% level of significance. Equivalence will be established for the PMDA, if the 95% 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 ±13%. For this comparison, a total sample size of 384 patients with 10% dropout ensures the lowest power of 96% with a two one-sided 2.5% level of significance.

4.4. Treatment Assignment and Blinding

At screening RAVE EDC will assign a unique patient identification number to the patient known as the patient number. The patient number assigned by the IWRS will be an 8-digit number consisting 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.

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

Randomization During Treatment Period 1:

Patients will be randomized at the first randomization to treatment (at Baseline visit) in a 1:1 ratio to Bmab 1200 or Stelara®, stratified by the following:

- Geographic region where the patient was enrolled (US 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)

Randomization at Treatment Period 2:

All continuing patients who receive study treatment at Weeks 0 and 4 and achieve at least PASI 50 response by Week 12 will be re-randomized 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 re-randomization 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).

Continuation in Treatment Period 3:

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.

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. 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.

4.5. Administration of Study Medication

Patients will receive either Bmab 1200 or Stelara® by subcutaneous (SC) injection via pre-filled syringe (PFS) at Baseline visit (Day 1), 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 sites. If possible, areas of the skin that show psoriasis should be avoided as injection sites.

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.

4.6. Schedule of Assessments

The schedule of assessments is presented as below:

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 (predose)	X (predose)	X
Immunogenicity 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)	
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 Protocol Section **Error! Reference source not found.**. 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 Protocol Section **Error! Reference source not found.** 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 Protocol 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 Protocol Section **Error! Reference source not found.** 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

5. Endpoints

5.1. Primary Efficacy Endpoint

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

5.2. Secondary 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 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 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 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)).

5.3. Immunogenicity Endpoints

- Proportion of patients developing antidrug antibodies (ADAs) and neutralizing antibodies (NAbs) during TP1 (Time Frame: Baseline [Day 1] through Week 16)
- Proportion of patients developing ADAs and NAbs during TP2 (Time Frame: post randomization/dosing on Week 16 through Week 28).
- Proportion of patients developing ADAs and NAbs during TP3 (Time Frame: post-dosing on Week 28 through Week 52).

5.4. Pharmacokinetics Endpoints

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

5.5. Safety Endpoints

The safety endpoints of this study are as follows:

- 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

6. Analysis Sets

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 BDRMs, to occur (with reports finalized) before each database lock. The final assignment of the PPS will only take place during the BDRM, at the time of the Week 28 database lock; see below for further details.

6.1. Analysis Sets During Treatment Period 1 (TP1)

The following analysis sets will be considered for analysis during TP1 (i.e., before re-randomization at Week 16 for treatment switch), and throughout the whole study (where applicable).

6.1.1. 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.

6.1.2. 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.

Protocol deviations affecting primary efficacy will be defined and reviewed in a standalone document during the Blinded Data Review Meeting before database lock.

The important protocol deviations leading to exclusion from PPS may include:

- Randomization criteria violations
- Inclusion/exclusion criteria violations
- Inadequate compliance with study drug
- Prohibited medications taken
- Incorrect medication administered: Incorrect trial medication taken, i.e., at least one kit number used and recorded on the eCRF before Week 12 does not correspond to the randomized treatment group.

Patients in the PPS will be analyzed under the treatment as randomized. The PPS will be used for supportive analyses of efficacy.

Other protocol deviation impacting primary efficacy will be defined and reviewed in the BDRMs 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.

6.1.3. Safety Set (SAF)

The SAF will consist of all patients who receive at least one full or partial 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.

6.1.4. Pharmacokinetic 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 (e.g., 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.

6.2. Analysis Sets During Treatment Period 2 (TP2)

The following analysis sets will be considered for analysis during TP2 (i.e., after re-randomization at Week 16 for treatment switch up to Week 28):

6.2.1. Full Analysis Set for TP2 (FAS2)

The FAS2 will consist of all patients who are re-randomized 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.

6.2.2. Safety Set for TP2 (SAF2)

The SAF2 will consist of all patients who receive the re-randomized full or partial 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.

6.2.3. Pharmacokinetic Set for TP2 (PKS2)

The PKS2 will consist of all patients who receive a full dose of re-randomized 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 (e.g., 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.

6.3. Analysis Sets During Treatment Period 3 (TP3)

The following analysis sets will be considered for analysis during TP3 (i.e., on or after Week 28 dosing to Week 52/End of Study):

6.3.1. Full Analysis Set 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.

6.3.2. Safety Set 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.

6.3.3. Pharmacokinetic Set 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.

7. Estimands

7.1. Intercurrent Events

The following intercurrent events (ICEs) are envisioned during the study, to be considered up to and including Week 16 PASI assessment (where "study treatment" refers to Bmab 1200 or Stelara®):

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 of the protocol.
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 deviation in dosing interval more than 14 days
ICE5 (Data obtained remotely)	Any data obtained from remote assessment due to COVID19 or for any other reason (for example, due to patient not being able to attend the site due to regional lockdown)

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.

Further ICEs may be added if any patients experience emergency unblinding, or other issues requiring ICE consideration. The full list of ICEs will be reviewed during the first BDRM, and an assessment of the completeness of the ICEs will be included.

The estimands for efficacy endpoints are detailed in Sections 7.2 and 7.3. Analysis of safety, pharmacokinetics, and immunogenicity is based on data as observed regardless of the intercurrent events.

7.2. 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 as follows:

	Primary Estimand	Secondary Estimand	Tertiary Estimand
Treatment conditions of interest	Bmab 1200 vs Stelara® Test: one injection (weight ≤ 100 kg) or two injections of Bmab 1200 (weight > 100 kg) 45 mg PFS Reference: one injection (weight ≤ 100 kg) or two injections of Stelara® (weight > 100 kg) 45 mg PFS	Bmab 1200 vs Stelara® Test: one injection (weight ≤ 100 kg) or two injections of Bmab 1200 (weight > 100 kg) 45 mg PFS Reference: one injection (weight ≤ 100 kg) or two injections of Stelara® (weight > 100 kg) 45 mg PFS	Bmab 1200 vs Stelara ® Test: one injection (weight ≤ 100 kg) or two injections of Bmab 1200 (weight > 100 kg) 45 mg PFS Reference: one injection (weight ≤ 100 kg) or two 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 without deviation up to Week 8 and having available PASI assessment at baseline and 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*	• ICE1 (Death) *Composite variable strategy* • ICE2 (Discontinuation of study treatment due to any reason other than death) *Treatment policy strategy*	• ICE1 (Death) *Not applicable, patient not considered in population* • ICE2 (Discontinuation of study treatment due to any reason other than death)

	Primary Estimand	Secondary Estimand	Tertiary Estimand
	• ICE3 (Prohibited therapy used for treatment of psoriasis) *Treatment Policy strategy* • ICE4 (Deviations in dosing) *Treatment Policy strategy* • ICE5 (Data obtained remotely) *Hypothetical strategy*	• ICE3 (Prohibited therapy used for treatment of psoriasis) *Hypothetical policy strategy* • ICE4 (Deviations in dosing) *Hypothetical policy strategy* • ICE5 (Data obtained remotely) *Hypothetical strategy*	*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* • ICE5 (Data obtained remotely) *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, pre-filled 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 10.3.2.4).
    - 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 10.3.2.4).Hypothetical strategy: Available data occurring on the ICE of "data obtained remotely" will be set to missing, and multiple imputed by a missing-at-random (MAR) application of SAS Proc MI (see Section 10.3.2.4). Data not obtained remotely after the ICE will not implement this strategy.
    - The primary estimand is aligned with a treatment policy approach for all ICEs except death and data obtained through remote assessment. The estimate of the treatment effect in this instance will be influenced by any effects of prohibited medication that are used to treat psoriasis, and/or premature discontinuation where a poor outcome may not be expected, but will not be affected by the confounding effects of obtaining data through remote assessment.

- 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 (see Section 10.3.2.4).
    - 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 10.3.2.4).
    - Hypothetical strategy: Available data occurring on or after the ICE3 and ICE4 will be set to missing, and multiple imputed by a missing not at random (MNAR) method (see Section 10.3.2.5). For ICE5 (data obtained remotely) available data occurring on the ICE will be set to missing and multiple imputed by MAR. Only the visit impacted by ICE5 where the ICE occurs will implement the hypothetical strategy; data not obtained remotely after the ICE will not implement this strategy.
    - The approach for the secondary estimand assumes that for patients discontinuing study treatment because of any reason other than death, a non-confounded estimate of the treatment effect is provided. For patients with deviations in study treatment dosing, in receipt of prohibited medication used for treatment of psoriasis, or with remote assessment, 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, prohibited medications that are used for treatment of psoriasis are not available and data are not able to be obtained remotely.

- 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, experience deviation of study treatment, receive prohibited medication that is used to treat psoriasis or have remote assessment a comparative assessment closer to that of a PPS analysis is gained.

7.3. Estimands for the 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 (i.e., during TP1, or as otherwise stated).

7.3.1. Definitions Applying to All Estimands of Secondary Efficacy

Criterion	Description
Treatment conditions of interest	Bmab 1200 versus Stelara® Test: one injection (weight ≤ 100 kg) or two injections of Bmab 1200 (weight > 100 kg) 45 mg PFS Reference: one injection (weight ≤ 100 kg) or two injections of Stelara® (weight > 100 kg) 45 mg PFS

7.3.2. Details of Each Estimand for Secondary Efficacy Endpoints

	Primary Estimand	Secondary Estimand	Tertiary Estimand
Percentage change from baseline in the PASI score at Weeks 4, 8, and 16			
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 without deviation up to Week 8 and having available PASI assessment at baseline and at each visit up to Week 16
Endpoint	Percentage change from baseline in the PASI score at Weeks 4, 8, and 16	Percentage change from baseline in the PASI score at Weeks 4, 8, and 16	Percentage change from baseline in the PASI score at Weeks 4, 8, and 16
Population-level summary	Difference between treatments (Bmab 1200 minus Stelara®) in mean percentage change from baseline in PASI score at Weeks 4, 8, and 16	Difference between treatments (Bmab 1200 minus Stelara®) in mean percentage change from baseline in PASI score at Weeks 4, 8, and 16	Difference between treatments (Bmab 1200 minus Stelara®) in mean percentage change from baseline in PASI score at Weeks 4, 8, and 16
ICEs and strategies to handle ICEs	Same as primary estimand for the primary efficacy endpoint	Same as secondary estimand for the primary efficacy endpoint	Same as tertiary estimand for the primary efficacy endpoint
PASI improvement of ≥50% (PASI 50), 75% (PASI 75) and 90% (PASI 90) relative to baseline at Weeks 4, 8, 12, and 16			
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 without deviation up to Week 8 and having available PASI assessment at baseline and at each visit up to Week 16

