24 July 2025
EMA/268909/2025
Committee for Medicinal Products for Human Use (CHMP)

Assessment report

Usrenty

International non-proprietary name: ustekinumab

Procedure No. EMEA/H/C/006794/0000

Note

Assessment report as adopted by the CHMP with all information of a commercially confidential nature deleted.

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List of abbreviations

ACE	Acid Capture Elution
ADA	Antidrug Antibody
ADR	Adverse Reaction
AE	Adverse Event
AESI	Adverse Event of Special Interest
ALT	Alanine Transaminase
ANCOVA	Analysis of Covariance
AST	Aspartate Aminotransferase
ATC	Anatomical Therapeutic Chemical
AUC	Area Under the Concentration-Time Curve
AUEC	Area Under Effect Curve
BBL	Biocon Biologics Limited
BLQ	Below Limit of Quantification
BMI	Body Mass Index
BSA	Body Surface Area
CI	Confidence Interval
CL	Clearance
Cmax	Maximum Observed Drug Concentration
COVID-19	Coronavirus Disease 2019
CRO	Clinical Research Organisation
CS	Clinically Significant
CSR	Clinical Study Report
CTCAE	Criteria for Adverse Events
Ctrough	Trough Concentration
CV	Coefficient of Variation
DLQI	Dermatology Life Quality Index
DP	Drug Product
DS	Drug Substance
ECG	Electrocardiogram
ECL	Electrochemiluminescence
ECLIA	Electrochemiluminescence Immunoassay
ELISA	Electrochemiluminescence immunoassay
EOS	End of Study
EPAR	European Public Assessment Report
FAS	Full Analysis Set
FPR	False positive rate
GLSM	Geometric Least Squares Mean
HPC	High Positive Control
HQC	High Quality Control
ICE	Intercurrent Event
ICF	Informed Consent form
iCP	Inhibition Cut Point
IDMC	Independent Data Monitoring Committee
Ig	Immunoglobulin
IMP	Investigational Medicine Product
ISP	Injection Site Pain
IL	Interleukin
IV	Intravenous

Kel	Elimination Rate Constant
LLOQ	Lower Limit of Quantification
LPC	Low Positive Control
LQC	Low Quality Control
LSM	Least Squares Mean
MAA	Marketing Authorisation Application
MCB	Master Cell Bank
MedDRA	Medical Dictionary for Regulatory Activities
MQC	Mid Quality Control
MPC	Mid Positive Control
MSD	Electro-Chemiluminescence Assay on the Mesoscale Discovery (MSD)
NAb	Neutralizing Antibody
n	Number of Subjects with Valid Observations
N	Number of Subjects
NC	Negative Control
NCS	Not clinically Significant
NGNA	N-glycolylneuraminic Acid
NMSC	Nonmelanoma Skin Cancer
PASI	Psoriasis Area and Severity Index
PD	Pharmacodynamics
PFS	Pre-Filled Syringe
PHS Act	Public Health Service Act
PK	Pharmacokinetic
PKS	Pharmacokinetic Set
PL	Parameter Logistic
PMDA	Pharmaceuticals and Medical Devices Agency
PPS	Per-Protocol Set
PRES	Posterior Reversible Encephalopathy Syndrome
PsO	Plaque Psoriasis
PsA	Active Psoriatic Arthritis
PT	Preferred Term
QC	Quality Control
QoL	Quality of Life
rCP	Screening Cut Point
RLU	Relative Light Unit
SAE	Serious Adverse Event
SAF	Safety Set
SAP	Statistical Analysis Plan
SC	Subcutaneous
sCF	Screening Correction Factor
SD	Standard Deviation
SOC	System Organ Class
sPGA	Static Physicians Global Assessment
STAT	Signal Transducer and Activator of Transcription
STP	Switch Treatment Period
SUSARs	Suspected Unexpected Serious Adverse Reactions
t1/2	Apparent Terminal Elimination Half-Life
TB	Tuberculosis
TP	Treatment Period
tCF	Titre Correction Factor

tCP	Titre Cut Point
tlast	Time of the Last Quantifiable Concentration
tmax	Time of the Maximum Observed Concentration
TEAE	Treatment-Emergent Adverse Event
TESAE	Treatment Emergent Serious Adverse Event
Th	T helper
TP	Treatment Period
TYK2	Tyrosine Kinase 2
UC	Ulcerative Colitis
UK	United Kingdom
ULOQ	Upper limit of quantification
URTI	Upper Respiratory Tract Infection
USPI	U.S. Prescribing Information
Vd/F	Apparent Volume of Distribution During the Terminal Phase
Vs	Versus
WCB	Working Cell Bank

1. Executive summary

On 24 July 2025, the Committee for Medicinal Products for Human Use (CHMP) adopted a positive opinion recommending the granting of a marketing authorisation application for the medicinal product Usrenty (ustekinumab) intended for the treatment of plaque psoriasis, paediatric plaque psoriasis, psoriatic arthritis, and Crohn's disease.