	Primary Estimand	Secondary Estimand	Tertiary Estimand
Endpoint	Percentage improvement from baseline in the PASI score of ≥50% (PASI 50), 75% (PASI 75) and 90% (PASI 90) at Weeks 4, 8, 12 and 16	Percentage improvement from baseline in the PASI score of ≥50% (PASI 50), 75% (PASI 75) and 90% (PASI 90) at Weeks 4, 8, 12 and 16	Percentage improvement from baseline in the PASI score of ≥50% (PASI 50), 75% (PASI 75) and 90% (PASI 90) at Weeks 4, 8, 12 and 16
Population-level summary	Difference between treatments (Bmab 1200 minus Stelara®) in the proportion of patients achieving PASI 50, PASI 75 and PASI 90 at Weeks 4, 8, 12 and 16	Difference between treatments (Bmab 1200 minus Stelara®) in the proportion of patients achieving PASI 50, PASI 75 and PASI 90 at Weeks 4, 8, 12 and 16	Difference between treatments (Bmab 1200 minus Stelara®) in the proportion of patients achieving PASI 50, PASI 75 and PASI 90 at Weeks 4, 8, 12 and 16
ICEs and strategies to handle ICEs	Same as primary estimand for the primary efficacy endpoint	Same as secondary estimand for the primary efficacy endpoint	Same as tertiary estimand for the primary efficacy endpoint
Raw PASI scores at Weeks 4, 8, 12, and 16			
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 without deviation up to Week 8 and having available PASI assessment at baseline and at each visit up to Week 16
Endpoint	PASI score at Weeks 4, 8, 12 and 16	PASI score at Weeks 4, 8, 12 and 16	PASI score at Weeks 4, 8, 12 and 16
Population-level summary	Difference between treatments (Bmab 1200 minus Stelara®) in mean PASI score at Weeks 4, 8, 12 and 16	Difference between treatments (Bmab 1200 minus Stelara®) in mean PASI score at Weeks 4, 8, 12 and 16	Difference between treatments (Bmab 1200 minus Stelara®) in mean PASI score at Weeks 4, 8, 12 and 16
ICEs and strategies to handle ICEs	Same as primary estimand for the primary efficacy endpoint	Same as secondary estimand for the primary efficacy endpoint	Same as tertiary estimand for the primary efficacy endpoint
Area under effect curves (AUECs) of PASI score from baseline to Week 12			

	Primary Estimand	Secondary Estimand	Tertiary Estimand
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 without deviation up to Week 8 and having available PASI assessment at baseline and at each visit up to Week 12
Endpoint	Area under the effect curves (AUECs) in the PASI score from baseline to Week 12	Area under the effect curves (AUECs) in the PASI score from baseline to Week 12	Area under the effect curves (AUECs) in the PASI score from baseline to Week 12
Population-level summary	Difference between treatments (Bmab 1200 minus Stelara®) in AUECs of PASI score from Baseline to Week 12	Difference between treatments (Bmab 1200 minus Stelara®) in AUECs of PASI score from Baseline to Week 12	Difference between treatments (Bmab 1200 minus Stelara®) in AUECs of PASI score from Baseline to Week 12
ICEs and strategies to handle ICEs	Same as primary estimand for the primary efficacy endpoint	Same as secondary estimand for the primary efficacy endpoint	Same as tertiary estimand for the primary efficacy endpoint
sPGA response of cleared or almost clear/minimal (PGA score of 0 or 1) at Weeks 4, 8, 12, and 16			
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 without deviation up to Week 8 and having available PASI assessment at baseline and at each visit up to Week 16
Endpoint	sPGA response of cleared or almost clear/ minimal (PGA score of 0	sPGA response of cleared or almost clear/ minimal (PGA score of 0	sPGA response of cleared or almost clear/ minimal (PGA score of 0

	Primary Estimand	Secondary Estimand	Tertiary Estimand
	or 1) at Weeks 4, 8, 12 and 16	or 1) at Weeks 4, 8, 12 and 16	or 1) at Weeks 4, 8, 12 and 16
Population-level summary	Difference between treatments (Bmab 1200 minus Stelara®) in the proportion of patients achieving sPGA of 0 or 1 at Weeks 4, 8, 12 and 16	Difference between treatments (Bmab 1200 minus Stelara®) in the proportion of patients achieving sPGA of 0 or 1 at Weeks 4, 8, 12 and 16	Difference between treatments (Bmab 1200 minus Stelara®) in the proportion of patients achieving sPGA of 0 or 1 at Weeks 4, 8, 12 and 16
ICEs and strategies to handle ICEs	Same as primary estimand for the primary efficacy endpoint	Same as secondary estimand for the primary efficacy endpoint	Same as tertiary estimand for the primary efficacy endpoint
Change from baseline in affected body surface area (BSA) at Weeks 4, 8, 12, and 16			
Population	Patients with moderate to severe chronic plaque psoriasis as defined by the inclusion/exclusion criteria	Not applicable	Not applicable
Endpoint	Change from baseline in affected BSA at Weeks 4, 8, 12 and 16	Not applicable	Not applicable
Population-level summary	Difference between treatments (Bmab 1200 minus Stelara®) in mean change from baseline in affected BSA at Weeks 4, 8, 12 and 16	Not applicable	Not applicable
ICEs and strategies to handle ICEs	• ICE1 (Death) *Treatment policy 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*	Not applicable	Not applicable

	Primary Estimand	Secondary Estimand	Tertiary Estimand
	• ICE4 (Deviations in dosing) *Treatment policy strategy* • ICE5 (Data obtained remotely) *Hypothetical strategy*		
Change from baseline in QoL as measured by Dermatology Life Quality Index (DLQI) scores at Weeks 4, 8, 12, and 16			
Population	Patients with moderate to severe chronic plaque psoriasis as defined by the inclusion/exclusion criteria	Not applicable	Not applicable
Endpoint	Change from baseline in DLQI at Weeks 8, 12 and 16	Not applicable	Not applicable
Population-level summary	Difference between treatments (Bmab 1200 minus Stelara®) in mean change from baseline in DLQI at Weeks 8, 12 and 16	Not applicable	Not applicable
ICEs and strategies to handle ICEs	• ICE1 (Death) *Treatment policy 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*	Not applicable	Not applicable

	Primary Estimand	Secondary Estimand	Tertiary Estimand
	• ICE5 (Data obtained remotely) *Hypothetical strategy*		

For the secondary efficacy endpoints related to PASI score and sPGA, the same handling as per the primary efficacy endpoint will be applied. For the endpoints related to BSA and DLQI, the following strategy (only primary estimand) will be applied:

- *Treatment policy strategy:* available data occurring on or after the ICE will be analyzed as observed. Any missing data for the corresponding assessment will be imputed by an MAR application of SAS Proc MI.
- Hypothetical strategy for ICE5: available data occurring on the ICE of "data obtained remotely" will not be considered, and will instead be imputed by an MAR application of SAS Proc MI. For this ICE, only the visit where the ICE occurs will implement the hypothetical strategy; data not obtained remotely after the ICE will not implement this strategy.

8. General Aspects for Statistical Analysis

8.1. General Methods

- Statistical methodology and analyses are in accordance with the principles outlined by the International Conference on Harmonization (ICH) E9 and ICH E9 addendum guidelines. All statistical evaluation will be performed using SAS® software version 9.4 or higher (SAS Institute, Cary, NC).
- Continuous variables will be summarized using the number of observations (n), mean, standard deviation (SD), median, minimum value, and maximum value. Categorical variables will be summarized using number of observations (n), frequency and percentages of patients.
- All relevant patient data will be included in data listings. All patients entered into the database will be included in patient data listings.
- Unless otherwise specified, only scheduled visits will be included in the summary tables, whereas all visits will be listed.
- 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 of the FDA, a two-sided 90% CI will be presented, and equivalence will be established if the 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 primary efficacy endpoint of the PMDA,, a two-sided 95% CI will be presented, and equivalence will be established if the CI falls entirely within the predefined margin of ±13%; this approach is equivalent to two one-sided tests (TOST) at the 2.5% significance level.
- Unless otherwise specified, analyses for TP1 will be presented by treatment group (Bmab 1200, Stelara®) up to pre-dose Week 16. Analyses for TP2 and TP3 will be presented by the treatment regimen (Bmab 1200-Bmab 1200, Stelara®-Bmab 1200, Stelara®-Stelara®).
- For efficacy endpoints PASI, sPGA and DLQI, whenever available vendor data will be windowed to scheduled visits and used for the analysis. If vendor data are not available or cannot be mapped to a scheduled visit, but eCRF data are captured (and can be mapped to a scheduled visit), then for such scenario eCRF data will be used for the analysis. All data (vendor and eCRF) will be listed.

8.2. Key Definitions

8.2.1. Date of Study Drug Administration

The first randomized study drug administration for the study (and for TP1) occurs at the Baseline visit (Day 1), after scheduled assessments. Additional study drug administration occurs after scheduled assessments at Week 4 and Week 16. The first study drug administration during TP2 occurs at Week 16, and the first study drug administration during TP3 occurs at Week 28.

8.2.2. Last Study Visit

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.

Patients who discontinue study treatment on or after Week 28 dosing (i.e., 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.

The last study visit for a patient is regarded as the latest available assessment prior to termination or completion of the study. The last scheduled visit in TP1 is the Week 16 visit (113±7 days), the last scheduled visit in TP2 is at Week 28 (197±7 days) and the last scheduled visit in TP3/across the study is at Week 52 (EOS visit, 365±7 days). If assessment is not required/cannot be performed at the EOS visit, the last available assessment will be used as the last non-missing on-study assessment.

8.2.3. Definition of Treatment Periods 1, 2 and 3

The following definitions will be used for assignment to Treatment Periods 1, 2 and 3:

Type of Data	Treatment Period 1 Start/Stop	Treatment Period 2 Start/Stop	Treatment Period 3 Start/Stop
Analysis based on scheduled visit/assessment	Baseline (Day 1) to Week 16 (Predosing)	Week 16 dosing to Week 28 (predosing)	Week 28 dosing to Week 52
Analysis based on treatment during period	On or after the date of study drug administration at Baseline (Day 1) up to one day before Week 16 study drug administration	On or after the date of study drug administration at Week 16 up to one day before Week 28 study drug administration	On or after the date of study drug administration at Week 28 up to Week 52

8.2.4. Baseline, Change from Baseline and Relative (%) Change from Baseline

Unless otherwise defined, baseline will be defined as the last non-missing valid value prior to the first administration of study treatment. Per footnote b of the protocol schedule of assessments (Table 1) of the protocol, administration of study treatment occurs after all scheduled assessments; thus baseline will be the latest available result on or before Baseline (Day 1) assessment.

Changes from baseline and relative changes from baseline are obtained, where applicable, as follows:

- Change from baseline = (post-baseline value – baseline value).
- Relative change from baseline (%) = (post-baseline value – baseline value) / (baseline value) * 100.

8.2.5. Study Day

Study day will be defined as the number of days since the first dose of study treatment administration. The day of first administration of study treatment is defined as study day 1. All assessments prior to study day 1 will have a negative study day (i.e., there is no study Day 0). Study day is calculated using the formulae below, regardless of whether the assessment/event occurs in TP1, TP2 or TP3:

Assessment/Event Date Relative to First Administration of Study Treatment	Study Day Calculation
Assessment/Event date < Date of first study treatment administration	Date of assessment/event - Date of first study treatment administration
Assessment/Event date ≥ Date of first study treatment administration	(Date of assessment/event – Date of first study treatment administration)+1

8.2.6. Duration of Event

Where the duration of an event is to be calculated, it will be derived as: (Date of stop of event – Date of start of event) + 1.

8.2.7. MedDRA and WHO Drug Coding Versions

Dictionary	Version
Medical Dictionary for Regulatory Activities (MedDRA)	25.1 or higher
World Health Organization Drug Dictionary (WHO-DD)	Version B3 Sep-2022 or higher

8.2.8. Inexact Values

If an inexact value is provided in the database (such as "<X", ">X" etc.) then unless otherwise stated the value of the integer (i.e. "X") will be used in the analysis for summary purposes. In the listings, the original text will be presented.

8.3. Missing Data

Missing data imputation rules for efficacy data are specified in Section 10.3.2. All other missing data not covered here will not be imputed. Analyses will be performed considering all data observed for the respective analysis sets.

8.3.1. Partial or Missing Event Dates

All partial or missing dates will be presented in the data listings as they are recorded on the electronic Case Report Form (eCRF). The analysis dataset will flag where day, month or year has been imputed for analysis start or stop date.

8.3.1.1. Adverse Events

In case the AE start date is missing or incomplete, the date will be imputed for the calculation according to the worst-case approach.

In case the AE start date is missing or incomplete, the following imputation rules will be used:

- If the AE start date is completely missing, it will be imputed with the date of first study treatment administration in the study (i.e. at Baseline, Day 1).
- For incomplete AE start dates:
    - If day and month are missing, the missing day will be imputed by the first day of the month and the missing month will be imputed as January.
    - If only day is missing, the missing day will be imputed by the first day of the month.
    - If the imputed AE start date is prior to the first dose date, and from the available month/year it is unclear whether the AE emerged on or after the first dose date, the AE start date will be set to the first dose date.
- If the start date of any TEAE is incomplete or missing, the event will be assumed to be in TP1, unless the incomplete start date (month and/or year) clearly indicates that the event started on or after the first dosing in TP2/TP3.

In case the AE end date is missing or incomplete, the following imputation rules will be used:

- If month and year are present and the day of the month is missing, the last day of the month is imputed.
- If only a year is present, the 31st of December is used.
- If the imputed date is later than the date of death (if available), the date of death will be used as the imputed end date instead.

8.3.1.2. Prior and Concomitant Medications/Procedures

Prior and concomitant medications/procedures with onset/end dates that are partially/completely missing will be imputed as follows.

In case the medication start date is missing or incomplete, the following imputation rules will be used:

- If the medication/procedure start date is completely missing, it will be imputed with the date 1 day before first study treatment administration in the study (at Baseline, Day 1).
- For incomplete medication/procedure start dates:
    - If day and month are missing, the missing day will be imputed by the first day of the month and the missing month will be imputed as January.
    - If only day is missing, the missing day will be imputed by the first day of the month.
- If the start date of any medication/procedure is incomplete or missing, and it is unclear when imputed whether the medication/procedure started in TP1, TP2 or TP3, the medication/procedure will be assumed to be concomitant with TP1, TP2 and TP3, unless the incomplete start date (month and/or year) clearly indicates that the medication/procedure started on or after the first dosing in TP2 or TP3.

In case the medication end date is missing or incomplete, the following imputation rules will be used:

- If the medication/procedure end date is completely missing, it will be imputed with the last day of the month (if day missing and month is present), or December 31st if both day and month are missing.
  If the date is completely missing, assign ‘continuing’ status to the end date.

8.4. Visit Windows

Efficacy by-visit summaries for PASI and sPGA will use the mapped analysis visit, based on windowed ranges. All assessments for PASI and sPGA will be windowed based on the following analysis visit window which is based on study day. If multiple assessments are performed within the same visit window, the one taken closest to the target study day for the analysis visit will be used for the analysis. If there are multiple assessments performed with the same difference from target day, the later assessment will be used for the analysis.

Table 8-1: Analysis Visit Window

Analysis Visit	Target Study Day	Visit Window for PASI and sPGA
Baseline	1	<=1
Week 4	29	26 to 32
Week 8	57	52 to 62
Week 12	85	80 to 90
Week 16	113	106 to 120
Week 20	141	134 to 148
Week 28	197	190 to 204
Week 40	281	274 to 288
Week 52	365	358 to 372

For all other efficacy analysis, all data from the eCRF will be analyzed according to the scheduled time points. Any additional or unscheduled assessments will not be used in the summary statistics per time point (unless otherwise discussed in the relevant section) but will be included in the data listings according to the date/time of assessment.

Safety and pharmacokinetics data will not be windowed for by-visit summary. i.e., scheduled visit data will be used for analysis, unless otherwise specified.

8.5. Pooling of Centers

No pooling of centers is planned for this study.

8.6. Subgroups

To evaluate the consistency in the primary efficacy endpoint (percent change from baseline in PASI at Week 12) over demographic and baseline characteristics, exploratory subgroup analyses will be performed. Subgroups include:

1) Demographic subgroups:
    a. Gender (Male vs. Female)
    b. Age Group (< 65 years vs. ≥ 65 years)
    c. Race (Asian, Black, Native Hawaiian or Pacific Islander, White, Other)
    d. Region where the patient was enrolled (US vs. Europe)
    e. Ethnicity (Hispanic or Latino vs Not Hispanic or Latino)
2) Baseline disease characteristics subgroups:
    a. Prior exposure to biologic therapies for psoriasis or psoriatic arthritis (Yes versus No)
    b. Concomitant psoriatic arthritis (Yes versus No)
    c. Baseline PASI score (< 20 vs. ≥ 20)
    d. Baseline sPGA (Moderate (sPGA=3) and severe to very severe (sPGA= 4 or 5)
    e. Baseline BSA involvement (10-30% and > 30%)
    f. Baseline Psoriatic Arthritis Status (Yes/No)

3) On-treatment status subgroup:
    a. ADA Status (positive/negative up to Week 12)
    b. nAbs Status (positive/negative up to Week 12)

9. Demographic, Other Baseline Characteristics and Medication

9.1. Patient Disposition and Withdrawals

Patient disposition and withdrawals will be summarized for all patients. The number and percentage of patients screened, screen failed, randomized, treated, completed, discontinued study treatment prematurely, and discontinued the study prematurely, together with the primary reasons for discontinuation will be presented for each treatment arm/regimen and overall for each treatment period and across the study.

Patients included in each analysis set, and reasons for exclusion from each of the analysis sets will be presented for each treatment arm/regimen and overall on the FAS.

The number of subjects in the FAS, FAS2 and FAS3 by region, country and center will also be presented, by treatment group and overall for each treatment period.

Important protocol deviations occurring during TP1 will be presented in a frequency table by treatment arm and overall on the FAS. All other protocol deviations will be listed.

9.2. Demographic and Baseline Characteristics

Demographic and baseline characteristics, including sex (male, female), age (years), geographical region (US, Europe), country (TBD), race (White, Black, Asian, Native Hawaiian or Pacific Islander, and Other), ethnicity (Hispanic or Latino, Not Hispanic or Latino), height (cm), body weight (kg), body mass index (kg/m^2), psoriatic arthritis status (yes, no), previous biologic use for psoriasis or psoriatic arthritis (yes, no), smoking status (Never Smoked, Ex-smoker, Smoker or Unknown) and alcohol consumption (Non Drinker, Ex-drinker, Current Drinker or unknown) will be summarized descriptively for each treatment group/regimen and overall for each treatment period. The summary will be presented for all patients in the FAS, FAS2, FAS3 and PPS.

Age, height, weight and BMI will be converted/derived as follows:

Variable	Derivation
Age at Study Day 1	(ICF date - date of birth + 1) / 365.25 and truncated to complete years
Height (in cm)	Height (in inches) * 2.54
Weight (in kg)	Weight (in lbs) * 0.4536
BMI (kg/m^2)	Weight(kg)/[Height(m)]^2

Similarly, psoriasis disease characteristics at Baseline including PASI score, sPGA, BSA and DLQI score, will also be summarized descriptively by treatment group and overall on the FAS.

Baseline characteristics are defined as all results of the examinations performed prior to the first dose of study drug. See Section 8.2.4 for the definition of baseline.

9.3. Other Baseline Characteristics

Hepatitis B, hepatitis C, HIV test, interferon-gamma release assay (IGRA), and chest radiography with x-ray performed at Screening will be listed.

Pregnancy test performed with serum at screening and with urine at other scheduled visits for females of childbearing potential will be listed only.

9.4. Medical History

Medical history and ongoing diseases will be coded into Preferred Term (PT) and System Organ Class (SOC) according to MedDRA (see Section 8.2.7 for version). The dictionary used will be specified in the data display footnote. Data will be summarized for all patients in the FAS.

Medical history and ongoing diseases will be summarized overall, by SOC and PT for each treatment group and overall, presenting the number and percentage of patients. A patient is counted once at the SOC level and once at each PT within the SOC level. Conditions are sorted by descending frequency of SOC (overall, then by Bmab 1200, then Stelara®) and then, within a SOC, by descending frequency of PT. In case of identical frequency, sorting will be done alphabetically.

9.5. Medication/Procedures

All medications will be coded according to WHO-DD (see Section 8.2.7 for version). Data will be summarized for all patients in the FAS.

Medications will be summarized overall, by Anatomical Therapeutic Chemical (ATC) level 2 and ATC level 4 for each treatment group/regimen and overall on the FAS/FAS2/FAS3, for each treatment period (concomitant medications only). For summaries under the FAS3, medications received across both TP2 and TP3 will be summarized.

The summaries will present the number and percentage of patients. A patient is counted once at the ATC level 2 and once at each ATC level 4 within the ATC level 2. Medications are sorted by descending frequency (overall, then by Bmab 1200, then Stelara®) of ATC level 2 and then, within ATC level 2, by descending frequency of ATC level 4. In case of identical frequency, sorting will be done alphabetically. Separate summaries will be provided for prior and concomitant mediations.

All data will be listed for patients in the FAS, separately for prior and concomitant medications.

9.5.1. Prior Medication

Medications started within 30 days prior to screening and stopped prior to the first dose of study treatment will be summarized by treatment group and listed as prior medications.

9.5.2. Concomitant Medication

Concomitant medications/procedures are defined as follows:

- Where the medication/procedure starts after the date of the first dose of study drug, OR
- Where the medication/procedure starts before the first dose of study drug and continues after the first dose of study drug until anytime up to the Week 52 visit

Concomitance will be assessed for TP1 on the FAS, TP2 on the FAS2 and TP2 plus TP3 on the FAS3. Thus, a medication/procedure may be concomitant over TP1 and TP2, TP2 and TP3, or TP1, TP2 and TP3 if it occurs during multiple treatment periods. Concomitant medications will be summarized and listed.

9.5.3. Subsequent Medication

Medications/procedures that start over 12 weeks after the last dose of study treatment are considered subsequent medications/procedures.

Subsequent medications/procedures will be analyzed in the same way as concomitant medications/procedures and will be included in the above listings of prior/concomitant/ subsequent medications/procedures.

9.5.4. Rescue and Prohibited Medication

Protocol Section 9.7 lists prohibited medications, that are not permitted to be received during the entire study period.

Protocol Section 9.8 lists permitted and rescue medications, that can be used during the entire study period.

Rescue and potentially prohibited medications will be identified and reviewed by the study team, and confirmed during the BDRM.

Subjects receiving rescue and prohibited medication will be presented in a data listing. The listing will include a flag for rescue/prohibited status. The extent of receipt of rescue and prohibited medication in relation to efficacy assessments is covered under Section 7.1.

10. Efficacy

10.1. Statistical Hypotheses

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

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

- H_0: ($\mu_{Bmab\ 1200} - \mu_{Stelara} \leq -13\%$) or ($\mu_{Bmab\ 1200} - \mu_{Stelara} \geq +13\%$)
- H_1: $-13\% < \mu_{Bmab\ 1200} - \mu_{Stelara} < +13\%$

Where the definitions of $\mu_{Bmab\ 1200}$ and $\mu_{Stelara}$ are the same as above.

A summary of the criterion of assessment of similarity is as follows:

Agency for submission	Estimate of treatment difference	CI for assessment of equivalence	Equivalence margin
FDA	Difference in means	90% ($\alpha = 0.05$)	±10%
PMDA and others	Difference in means	95% ($\alpha = 0.025$)	±13%

Abbreviations: FDA, US Food and Drug Administration; PMDA, Japan Pharmaceuticals and Medical Devices Agency.

For all agency comparisons, equivalence testing will be conducted using the primary estimand.