Usrenty will be available as a solution for injection for subcutaneous use (45 mg in a vial, 45 mg in pre-filled syringe, and 90 mg in pre-filled syringe) and as a concentrate for solution for infusion (130 mg in a vial). Usrenty (ustekinumab) is a fully human monoclonal antibody composed of an IgG1 heavy chain isotype and a kappa light chain isotype with an approximate molecular weight of 148,600 Daltons. Ustekinumab neutralises IL-12 and IL-23 bioactivity by binding to IL-12/23p40 and preventing IL-12 and IL-23 binding to the IL-12Rβ1 receptor protein expressed on the surface of natural killer (NK) or T cells. Through this mechanism of action, Ustekinumab neutralises IL-12 (Th1) and IL- 23 (Th17) mediated cellular responses.

Usrenty is a biosimilar medicinal product. It is highly similar to the reference product Stelara (ustekinumab), which was authorised in the EU on 15 January 2009.

Data show that Usrenty has comparable quality, safety and efficacy to Stelara (ustekinumab).

The main evidence of bioequivalence of Usrenty was based on 2 studies: BM12H-NHV-01-G-01 (Phase 1) and BM12H-PSO-03-G-02 (pivotal PK Phase 3 study).

The full indications for Usrenty are:

Plaque psoriasis

Usrenty is indicated for the treatment of moderate to severe plaque psoriasis in adults who failed to respond to, or who have a contraindication to, or are intolerant to other systemic therapies including ciclosporin, methotrexate (MTX) or PUVA (psoralen and ultraviolet A) (see section 5.1).

Paediatric plaque psoriasis

Usrenty is indicated for the treatment of moderate to severe plaque psoriasis in children and adolescent patients from the age of 6 years and older, who are inadequately controlled by, or are intolerant to, other systemic therapies or phototherapies (see section 5.1).

Psoriatic arthritis (PsA)

Usrenty, alone or in combination with MTX, is indicated for the treatment of active psoriatic arthritis in adult patients when the response to previous non-biological disease-modifying anti-rheumatic drug (DMARD) therapy has been inadequate (see section 5.1).

Crohn's Disease

Usrenty is indicated for the treatment of adult patients with moderately to severely active Crohn's disease who have had an inadequate response with, lost response to, or were intolerant to either conventional therapy or a TNFα antagonist.

Usrenty should be prescribed and supervised by a physician experienced in the treatment of conditions for which Usrenty is indicated.

Detailed recommendations for the use of this product are described in the summary of product characteristics (SmPC), which will be published on the EMA website in all official European Union languages after the marketing authorisation has been granted by the European Commission.

This report summarises the scientific review leading to the opinion adopted by the Committee for Medicinal Products for Human Use (CHMP).

2. Administrative/regulatory information and recommendations on the procedure

2.1. Information on the product

Product data	
Product name	Usrenty
Active substance	ustekinumab
INN or common name	ustekinumab
Applicant	Biosimilar Collaborations Ireland Limited Unit 35/36, Grange Parade Baldoyle Industrial Estate Dublin 13 D13 R20R IRELAND
EMA product number	EMEA/H/C/006794
ATC code and pharmacotherapeutic group	immunosuppressants, interleukin inhibitors (L04AC05)
Pharmaceutical form(s) and strength (s)	Solution for injection 45 mg (vial and pre-filled syringe), and 90 mg (pre-filled syringe) Concentrate for solution for infusion; 130 mg (vial)
Packaging	pre-filled syringe (glass) and vial (glass)
Package size(s)	1 pre-filled syringe and 1 vial
Route of administration	Intravenous use and Subcutaneous use
Device or diagnostic	Prefilled Single Use Syringe A single use, pre-filled syringe intended to deliver a fixed dose of ustekinumab in two fill volumes of 0.5 mL (45 mg) and 1 mL (90 mg) for subcutaneous administration
Orphan designation	No
Orphan indication status confirmed	Not applicable
PRIME scheme	Not applied for
Type of marketing authorisation granted at opinion	Standard
Legal basis	Article 10(4) of Directive 2001/83/EC
Final indication	Plaque psoriasis Usrenty is indicated for the treatment of moderate to severe plaque psoriasis in adults who failed to respond to, or who have a contraindication to, or are intolerant to other systemic therapies including ciclosporin, methotrexate (MTX) or PUVA (psoralen and ultraviolet A).