10.2. Definition for Efficacy Endpoints

For all efficacy endpoints where a derived categorization is defined in this section, if the category is collected on the eCRF then it will be used in the analysis, and will not be derived.

10.2.1. PASI Score

PASI score involves specifying skin involvement area of the following regions:

- Head
- Upper extremities
- Trunk
- Lower extremities including buttocks.

It is evaluated at Screening, Baseline (Day 1), and at Weeks 4, 8, 12, 16, 20, 28, 40 and 52/EOS. Within each region, three main categories are assessed: the body surface area (%), the rating (0-4) of erythema, infiltration or desquamation, and a score (0-6) related to the % of the body region affected the % area of involvement:

Component 1: Body Region	**Body Surface Area (%)**
Head	10
Upper Extremities	20
Trunk	30
Lower Extremities (including buttocks)	40
Component 2: Rating of Individual Parameter	**0 = Nil, 4 = Severe**
Erythema	0-4
Infiltration	0-4
Desquamation	0-4
Component 3: % of Body Region Affected	**Extent Indicator**
No involvement	0
< 10	1
10 to < 30	2
30 to < 50	3
50 to < 70	4
70 to < 90	5
90 to 100	6

The PASI score is then calculated as:

$$PASI = (0.1 \times (E_h + I_h + D_h) \times A_h) + (0.2 \times (E_u + I_u + D_u) \times A_u) + (0.3 \times (E_t + I_t + D_t) \times A_t) + (0.4 \times (E_l + I_l + D_l) \times A_l)$$

Where E = erythema, I = infiltration, D = desquamation, A = area of psoriatic involvement, h = head, t = trunk, u = upper extremities, l = lower extremities. For example, E_h, I_h, and D_h are the ratings of erythema, infiltration and desquamation for the head, respectively. E_h, I_h, or D_h range from 0 to 4. A_h is the extent indicator for the head with range from 0 to 6.

Total PASI score ranges from 0 to 72, with higher scores indicating a worse state of disease. If any individual component of PASI score is missing, the PASI score will be regarded as missing.

10.2.2. PASI 50, PASI 75 and PASI 90 Response

The PASI XX response is defined as an improvement from baseline in PASI score of XX% or greater. Thus, PASI 50 response is defined for a patient as a 50% or greater improvement from baseline in PASI score, PASI 75 is defined for a patient as a 75% or greater improvement from baseline in PASI score, and PASI 90 is defined for a patient as a 90% or greater improvement from baseline in PASI score. Relative change from baseline is calculated as:

((PASI score at visit – PASI score at Baseline)/PASI score at Baseline) x 100.

10.2.3. Area Under the Effect Curves (AUECs) of PASI Score

The linear trapezoidal method will be used to derive the AUEC of PASI between Baseline and Week 12. For this purpose, the PASI scores at Baseline, and at Weeks 4, 8 and 12 will be used, and the area within each set of adjacent timepoints will be calculated as:

$$((P_X + P_{X+1})*(0.5))*(T_{X+1} – T_X)$$

Where P_X = PASI score at time X, P_{X+1} = PASI score at time X+1, T_X = Time in weeks at timepoint X, T_{X+1} = Time in weeks at timepoint X+1. The AUEC will then be the sum of all segments (3 segments) between Baseline and Week 12.

10.2.4. Static Physician's Global Assessment (sPGA) Score

The sPGA is the physician's global assessment of the patient's psoriasis based on severity of induration, scaling, and erythema. The sPGA is a scale from 0 to 5 where 0 indicates clear and 5 indicates severe disease. sPGA is evaluated at Screening, Baseline (Day 1), and at Weeks 4, 8, 12, 16, 20, 28, 40 and 52/EOS.

10.2.5. Body Surface Area (BSA)

The extent (%) to which each body region as well the total body surface is involved with psoriasis will be evaluated using the palm method with one entire palmar surface or "handprint" (including the fingers) equating to approximately 1% of total BSA. For each body region of the PASI, the affected area calculated by the palm method is to be adapted to the surface of that region with respect to the total BSA (e.g., head and neck region accounts for 10% [or 10 palms] of total BSA therefore 5 palms on the face equates to 50% of the H&N region).

To derive total BSA, the number of patient's palms covering psoriasis all over the body across the different regions is summed (eg, 15 palms=15%). The minimum total BSA for a patient at a visit is 0% and the maximum is 100%. The minimum BSA at Screening and Baseline visit to consider a patient eligible for the study is 10%.

10.2.6. Dermatology Life Quality Index (DLQI)

The DLQI is a self-administered questionnaire designed to measure the health-related quality of life of adults suffering from skin disease. The DLQI consists of 10 questions covering the following: symptoms, embarrassment, shopping and home care, clothes, social and leisure, sport, work or study, close relationships, sex, and treatment. Each question refers to the impact of the skin disease on the subject/patient's life over the previous week.

The questions assessed are as follows:

Question	Score
1. Over the last week, how itchy, sore, painful or stinging has your skin been?	3 = Very much, 2 = A lot, 1 = A little, 0 = Not at all
2. Over the last week, how embarrassed or self-conscious have you been because of your skin?	3 = Very much, 2 = A lot, 1 = A little, 0 = 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?	3 = Very much, 2 = A lot, 1 = A little, 0 = Not at all, or Not relevant

4. Over the last week, how much has your skin influenced the clothes you wear?	3 = Very much, 2 = A lot, 1 = A little, 0 = Not at all, or Not relevant
5. Over the last week, how much has your skin affected any social or leisure activities?	3 = Very much, 2 = A lot, 1 = A little, 0 = Not at all, or Not relevant
6. Over the last week, how much has your skin made it difficult for you to do any sport?	3 = Very much, 2 = A lot, 1 = A little, 0 = Not at all, or Not relevant
7. Over the last week, has your skin prevented you from working or studying? • If "No", over the last week how much has your skin been a problem at work or studying?	3 = Yes, 0 = No, or Not relevant 2 = A lot, 1 = A little, 0 = 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?	3 = Very much, 2 = A lot, 1 = A little, 0 = Not at all, or Not relevant
9. Over the last week, how much has your skin caused any sexual difficulties?	3 = Very much, 2 = A lot, 1 = A little, 0 = Not at all, or 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?	3 = Very much, 2 = A lot, 1 = A little, 0 = Not at all, or Not relevant

The DLQI total score is calculated as the sum of scores for each of the questions. DLQI total score ranges from 0 (no effect on patient/subject's life) to 30 (extremely large effect).

The interpretation of scores is as follows:

Total DLQI Score	Interpretation
0 to 1	No effect at all on subject's life
2 to 5	Small effect on subject's life
6 to 10	Moderate effect on subject's life
11 to 20	Very large effect on subject's life
21 to 30	Extremely large effect on subject's life

DLQI is evaluated at Baseline (Day 1), and at Weeks 4, 8, 12, 16, 20, 28, 40 and 52/EOS.

10.3. Estimand Related Data Handling

10.3.1. Estimand Related Data Handling for the Primary Efficacy Endpoint (Percentage Change from Baseline to Week 12 in PASI Score)

The estimands discussed in Section 7.2 will be handled as described here, including process for imputation of missing data.

10.3.1.1. Primary Estimand

The primary estimand for the primary efficacy endpoint is based on a composite strategy for deaths, a treatment policy strategy for discontinuation of study treatment not due to death, prohibited therapy used for medication (used to treat psoriasis) and deviations in dosing, and a hypothetical strategy for data obtained remotely.

As a first step, any PASI score affected by an ICE to be handled using a hypothetical strategy will be set to missing. As a second step, all missing data (non-monotone or monotone) at this point will be imputed using an MCMC MAR approach, and then any data affected by an ICE to be handled using a composite variable strategy will be imputed using a return-to-baseline MI approach detailed in Section 10.3.2.3. As a third step. any monotone data that were missing at the beginning of Step 2 that were not to be handled under a composite variable strategy will be set back to missing, and any missing data at this point to be handled under a treatment policy strategy will be multiple imputed using a MAR approach per Section 10.3.2.4.

10.3.1.2. Secondary Estimand

The secondary estimand for the primary efficacy endpoint is based on a composite strategy for deaths, a treatment policy strategy for discontinuation of study treatment not due to death, a hypothetical strategy for handling deviations in study treatment dosing, prohibited medication (used to treat psoriasis) and data obtained remotely.

For this estimand, as a first step, any PASI score affected by an ICE to be handled using a hypothetical strategy will be set to missing. As a second step, all missing data (non-monotone or monotone) at this point will be imputed using an MCMC MAR approach, and then any data affected by an ICE to be handled using a composite variable strategy will be imputed using a return-to-baseline MI approach detailed in Section 10.3.2.3. As a third step. any monotone data that were missing at the beginning of Step 2 that were not to be handled under a composite variable strategy will be set back to missing, and any missing data at this point to be handled under a treatment policy strategy will be multiple imputed using a MAR approach per Section 10.3.2.4.Lastly, any data occurring under influence of ICE3 or ICE4 to be handled using a hypothetical strategy will be set back to missing, and multiple imputed using a MNAR approach utilizing the distribution of data from the corresponding treatment arm for all subjects not having experienced an ICE up to and including the timepoint of interest (per Section 10.3.2.5).

All multiple imputations for the primary and secondary estimands will occur on total PASI score.

10.3.1.3. Tertiary Estimand

The tertiary estimand for the primary efficacy endpoint is based on a principal stratum strategy for all ICEs. For this estimand, no missing data is expected, and no patients will have PASI data affected by an ICE. Thus, no imputation will occur other than non-monotone MAR imputation where required.

10.3.2. General Multiple Imputation Approach for Primary and Secondary Estimands

The primary method of imputation for missing data will be MI (Multiple Imputation); the MI procedure of the SAS system will be used to generate sets of data with missing values imputed from observed data. Total PASI score will be imputed in this manner.

For the imputation of the primary endpoint, where a multiple imputation (MI) approach is described, the continuous PASI score between 0 and 72 will be multiple imputed, and subsequently the (percentage) change from baseline will be calculated for each imputation. The number of imputations will be 10 per MI step, representing the set of 10 plausible values obtained from a prediction model based primarily on observed data. The number of imputations and/or burn-in iterations may be increased if there are convergence issues.

For the primary endpoint, both monotone and non-monotone missing data are to be expected. Thus, any non-monotone missing data will be handled as MAR first prior to any subsequent imputation using a composite variable strategy, monotone MAR and/or MNAR imputation step.

The full MI approach will comprise of 7 steps, as follows:

- Any data to be imputed using a hypothetical strategy will be set to missing.
- Initial MAR Imputation Step (10 imputations – see below): Any missing data at this point will be multiple imputed using a Markov Chain Monte Carlo (MCMC) imputation approach, per Section 10.3.2.2. This step will be taken in order to impute non-monotone missing data (including missing due to handling of ICE5), and to set up the return-to-baseline imputation below. For the tertiary estimand, only this step will be conducted, for missing data not affected by an ICE, implementing non-monotone data imputation only.
- Composite Variable Strategy Step (1 imputation): After the above MAR missing data imputation step is implemented, any missing data to be handled using a composite variable strategy will be imputed using a return-to-baseline MI approach, per Section 10.3.2.3. After this step is implemented, any data that is affected by any ICE other than ICE1 or ICE5 will be set back to missing to allow for the below imputation steps.
- Monotone MAR Imputation Step (10 imputations): After missing data handled using composite variable strategy is imputed, any patient with monotone missing data will be multiple imputed using a monotone regression approach, per Section 10.3.2.4. For the Primary estimand, this step will be the final imputation step.
- Monotone MNAR Imputation Step (10 imputations):
    - Primary estimand: This step will not occur, as no ICEs are handled using a hypothetical strategy implementing an MNAR imputation approach. .
    - Secondary estimand: Any patient with either available or originally missing PASI data occurring under ICE3 or ICE4 with hypothetical handling strategy, will have their imputed data from the MAR step above set to missing and subsequently multiple imputed using a monotone regression approach using as input all data for patients that did not experience an ICE affecting the timepoint to be imputed, per Section 10.3.2.5.
- Analysis Step: The analysis as described in Section 10.3.2.6 is conducted for each of the 10*1*10=100 imputations (primary estimand), 10*1*10*10=1000 imputations (secondary estimand), and 10 imputations for the tertiary estimand.
- Combining Step: Rubin's rules (SAS PROC MIANALYZE) are used to combine the 100/1000/10 point estimates and standard errors, in order to provide a single point estimate, confidence interval and p-value that can be compared to the respective null hypotheses described in Section 10.1 to provide rejection or acceptance.

During imputation, if any of the variables to be imputed at a visit are not affected by an ICE, then the specific ICE term for the visit will not be included in the model for imputation.

10.3.2.1. Step 1: Set Data Affected by an ICE to be Handled using Hypothetical Strategy to Missing

As a first step, any data affected by ICE5 (primary and secondary estimands) or ICE3 and ICE4 (secondary estimand) will be set to missing.

At this point, numeric indicator variables (i.e., 0 or 1) for each of the ICEs at each visit will be set up, to allow for inclusion in the below modelling steps.

10.3.2.2. Step 2: Initial MAR Imputation Step (MCMC)

Any patient with missing data for PASI score at this point will be multiple imputed using a full MCMC approach, with multiple chains, including factors for study treatment, stratification factors, baseline PASI score, and binary variables for ICE occurrence at the visit. This approach treats all missing data as MAR. At this point, 10 imputations will be available for the primary, secondary and tertiary estimands.

Example SAS syntax for the primary, secondary and tertiary estimands (imputes non-monotone missing data and sets up monotone missing structure for implementing Step 4):

```
proc mi data=DATIN out=DATOUT nimpute=10 seed=XXXXX min =.....0 0 0 0
                                                          max =..... 72 72 72 72;
        var TRTPN STRAT1N STRAT2N STRAT3N BASE W4 W8 W12 ICE1_W4 ICE2_W4 …;
        MCMC chain=multiple impute=monotone;
        em  maxiter=500 converge = 0.00001;
run;
```

In order to implement the MI return-to-baseline approach (Step 3) detailed in Section 10.3.2.3 for the primary and secondary estimands all missing data (monotone and non-monotone) must be imputed. Thus, for the initial step of return-to-baseline MI, the following SAS syntax is applicable for setup of the MI RTB implementation only:

```
proc mi data=DATIN out=DATOUT nimpute=10 seed=XXXXX min =.....0 0 0 0
                                                          max =..... 72 72 72 72;
        var TRTPN STRAT1N STRAT2N STRAT3N BASE W4 W8 W12 ICE1_W4 ICE2_W4 …;
        MCMC chain=multiple;
        em  maxiter=500 converge = 0.00001;
run;
```

10.3.2.3. Step 3: Return-To-Baseline MI Approach for Composite Variable Strategy

Monotone missing data implementing the composite variable strategy will be imputed using a return-to-baseline approach as per Qu and Dai (2021)[6]. The mean at each visit for each treatment arm (Y1x, Y2x where 1 is the Bmab 1200 arm, 2 is the Stelara® arm, and x is the visit concerned) and the mean for the baseline visit across both treatments pooled ($\bar{X}$) will be calculated at this point using SAS PROC MEANS, and the result at each visit will be adjusted for the baseline as follows:

```
data DATOUT2;
  set DATOUT;
  if COMPVAR=1 then do;
    if TRTPN = 1 then y1 = y1 - mu_y + mu_x;
    if TRTPN = 2 then y1 = y1 - mu_y + mu_x;
  end;
run;
```

Once the composite variable strategy has been implemented, where a record exists that occurs under an ICE to be handled using a treatment policy strategy, or for data affected by ICE3 and ICE4 (secondary estimand), if the record was originally missing and was subsequently imputed in Step 2, it will be set back to missing, to allow for the following imputation steps.

10.3.2.4. Step 4: Monotone MAR Imputation Step

, At this point, any monotone missing data will be imputed using a MAR monotone regression model, including factors for treatment arm, stratification factors, baseline PASI score, all score data for each visit up to the timepoint, and binary variables for ICE occurrence at the visit. Ten imputations will be implemented for this step.

Example SAS syntax is as follows:

```
proc mi data=DATOUT2 out=DATOUT3(rename=(_IMPUTATION_=MARIMP)) seed=XXXXX nimpute=10
min = . . . . . 0 0 0 0 0 max = .....72 72 72 72 72;
        by RTBIMP;
        class TRTPN STRAT1N STRAT2N STRAT3N ICE1_W4 ICE2_W4 .....;
        monotone regression(W4=TRTPN STRAT1N STRAT2N STRAT3N ICE1_W4 ICE2_W4 . . .
                            BASE W2 /details);
        monotone regression(W8=TRTPN STRAT1N STRAT2N STRAT3N ICE1_W4 ICE2_W4 . . .
                            BASE W2 W4 /details);
        monotone regression(W12=TRTPN STRAT1N STRAT2N STRAT3N ICE1_W4 ICE2_W4 . . .
                            BASE W2 W4 W8 /details);
        var TRTPN STRAT1VN STRAT2VN ICE1_W4 ICE2_W4 .....BASE W2 W4 W8 W12;
run;
```

10.3.2.5. Step 5: Monotone MNAR Imputation Step (Hypothetical Strategies)

For the secondary estimand, any patient that experiences ICE3 and/or ICE4 to be handled under hypothetical strategies will have data occurring on or after the ICE set to missing, and will subsequently be multiple imputed using a MNAR approach similar to the MAR approach above, but utilizing all data from the corresponding treatment arm for which the patient did not experience an ICE at the visit to inform the imputation of missing data. This approach treats the missing data as being missing not at random (MNAR), and applies an approach considering the treatment effect where ICEs could not occur. The same factors as for the MAR step above will be included. The monotone MNAR imputation step will be conducted for 10 imputations.

Example SAS syntax is as follows:

```
proc mi data = DATOUT3 out = DATOUT4 nimpute=10 seed=XXXX min =..... 0 0 0 0
                                                          max =..... 72 72 72 72;
        by MARIMP;
        class TRTPN STRAT1N STRAT2N STRAT3N NOICE1_0 NOICE1_4 NOICE1_8 NOICE1_12;
        monotone regression;
        MNAR model (W4 /modelobs=(NOICE1_4="1"));
        MNAR model (W8 /modelobs=(NOICE1_8="1"));
        MNAR model (W12 /modelobs=(NOICE1_12="1"));
        var TRTPN STRAT1N STRAT2N STRAT3N BASE W4 W8 W12;
run;
```

10.3.2.6. Step 6: Analysis Step

Each of the imputations will be analyzed using an ANCOVA model to fit the percentage change from baseline in the PASI score at Week 12 on the FAS in each imputed dataset. Further details (including code) are provided in Section 10.3.3.

10.3.2.7. Step 7: Combining Step (Rubin's Rule)

SAS Proc MIANALYZE will be used to combine the 10 to 1000 point estimates (dependent on estimand) for the difference in mean change from baseline between treatments and standard errors, allowing appropriate statistical inference as described below:

```
PROC MIANALYZE DATA=DATIN ALPHA=0.1;
  MODELEFFECTS ComProbDiff;
  STDERR StdErr;
  ODS OUTPUT ParameterEstimates=DATOUT;
RUN;
```

Note that for the analysis of the FDA, alpha needs to be specified as 0.1; if not specified (such as for the analyses of the PMDA and agencies other than the FDA) then the alpha level of 0.05 will be applied as standard.

10.3.2.8. Seeds to be Used for Imputation

Step	Seed
Initial MAR	365897
Monotone MAR (Primary estimand)	436987
Monotone MNAR (Primary estimand)	912778

10.3.3. Analysis of Estimands for the Primary Endpoint

10.3.3.1. Analysis of the Primary Estimand

The derivation of PASI score is described in Section 10.2.1.

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 (region, body weight at baseline category, baseline psoriatic arthritis status, and previous biologic use) used for the randomization at baseline as fixed factors. The covariance parameters will be estimated by restricted maximum likelihood method, and the degrees of freedom will be calculated using the procedure of Kenward and Roger (1997). 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 (see Section 10.3.2.7) as a single estimate of treatment difference presented together with 90% and 95% CIs.

Example code for ANCOVA:

```
ods output lsmeans=LSMEANS diffs=DIFFS covparms= SOLF1;
proc mixed data = DATIN method = reml ;
   by MNARIMP;
   class TRTPN(ref="1") STRAT1N STRAT2N STRAT3N STRAT4N;
   model CHG = TRTPN STRAT1N STRAT2N STRAT3N STRAT4N / solution cl covb ddfm=KR s;
   lsmeans TRTPN / pdiff cl alpha=0.1; *
run;
```

**alpha=0.05 for the PMDA analysis*

Equivalence will be concluded for the FDA if the 90% CI at Week 12 falls entirely within the predefined equivalence margin of ±10%. Equivalence will be concluded for the PMDA and other agencies if the 95% CI at Week 12 falls entirely within the predefined equivalence margin of ±13%. See Section 10.1 for the statistical hypotheses corresponding to the primary efficacy endpoint.

10.3.3.2. Analysis of the Secondary and Tertiary Estimands

The secondary and tertiary estimands for the primary efficacy endpoint will be analyzed similarly to the primary estimand. 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 Rubin's rules (see Section 10.3.2.7) as a single estimate of treatment difference presented together with 90% and 95% CIs.

10.3.4. Sensitivity and Supportive Analyses

The following sensitivity and supportive measures in Table a will also be conducted:

Table a. Sensitivity and Supportive Measures

Analysis Set	Modelling Method	Data Handling
Sensitivity Analyses Performed on Primary Estimand		
FAS	ANCOVA model (See Section 10.3.3.1)	Tipping Point Analysis.
	ANCOVA model (See Section 10.3.3.1)	Considering all visit data (data obtained on-site and data obtained remotely)
	MMRM (See Section 10.3.4.2)	No imputation, analyzed as observed. Available data occurring under ICE5 to be handled under hypothetical strategy will be set to missing and will not be imputed.
Supportive Analyses Conducted on Primary, Secondary, and Tertiary 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. This modelling method will be the same as the primary efficacy analysis.	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; PASI, Psoriasis Area and Severity Index; PPS, Per-Protocol Set

Further details on these analyses are provided in the following sections. As with the primary and secondary estimands, where MI is used, modelled results will be combined using Rubin's rules (PROC MIANALYZE) for tabulation.

10.3.4.1. Tipping Point Analysis

If clinical equivalence is observed in the primary estimand, a two-dimensional tipping point analysis will be conducted, assessing different levels of delta shift for the imputation in each treatment group. The base dataset will be the primary estimand with the initial MAR and composite strategy imputation implemented; the tipping point will then assess the effects of delta shift on the monotone MAR imputation employed for the primary estimand.

For each level of delta shift, the LSMeans for each treatment group along with the difference between treatments and 90% and 95% CIs for the difference will be presented. A heat plot will additionally be presented showing the levels of tip for each delta shift.