Product data	
	Paediatric plaque psoriasis Usrenty is indicated for the treatment of moderate to severe plaque psoriasis in children and adolescent patients from the age of 6 years and older, who are inadequately controlled by, or are intolerant to, other systemic therapies or phototherapies. Psoriatic arthritis (PsA) Usrenty, alone or in combination with MTX, is indicated for the treatment of active psoriatic arthritis in adult patients when the response to previous non-biological disease-modifying anti-rheumatic drug (DMARD) therapy has been inadequate. Crohn's Disease Usrenty is indicated for the treatment of adult patients with moderately to severely active Crohn's disease who have had an inadequate response with, lost response to, or were intolerant to either conventional therapy or a TNFα antagonist.
New active substance status	Not applied for

2.2. Scientific advice

Table 1. Scientific advice and protocol assistance

Date	Topic (quality/ non-clinical/ clinical)	Reference number / Coordinator(s)	Brief summary of the advice
26 March 2020	Quality, Non-clinical, and Clinical	EMEA/H/SA/4410/1/2020/III *Dr Ewa Balkowiec-Iskra, Dr Juha Kolehmainen and Dr Stephan Lehr*	The scientific advice pertained to the following quality, non-clinical, and clinical aspects: • The batch release and stability testing strategy, the reference standard establishment, qualification and characterisation strategy, and the overall proposed analytical similarity strategy. • Non-clinical development plan. • Study design, plan and choice of reference product for a pharmacokinetic study destined to establish pharmacokinetic equivalence between BMab1200 and Stelara in the SC route of administration. • Study design, plan for Phase III safety/efficacy study in moderate to severe plaque psoriasis to demonstrate similarity of safety/efficacy between BMab1200 (PFS) with EU-Approved Stelara (PFS). Strategy for extrapolation to all approved indications and presentations of Stelara.
14 Decem	Quality and	EMA/SA/000015	The scientific advice pertained to the following quality, and

ber 2023	Clinical	5564 *Dr Elisabeth Wischnitzki and Dr Sheila Killalea*	clinical aspects: • Shelf life of Bmab1200 drug product presentations. • Phase I and Phase III neutralizing antibody assessment. • Marketing authorisation application submission strategy.

2.3. Eligibility to the centralised procedure

The applicant Biosimilar Collaborations Ireland Limited submitted on 26 March 2025 an application for marketing authorisation to the European Medicines Agency (EMA) for Usrenty (ustekinumab), through the centralised procedure falling within the Article 3(1) and point 1 of Annex of Regulation (EC) No 726/2004.

The applicant applied for the following indications:

Plaque psoriasis

Usrenty is indicated for the treatment of moderate to severe plaque psoriasis in adults who failed to respond to, or who have a contraindication to, or are intolerant to other systemic therapies including ciclosporin, methotrexate (MTX) or PUVA (psoralen and ultraviolet A) (see section 5.1).

Paediatric plaque psoriasis

Usrenty is indicated for the treatment of moderate to severe plaque psoriasis in children and adolescent patients from the age of 6 years and older, who are inadequately controlled by, or are intolerant to, other systemic therapies or phototherapies (see section 5.1).

Psoriatic arthritis (PsA)

Usrenty, alone or in combination with MTX, is indicated for the treatment of active psoriatic arthritis in adult patients when the response to previous non-biological disease-modifying anti-rheumatic drug (DMARD) therapy has been inadequate (see section 5.1).

Crohn's Disease

Usrenty is indicated for the treatment of adult patients with moderately to severely active Crohn's disease who have had an inadequate response with, lost response to, or were intolerant to either conventional therapy or a TNFα antagonist or have medical contraindications to such therapies.

Crohn's Disease

Usrenty is indicated for the treatment of adult patients with moderately to severely active Crohn's disease who have had an inadequate response with lost response to, or were intolerant to either conventional therapy or a TNFα (*tumour necrosis factor alpha*) antagonist or have medical contraindications to such therapies.