Example code for tipping point:

```
proc mi data=DATIN out=DATOUT seed=XXXXXX nimpute=10 min = . . . . . 0 0 0 0 max =..... 72 72 72
72 minmaxiter=10000;
        by _IMPUTATION_;
        class TRTP STRAT1N STRAT2N STRAT3N STRAT4N;
        monotone reg;
        mnar adjust(W4 / shift=&sj  adjustobs=(TRTP="Bmab 1200"));
        mnar adjust(W4 / shift=&st  adjustobs=(TRTP="Stelara"));
        mnar adjust(W8 / shift=&sj  adjustobs=(TRTP="Bmab 1200"));
        mnar adjust(W8 / shift=&st  adjustobs=(TRTP="Stelara"));
        mnar adjust(W12 / shift=&sj  adjustobs=(TRTP="Bmab 1200"));
        mnar adjust(W12 / shift=&st  adjustobs=(TRTP="Stelara"));
        var TRTP STRAT1N STRAT2N STRAT3N STRAT4N BASE W4 W8 W12;
run;
```

10.3.4.2. Mixed Effect Model for Repeated Measures

The primary estimand will be analyzed using an MMRM including changes from baseline at Weeks 4, 8, 12, and 16 as responses. For this analysis, available data occurring under ICE5 to be handled under hypothetical strategy will be set to missing and will not be imputed.

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 together with 90% CIs.

While applying the model, if convergence criteria not met with unstructured covariance matrix, then below mentioned covariance matrix will be applied to achieve convergence of the model. The matrix with the minimum AIC criteria will be selected for the further analysis.

- Ar(1) – Autoregressive (1)
- ARH (1) – Heterogeneous AR (1)
- TOEP – Toeplitz
- TOEPH – Heterogeneous TOEP

Example code for MMRM:

```
ods output diffs=DIFFS lsmeans=LSMEANS tests3=EFFECTS;
proc mixed data = DATIN method = reml;
        class TRTPN(ref="1") STRAT1N STRAT2N STRAT3N STRAT4N AVISITN SUBJID.;
        model PCHG = TRTPN STRAT1N STRAT2N STRAT3N STRAT4N AVISITN BASE
                        TRTPN*AVISITN / ddfm=KR solution ;
        repeated AVISITN /  subject=SUBJID type=UN r rcorr ;
        lsmeans TRTPN*AVISITN / pdiff=all cl alpha=0.1;*
run ;

*alpha=0.05 for PMDA analysis
```

10.3.5. Subgroup Analysis of the Primary Estimand

To evaluate the consistency in the primary efficacy endpoint over demographic and baseline characteristics, exploratory subgroup analyses will be performed. The subgroups are defined in Section 8.6. The difference in LSMeans and the respective two-sided 90% and 95% CIs based on the ANCOVA modelling will be used for all subgroup comparisons. In addition, the p-values for the interaction of the treatment groups and subgroups will also be provided, wherever appropriate. Forest plots will additionally be presented to provide a visual comparison of the differences in effect on equivalence between subgroups.

10.4. Secondary Efficacy Endpoints and Analyses

The high-level handling approaches for the secondary endpoints are as follows:

Table b. Secondary Efficacy Endpoint Handling

Endpoint	Analysis Set	Modelling Method	Data Handling
PASI			
Percentage change from baseline in the PASI score at Weeks 4, 8, and 16	FAS and PPS	ANCOVA	As per primary, secondary and tertiary estimands.
PASI 50, PASI 75, and PASI 90 relative to baseline at Weeks 4, 8, 12, and 16	FAS and PPS	CMH test	As per primary, secondary and tertiary estimands.
Raw PASI scores at Weeks 4, 8, 12, and 16	FAS	MMRM	Treatment policy approach for all ICEs except ICE5 (hypothetical – set available data to missing); No imputation of missing data
AUECs of PASI score from baseline to Week 12	FAS and PPS	ANCOVA	As per primary, secondary and tertiary estimands.
(Percentage) change from baseline in PASI score to Weeks 4, 8, 12, and 16.	FAS	Descriptive statistics	Treatment policy approach; No imputation of missing data
(Percentage) change from baseline in PASI score to Weeks 20 and 28. Includes raw scores	FAS2	Descriptive statistics	Treatment policy approach; No imputation of missing data
(Percentage) change from baseline in PASI score to Weeks 20, 28, 40 and 52. Includes raw scores	FAS3	Descriptive statistics	Treatment policy approach; No imputation of missing data
PASI 50, PASI 75, and PASI 90 relative to baseline at Weeks 20 and 28	FAS2	Frequency count, percentage	Treatment policy approach; No imputation of missing data
PASI 50, PASI 75, and PASI 90 relative to baseline at Weeks 20, 28, 40 and 52	FAS3	Frequency count, percentage	Treatment policy approach; No imputation of missing data

Endpoint	Analysis Set	Modelling Method	Data Handling
sPGA			
sPGA response of cleared or almost clear/minimal (PGA score of 0 or 1) at Weeks 4, 8, 12, and 16	FAS and PPS	CMH test	As per primary, secondary and tertiary estimands.
Change from baseline in sPGA to Weeks 4, 8, 12, 16, 20, 28, 40 and 52	FAS	Up to Week 16: Descriptive statistics	Treatment policy approach; No imputation of missing data
	FAS2	At Weeks 20 and 28: Descriptive statistics	Treatment policy approach; No imputation of missing data
	FAS3	At Weeks 20, 28, 40 and 52: Descriptive statistics	Treatment policy approach; No imputation of missing data
BSA			
Change from baseline in affected BSA at Weeks 4, 8, 12, 16, 20 28, 40 and 52	FAS	Up to Week 16: MMRM	Treatment policy approach for all ICEs except ICE5 (hypothetical – set available data to missing); No imputation of missing data
	FAS2	At Weeks 20 and 28: Descriptive analysis	Treatment policy approach; No imputation of missing data
	FAS3	At Weeks 20, 28, 40 and 52: Descriptive statistics	Treatment policy approach; No imputation of missing data
DLQI			
Change from baseline in QoL as measured by DLQI scores at Weeks 4, 8, 12, 16,20 28, 40 and 52	FAS	Up to Week 16: MMRM	Treatment policy approach for all ICEs except ICE5 (hypothetical – set available data to missing); No imputation of missing data
	FAS2	At Weeks 20 and 28: Descriptive analysis	Treatment policy approach; No imputation of missing data
	FAS3	At Weeks 20, 28, 40 and 52: Descriptive statistics	Treatment policy approach; No imputation of missing data

10.4.1. Percentage change from baseline in the PASI score at Weeks 4, 8, and 16

Analysis of percentage change in the PASI score at Weeks 4, 8 and 12 is additionally included in the sensitivity analysis of the primary efficacy endpoint using MMRM (see Section 10.3.4.2). Further to that the secondary efficacy analysis of percentage change at each of Week 4, 8 and 16 will be analyzed for the primary, secondary and tertiary estimands on the FAS using the same analysis method as described in Sections 10.3.3.1 and 10.3.3.2.

10.4.2. PASI 50, PASI 75, and PASI 90 relative to baseline at Weeks 4, 8, 12, and 16

Section 10.2.2 describes the derivation of PASI 50, PASI 75 and PASI 90. PASI 50, PASI 75 and PASI 90 response will be derived based on the multiple imputed primary, secondary and tertiary estimands for the PASI score.

Each of these 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 90% and 95% CIs, 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.

Example code for CMH test:

```
ods output commonpdiff=cmh;
proc freq data=input-dataset;
      tables STRAT1N*STRAT2N*STRAT3N*STRAT4N*TRTPN*Response / alpha=0.05 CMH
RISKDIFF(Common);
run;
```

10.4.3. Raw PASI scores at Weeks 4, 8, 12 and 16

Raw PASI scores are described in Section 10.2.1. Raw PASI scores at Weeks 4, 8, 12 and 16 will be analyzed in the same manner as the sensitivity analysis of the primary efficacy endpoint using MMRM (see Section 10.3.4.2) on the FAS.

10.4.4. AUECs of PASI score from Baseline to Week 12

Derivation of AUEC of PASI score is described in Section 10.2.3. AUECs of PASI score from Baseline to Week 12 will be analyzed for the primary, secondary and tertiary estimands on the FAS using the same analysis method as described in Sections 10.3.3.1 and 10.3.3.2.

10.4.5. Descriptive Statistics Related to PASI Score

The following secondary efficacy endpoints will be analyzed descriptively. For all descriptive analyses, a treatment policy approach will be used for all ICEs, with no imputation of missing data.

- (Percentage) change from baseline in PASI score to Weeks 4, 8, 12, and 16, on the FAS by treatment arm
- (Percentage) change from baseline in PASI score and raw PASI score to Weeks 20 and 28, on the FAS2 by treatment regimen
- PASI 50, PASI 75, and PASI 90 relative to baseline at Weeks 20 and 28, on the FAS2 by treatment regimen
- (Percentage) change from baseline in PASI score and raw PASI score to Weeks 20, 28, 40 and 52, on the FAS3 by treatment regimen
- PASI 50, PASI 75, and PASI 90 relative to baseline at Weeks 20, 28, 40 and 52, on the FAS3 by treatment regimen.

10.4.6. sPGA response of cleared or almost clear/minimal (PGA score of 0 or 1) at Weeks 4, 8, 12, and 16

Section 10.2.4 describes the derivation of sPGA response. sPGA response will be derived based on the same estimand framework (primary, secondary and tertiary) and multiple imputation procedures as detailed in Section 10.3.

sPGA response will be analyzed using a CMH test, in the same way as detailed in Section 10.4.2.

10.4.7. Descriptive Statistics Related to sPGA

The following secondary efficacy endpoints will be analyzed descriptively. For all descriptive analyses, a treatment policy approach will be used for all ICEs, with no imputation of missing data.

- Change from baseline in sPGA to Weeks 4, 8, 12, and 16, on the FAS by treatment arm
- Change from baseline in sPGA to Weeks 20 and 28, on the FAS2 by treatment regimen.
- Change from baseline in sPGA to Weeks 20, 28, 40 and 52, on the FAS3 by treatment regimen.

10.4.8. Change from Baseline in Affected BSA at Weeks 4, 8, 12, 16, 20, 28, 40 and 52

Affected BSA is described in Section 10.2.5. Change from baseline in affected BSA at Weeks 4, 8, 12 and 16 will be analyzed in the same manner as the sensitivity analysis of the primary efficacy endpoint using MMRM (see Section 10.3.4.2) on the FAS.

Data obtained from remote visits will not be included for the analysis. It will be handled as hypothetical strategy and considered as missing (See Section 7.3.2). Analysis considering all data (on-site+remotely) will be provided as sensitivity analysis.

Additionally, at Weeks 20 and 28, change from baseline in affected BSA will be analyzed descriptively on the FAS2 by treatment regimen. Also, at Weeks 20, 28, 40 and 52, change from baseline in affected BSA will be analyzed descriptively on the FAS3 by treatment regimen.

10.4.9. Change from baseline in QoL as measured by DLQI scores at Weeks 4, 8, 12, 16, 20, 28, 40 and 52

DLQI is described in Section 10.2.6. Change from baseline in DLQI at Weeks 4, 8, 12 and 16 will be analyzed in the same manner as the sensitivity analysis of the primary efficacy endpoint using MMRM (see Section 10.3.4.2) on the FAS.

Data obtained from remote visits will not be included for the analysis. It will be handled as hypothetical strategy and considered as missing (See Section 7.3.2). Analysis considering all data (on-site+remotely) will be provided as sensitivity analysis.

Additionally, at Weeks 20 and 28, change from baseline in DLQI will be analyzed descriptively on the FAS2 by treatment regimen. Also, at Weeks 20, 28, 40 and 52, change from baseline in DLQI will be analyzed descriptively on the FAS3 by treatment regimen.

11. Analysis of Pharmacokinetics

The blood samples will be collected for PK analysis to measure ustekinumab serum concentrations from all patients at week 0, 4, and 16 prior to study drug administration. At Weeks 2, 8, 12, 20, 28, 40 and 52 samples will be taken where no dose is received. The PK of ustekinumab will be assessed using a validated bioanalytical method for serum concentration at a central laboratory. It will be specified in a separate method validation report.

- **PK Endpoint**:
  The serum concentration of ustekinumab (Ctrough) at pre-dose over the course of the study for both arms is the main study PK endpoint.

- **Handling of Dropouts, Missing Data or Data below the Lower Limit of Quantification**:
  Missing concentration data for all patients who are administered study drug will be considered as non-informative missing and will not be imputed. No concentration estimates will be provided for missing sample values.

- **Data summarization**
  Serum ustekinumab concentration data will be summarized by each treatment using the following descriptive statistics:

Variable	Summarized with:
serum ustekinumab concentration at each time point	n, number and % BLQ, arithmetic mean, SD, coefficient of variance (CV) %, Geometric mean and CV%, minimum, median and maximum

  CV% = SD/mean in %.

  %BLQ = 100 * (total number of patients who have BLQ values/total number of exposed patients within treatment group, with a PK assessment at each time point).

  Serum ustekinumab concentration data will be listed and descriptively summarized by:
  - Treatment (Bmab 1200, Stelara®) and visit for TP1, on the PKS
  - Treatment regimen (Bmab 1200-Bmab 1200, Stelara®-Bmab 1200, Stelara®-Stelara®) and visit for TP2, on the PKS2
  - Treatment regimen (Bmab 1200-Bmab 1200, Stelara®-Bmab 1200, Stelara®-Stelara®) and visit for TP2 and TP3, on the PKS3.

  Additionally, PK data will also be presented by ADA and nAbs Status up to the timepoint (positive or negative) by treatment arm.

The following figures will be produced:

- Mean ± SD concentration-time profiles combining the curves of all patients, on linear and log-linear scales vs. nominal time for TP1 (PKS), TP2 (PKS2) and TP2+TP3 (PKS3).
- Individual patient profile for concentration data vs. nominal time for TP1 (PKS), TP2 (PKS2) and TP2+TP3 (PKS3).

12. Analysis of Immunogenicity

Blood samples for evaluation of presence of ADAs will be taken from all subjects at predose for study treatment days (Baseline, Week 4, and Week 16) and once at Weeks 2, 8, 12, 20, 28, 40 and at Week 52/EOS.

The ADA and Nab levels will be measured using validated methods at the central laboratory. In case of positive results in the ADA evaluation, the ADA titer will be evaluated, also the Nab will be tested. Details of the method validation and sample analysis will be described in the ADA & validation reports and ADA & Nab analysis report.

Incidence of ADAs to Bmab 1200 and Stelara® and their neutralizing potential will be summarized for the SAF, SAF2 and SAF3 using frequency of ADA-positive and Nab positive samples for each timepoint and the following treatment periods:TP1 will be presented for the SAF, TP2 will be presented for the SAF2, and TP2+TP3 will be presented for the SAF3.

The frequency of ADA occurrence will be presented at each assessment, including 90% Clopper-Pearson exact CIs around the point estimate for each treatment group. The titer of ADA positive will also be summarized by treatment group/regimen using descriptive statistics, including arithmetic and geometric mean, SD, coefficient of variation and geometric coefficient of variation, minimum [min], maximum [max], and median, plus percentage of concentration values below the lower limit of quantification.

Exploratory analyses assessing the effects of ADA and Nab incidence will be conducted for the primary estimand of the primary efficacy endpoint (percentage change from baseline in PASI score at Week 12) on the SAF. The primary analysis of the primary estimand will be reproduced for the SAF, split by ADA positive subjects up to Week 12, ADA Negative subjects up to Week 12, Nab positive subjects up to Week 12, and Nab Negative subjects up to Week 12. At each timepoint, the subgroup will include all subjects in the SAF that achieve the ADA/Nab status up to and including the visit presented. For example, ADA positive subgroup up to Week 12 will include all subjects that are shown to be ADA positive up to and including Week 12; if the subject becomes ADA positive at a later point they will not be included in the Week 12 ADA positive subgroup.

Additionally, this efficacy analysis will be implemented using a forest plot, presenting the difference in proportion for the subgroups of

a) ADA positive up to and including Week 12,

b) ADA negative up to and including Week 12,

c) Nab positive up to and including Week 12,

d) Nab negative up to and including Week 12 and

e) All Subjects in the SAF.

An additional exploratory analysis will be conducted to assess the effects of ADA incidence on the concentration data. The summary of ustekinumab serum concentrations will be reproduced on the PKS, similarly split by ADA Positive, ADA Negative, Nab Positive, and Nab Negative subjects up to Week 12. Additionally, mean ustekinumab serum concentrations on the linear scale will be presented using a line graph by visit, separately presented for the following 3 ADA subgroups: a) ADA positive at any point up to and including Week 12, b) ADA negative at all timepoints up to and including Week 12, and c) All subjects in the PKS.

13. Safety

The safety data will be summarized for all patients in the SAF, SAF2 and SAF3. Safety will be assessed based on exposure and compliance, AEs, laboratory evaluations, vital signs, ECG, physical examination.

13.1. Extent of Exposure

The total number of doses administered, cumulative dose (mL) administered and total treatment duration will be summarized descriptively for all subjects in the SAF/SAF2/SAF3, by treatment arm/regimen and treatment period. Additional to the summaries for each treatment period, a summary of all patients treated in TP2 across both TP1 and TP2, and a summary of all patients treated in TP3 across TP1 and TP2, TP2 and TP3, and TP1, TP2 and TP3 together will be presented. Patients with total dose administered that is less than expected will be additionally listed.

Treatment duration in days will be derived as follows:

- Treatment Duration = Last Treatment Intake Date – First Treatment Intake Date + 1.

13.2. Treatment Compliance

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. Percent compliance will be calculated as below.

- Percent compliance = (cumulative dose administered / cumulative dose planned)*100

The percent compliance will be summarized with quantitative descriptive statistics and with frequency and percentages of subjects with <80%, 80-<90%, and 90-100% compliance. Compliance will be presented by treatment arm/regimen for TP1 on the SAF, TP2 on the SAF2, TP3 on the SAF3, TP1 plus TP2 on the SAF2, TP1+TP2+TP3 for the SAF3 and additionally for the whole study on the SAF.

13.3. Adverse Events

Adverse events will be coded into PT and SOC according to MedDRA (see Section 8.2.7 for version). The severity of AEs will be graded according to the CTCAE v5.0.

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. Partial or missing AE start dates will be imputed as described in Section 8.3.1.1. Treatment emergence will be assigned for each treatment period, TP1, TP2 and TP3, based on the start date of the AE versus the first dose date during TP1 (date of dose at Baseline (Day 1)), during TP2 (date of dose at Week 16), and during TP3 (date of dose at Week 28).

Treatment-related TEAEs are defined as events being judged by the investigator to be related to study treatment. AEs with relationship recorded as “Possibly”, “Probably” and “Definitely” related will be regarded as treatment-related. For summaries, AEs with missing relationship to study treatment will be counted as ‘Related’. Adverse events with missing CTCAE severity grade will not have the grade imputed.

A post-treatment AE will be defined as any AE starting 12 weeks or more after last dose of study treatment.

If a patient experiences more than 1 occurrence of the same AE, the occurrence with the greatest CTCAE severity grade and the closest relationship with the study treatment will be used in the summary tables. All AEs will be included in the data listings.

With the exception of post-treatment AEs, unless otherwise specified only TEAEs will be included in the summary tables, but all AEs will be displayed in the data listings. Non-TEAEs will be flagged in the listings. Summary tables will present the number and percentage of patients and number of events. Summaries by worst CTCAE severity grade or maximum relationship to study treatment will not show the number of events. Adverse Events are sorted by descending frequency of SOC and then, within a SOC, by descending frequency of PT. In case of identical frequency, sorting will be done alphabetically.

In the following summaries discussed, AEs will be presented by the following treatment periods/analysis sets:

- TP1, by treatment arm on the SAF
- TP2, by treatment regimen on the SAF2
- TP2 and TP3 combined, by treatment regimen on the SAF3.

An overall summary of AEs by treatment group/regimen and treatment period will show the number and percentage of patients and number of events reporting at least one:

- AE
- TEAE
- TEAEs with CTCAE severity grade 3 or higher
- Treatment-related TEAE
- Treatment-related TEAE with CTCAE severity grade 3 or higher
- Serious TEAE
- Serious treatment-related TEAE
- TEAE leading to study treatment discontinuation
- Treatment-related TEAE leading to study treatment discontinuation
- TEAE of special interest
- TEAE leading to Treatment interruption
- TEAE leading to death

The following summaries will be provided for TEAEs overall, by SOC and PT for each treatment group/regimen and treatment period, presenting the number and percentage of patients and number of events. A patient is counted once at the SOC level and once at each PT within the SOC level:

- All TEAEs
- TEAEs with worst CTCAE Severity Grade
- TEAEs with maximum relationship
- TEAEs with CTCAE severity grade 3 or higher
- Treatment-related TEAEs
- Treatment-related TEAEs with CTCAE severity grade 3 or higher
- Serious TEAEs
- Treatment related Serious TEAEs
- TEAEs leading to study treatment discontinuation
- TEAEs of Special Interest
- TEAEs leading to interruption of study medication.
- TEAEs leading to death
- Post-treatment AEs

For the summary of TEAEs with worst CTCAE grade by SOC and PT, a patient is counted once at the highest (worst) CTCAE severity grade for which the event occurred at the SOC level and the highest (worst) CTCAE severity grade for each unique PT within that SOC level. Therefore, patients may only contribute once to each PT and once to each SOC level.

For the summary of TEAEs with maximum relationship by SOC and PT, a patient is counted once at the highest relationship level for which the event occurred at the SOC level and the highest relationship level for each unique PT within that SOC level. Therefore, patients may only contribute once to each PT and once to each SOC level.

Data listings will be provided for

- All AEs,
- SAEs
- AEs leading to study treatment discontinuation,
- AEs of special interest,
- AEs leading to death.

13.4. Laboratory Evaluations

Laboratory test samples for hematology, blood chemistry and urinalysis will be assessed locally on designated assessment days as detailed in the Schedule of Assessments (Section 4.6). Laboratory assessment parameters are as follows, to be assessed at Screening, Baseline, Weeks 4, 8, 12, 16, 20, 28, 40 and 52:

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, hs-CRP, 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

Separate summary tables and listings will be produced for each of the separate groups above (e.g. separate table for hematology, chemistry and urinalysis). Summary tables will be provided for each laboratory parameter by treatment group/regimen and visit, considering actual values and changes from baseline. Baseline (and change from baseline) is defined as per Section 8.2.4.

Summaries will be presented for the following treatment periods:

- TP1, by treatment arm on the SAF
- TP2, by treatment regimen on the SAF2
- TP2 and TP3, by treatment regimen on the SAF3.

Laboratory values will be categorized as clinical grade (low/normal/high) according to normal ranges. Shifts from baseline clinical grade (low/normal/high) to last post-baseline visit will be presented by treatment group/regimen for hematology, chemistry and urinalysis. In addition, shift table will be provided from baseline clinical grade to last on-treatment and worst on-treatment grade by treatment group/regimen. For these shift summaries, for the last on-treatment summary only scheduled visits will be taken; for the worst on-treatment summaries unscheduled assessments will be included in the assessment of worst. Both worst low and worst high will be summarized. “Missing” value will remain as a separate category.

13.5. Vital Signs

Vital signs include body temperature, systolic and diastolic blood pressure, pulse rate and respiratory rate. Vital signs will be evaluated on the assessment days indicated in the Schedule of Activities (Section 4.6). Temperature will be displayed in °C. If collected in °F, values will be converted by using °C= (°F – 32) x 5/9.

Summary tables will be provided for each vital signs parameter by treatment arm/regimen and visit, considering actual values and changes from baseline.

Summaries will be presented for the following treatment periods:

- TP1, by treatment arm on the SAF
- TP2, by treatment regimen on the SAF2
- TP2 and TP3, by treatment regimen on the SAF3.

Additionally, vital signs values will be categorized as clinical grade (low/normal/high) according to normal ranges. Shifts from baseline clinical grade (low/normal/high) to last post-baseline visit will be presented by treatment group/regimen. A shift table will be provided presenting baseline clinical grade to last on-treatment and worst on-treatment grade by treatment group/regimen. Similar to labs, for the last on-treatment summary only scheduled visits will be taken; for the worst on-treatment summaries unscheduled assessments will be included in the assessment of worst. Both worst low and worst high will be summarized. “Missing” value will remain as a separate category.

13.6. ECG

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Electrocardiogram results together with the classification of within normal limits, abnormal NCS, and abnormal CS with a description for abnormal findings will be summarized and listed by treatment arm/regimen on the SAF.

Shift tables from baseline against the worst post-baseline ECG interpretation will be presented. The following is the hierarchy for ECG interpretation result (starting from the worst interpretation): Abnormal CS, Abnormal NCS and Normal.

Summaries will be presented for the following treatment periods:

- TP1, by treatment arm on the SAF
- TP2, by treatment regimen on the SAF2
- TP2 and TP3, by treatment regimen on the SAF3.

13.7. Physical Examination

A complete physical examination (Head and Neck, Dermatologic, Respiratory, Cardiovascular, gastrointestinal, Neurologic and other) will be performed at all study visits. Body systems are classified as within normal, abnormal NCS, and abnormal CS with a description for abnormal findings. A symptom-directed physical examination will be performed only if clinical indicated.

The physical examination will be summarized and listed by treatment arm/regimen on the SAF.

13.8. Other Safety

13.8.1. TB Clinical monitoring

At all study visits, patients will be monitored for the clinical signs and symptoms of TB. An additional IGRA or Chest X-ray may 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 each visit.

All the data of TB clinical monitoring will be listed for each assessment by treatment arm/regimen on the SAF.

14. Interim Analyses

No interim analysis has been planned.

15. Changes from Analysis Planned in Protocol

NA.

16. Reference List

1. International Conference on Harmonization of Technical Requirements for Registration of Pharmaceuticals for Human Use, ICH Harmonized Tripartite Guideline, Statistical Principles for Clinical Trials (E9), 5 February 1998.
2. International Conference on Harmonization of Technical Requirements for Registration of Pharmaceuticals for Human Use, ICH Harmonized Tripartite Guideline, Structure and Content of Clinical Study Reports (E3), 30 November 1995.
3. SAS® Version 9.4. SAS Institute Inc., Cary, NC
4. Leonardi, Craig L., et al. "Efficacy and safety of ustekinumab, a human interleukin-12/23 monoclonal antibody, in patients with psoriasis: 76-week results from a randomised, double-blind, placebo-controlled trial (PHOENIX 1)." The Lancet 371.9625 (2008): 1665-1674.
5. Papp, Kim A., et al. "Efficacy and safety of ustekinumab, a human interleukin-12/23 monoclonal antibody, in patients with psoriasis: 52-week results from a randomised, double-blind, placebo-controlled trial (PHOENIX 2)." The Lancet 371.9625 (2008): 1675-1684.
6. Qu, Y.; Dai, B.; Return-to-baseline multiple imputation for missing values in clinical trials; https://doi.org/10.48550/arXiv.2111.09423

17. Programming Considerations

All TFLs, and statistical analyses will be generated using SAS for Windows, Release 9.4 or higher (SAS Institute Inc., Cary, NC, USA).

17.1. General Considerations

- A separate SAS program will be created for each unique output.
- Each output will be stored in a separate file.
- Output files will be delivered as single RTF files and combined PDF files.
- Numbering of TFLs will follow ICH E3 guidance.

17.2. Table, Figure, and Listing Format

17.2.1. General

- All TFLs will be produced in landscape format on A4 paper size, unless otherwise specified.
- All TFLs will be produced using the Courier New font, size 8.
- The data displays for TFLs will have a minimum blank 1-inch margin on all 4 sides.
- Headers and footers for figures will be in Courier New font, size 8.
- Legends will be used for all figures with more than one variable, group, or item displayed.
- TFLs will be in black and white (no color), unless otherwise specified.
- Specialized text styles, such as bolding, italics, borders, shading, and superscripted and subscripted text, will not be used in the TFLs, unless otherwise specified. On some occasions, superscripts 1, 2, or 3 may be used (see below).
- Only standard keyboard characters will be used in the TFLs. Special characters, such as non-printable control characters, printer-specific, or font-specific characters, will not be used. Hexadecimal-derived characters will be used, where possible, if they are appropriate to help display math symbols (e.g., µ). Certain subscripts and superscripts (e.g., cm^2 , kg/m^2) will be employed on a case-by-case basis.
- Mixed case will be used for all titles, footnotes, column headers, and programmer-supplied formats, as appropriate.

17.2.2. Headers

All outputs will have the following header at the top of each page:

Biocon Biologics UK Limited Protocol BM12H-PSO-03-G-02 [redacted]
[redacted]*)*
DRY/DRAFT/FINAL RUN

17.2.3. Display Titles

Each Tables, Figures and listings (TFLs) will be identified by the designation and a numeral. (i.e., Table 14.1.1). A decimal system (x.y and x.y.z) are used to identify TFLs with related contents. The title will be

centered and single spaced (if possible). A solid line spanning the margins will separate the display titles from the column headers. There will be one blank line between the title and the solid line.

Table <x.y.z>: <Title> - Safety Population

17.2.4. Column Headers

- Column headings will be displayed immediately below the solid line described above in initial upper-case characters.
- For numeric variables, include 'unit' in column or row heading when appropriate.
- Analysis population sizes will be presented for each treatment arm in the column heading as (N=xx) (or in the row headings, if applicable). This is distinct from the 'n' used for the descriptive statistics representing the number of patients with data available in the analysis population.

17.2.5. Body of the Data Display

17.2.5.1. *General Conventions*

Data in columns of a table or listing are formatted as follows:

- Alphanumeric values will be left-justified;
- Whole numbers (e.g., counts) will be right-justified; and
- Numbers containing fractional portions will be decimal aligned.

17.2.5.2. *Table Conventions*

- Units will be included where available
- For categorical parameters, all categories will be presented in the table, even if n=0 for all treatment groups in a given category. For example, the frequency distribution for symptom severity would appear as:

Severity	N
severe	0
moderate	8
mild	3

  Where percentages are presented in these tables, zero percentages will not be presented and so counts of 0 will be presented as 0 and not as 0 (0%).
- An Unknown or Missing category will be added to each parameter for which information is not available for 1 or more patients.
- Unless otherwise specified, the estimated mean, median, first and third quartile for a set of values will be printed out to 1 more decimal place than the original values, and SD will be printed out to 2 more decimal places than the original values. The minimum and maximum will report the same decimal places as the original values.
- P-values will be output in the format: '0.xxxxx', where xxxxx is the value rounded to 5 decimal places. Every p-value less than 0.00001 will be presented as <0.00001. If the p-value is returned as >0.999, then present as >0.999.

- Percentage values will be printed to one decimal place, in parentheses with no spaces, one space after the count [e.g., 7 (12.8), 13 (5.4)]. If a value rounds down to 0.0 it will be displayed as '<0.1. Unless otherwise noted, for all percentages, the number of patients in the analysis population for respective treatment group will be the denominator. Percentages after zero counts will not be displayed and percentages equating to 100% will be presented as 100, without decimal places.
- Tabular display of AEs and medical history will be presented by SOC and PT and sorted by descending frequency of SOC and then, within a SOC, by descending frequency of PT. Tabular display of prior/concomitant medications will be presented by ATC levels 2 and 4 and sorted by descending frequency of ATC level 2 and then, within an ATC level 2, by descending frequency of ATC level 4. In case of identical frequency, sorting will be done alphabetically.
- Missing descriptive statistics or p-values which cannot be estimated will be reported as '-'.
- For categorical summaries (number and percentage of patients) where a patient can be included in more than one category, a footnote or programming note will be added describing whether the patient is included in the summary statistics for all relevant categories or just 1 category as well as the selection criteria.
- The order of treatment arms in the tables will be 'Bmab 1200' first, 'Stelara' second, followed by a 'Total' column (if applicable).

17.2.5.3. *Listing Conventions*

- Listings will be presented by treatment arm ('Not Randomized' first [where applicable] then 'Bmab 1200' then 'Stelara'), patient number, visit or collection day/time (if applicable).
- Dates will be printed in SAS DATE9.format ('ddMMMyyyy': 01JUL2000). Missing portions of dates will be represented on data listings as dashes (--JUL2000).
- All observed time values will be presented using a 24-hour clock HH:MM or HH:MM:SS format (e.g., 11:26:45, or 11:26). Time will only be reported if it was measured as part of the study
- Units will be included where available

17.2.5.4. *Figure Conventions*

- Unless otherwise specified, for all figures, study visits/time will be displayed on the X-axis and endpoint (e.g., mean change from Baseline) values will be displayed on the Y-axis

17.2.6. Footnotes

- A solid line spanning the margins will separate the body of the data display from the footnotes.
- All footnotes will be left justified with single-line spacing immediately below the solid line underneath the data display.
- Each new footnote will start on a new line, where possible
- Patient specific footnotes are avoided, where possible
- Footnotes will be used sparingly and add value to the TFL. If more than six lines of footnotes are planned, then a cover page is strongly recommended to be used to display footnotes, and only those essential to comprehension of the data will be repeated on each page

- The last 3 lines of the footnote section will be standard source lines that indicate the Analysis Dataset Model (ADaM) source, the listing source (for tables only), the data cut-off date, name of the program used to produce the data display, and the date/time the program was run.

  Source: AdaM dataset: xxx, Listing: xxxx
  Data Cut-off date: DDMMMYYYY
  Program name: xxxxx.sas, Run date/time: DDMMMYYYY HH:MM

- Sources and/or cross-references in footnotes will use the keyword prefix (in singular form) for each reference and will be separated by a comma when multiple cross-references are displayed. Example: Listing 16.2.4.1.1, Listing 16.2.4.1.2, Listing 16.2.4.2.1

- All outputs will have Page n of N at the bottom right corner of each page. TFLs are internally paginated in relation to the total length (i.e., the page number will appear sequentially as page n of N, where N is the total number of pages in the output).

18. Quality Control

SAS programs are developed to produce output such as analysis data sets, summary tables, data listings, figures or statistical analyses. An overview of the development of programs is detailed in [redacted], Conducting the Transfer of Biostatistical [redacted] the SAS Programming and Validation Plan describes the quality control procedures that are performed for all SAS programs and output. Quality control is defined here as the operational techniques and activities undertaken to verify that the SAS programs produce the output by checking for their logic, efficiency and commenting and by review of the produced output.

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14.2.3.6	Individual Time-Concentration Profiles (TP2)	PKS2
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22. Shells

TFL shells will be provided as a separate document.

23. Appendices

Not applicable.