2.4. Legal basis, dossier content and multiples

The legal basis for this application refers to:

Article 10(4) of Directive 2001/83/EC – relating to applications for biosimilar medicinal products.

The application submitted is composed of administrative information, complete quality data, and appropriate non-clinical and clinical data for a similar biological medicinal product.

This application is submitted as a multiple of Yesintek, authorised on 14 February 2025 in accordance with Article 82.1 of Regulation (EC) No 726/2004.

The chosen reference product is:

Medicinal product which is or has been authorised in accordance with European Union provisions in force for not less than 8 years in the EEA:

Product name, strength, pharmaceutical form:	Stelara (ustekinumab): - Solution for injection in vial, 90 mg/ml (45 mg); - Solution for injection in pre-filled syringe, 90 mg/ml (45 mg & 90 mg); - Concentrate for solution for infusion, 5 mg/ml (130 mg)
Marketing authorisation holder:	Janssen-Cilag International NV
Date of authorisation:	15-January-2009
Marketing authorisation granted by:	European Union
Marketing authorisation number:	EU/1/08/494/001, EU/1/08/494/003, EU/1/08/494/004, EU/1/08/494/005

Medicinal product authorised in the European Union/Member States where the application is made for European reference medicinal product:

Product name, strength, pharmaceutical form:	Stelara (ustekinumab): - Solution for injection in vial, 90 mg/ml (45 mg); - Solution for injection in pre-filled syringe, 90 mg/ml (45 mg & 90 mg); - Concentrate for solution for infusion, 5 mg/ml (130 mg)
Marketing authorisation holder:	Janssen-Cilag International NV
Date of authorisation:	15-January-2009
Marketing authorisation granted by:	European Union
Marketing authorisation number:	EU/1/08/494/001, EU/1/08/494/003, EU/1/08/494/004, EU/1/08/494/005

Medicinal product which is or has been authorised in accordance with European Union provisions in force and to which bioequivalence has been demonstrated by appropriate bioavailability studies:

Product name, strength, pharmaceutical form:	Stelara (ustekinumab): - Solution for injection in pre-filled syringe, 90 mg/ml (45 mg),
Marketing authorisation holder:	Janssen-Cilag International NV
Date of authorisation:	15-January-2009
Marketing authorisation granted by:	European Union
Marketing authorisation number:	EU/1/08/494/003,
Bioavailability studies numbers:	BM12H-NHV-01-G-01 (Phase 1), EudraCT no: 2021-006630-39 BM12H-PSO-03-G-02 (Phase 3), EudraCT no: 2021-006668-25

2.5. Information on paediatrics

Not applicable

2.6. Information on orphan market exclusivity

2.6.1. Similarity with authorised orphan medicinal products

Pursuant to Article 8 of Regulation (EC) No 141/2000 and Article 3 of Commission Regulation (EC) No 847/2000, the applicant did not submit a critical report addressing the possible similarity with authorised orphan medicinal products from the start of the procedure because there is no authorised orphan medicinal product for a condition related to the proposed indication.

2.7. Steps taken for the assessment of the product

The rapporteur and Co-rapporteur appointed by the CHMP were:

rapporteur:	Jan Mueller-Berghaus
Co-rapporteur:	Christophe Focke

The application was received by the EMA on	6 May 2025
The procedure started on	26 May 2025
The CHMP rapporteur's first assessment report was received on	30 June 2025
The CHMP Co-rapporteur's first assessment report was added to the rapporteur's report on	30 June 2025
The PRAC rapporteur's first assessment report was added to the rapporteurs' report and circulated to all PRAC and CHMP members on	30 June 2025
The PRAC agreed on the PRAC assessment overview and advice to CHMP during the meeting on	10 July 2025

The CHMP rapporteur circulated the CHMP and PRAC rapporteurs joint assessment report on the applicant's responses to the list of questions (LoQ) to all CHMP and PRAC members on	17 July 2025
The CHMP, in the light of the overall data submitted and the scientific discussion within the Committee, issued a positive opinion for granting a marketing authorisation to Usrenty on	24 July 2025

2.8. Final CHMP outcome

2.8.1. Considerations related to orphan market exclusivity

The requirements of the submitted dossier in relation to orphan market exclusivity are described in section 2.6 of this report.

2.8.2. Final opinion

Based on the CHMP review of data on quality, safety and efficacy, the CHMP considers by consensus that the benefit-risk balance of Usrenty is favourable in the following indications:

Plaque psoriasis

Usrenty is indicated for the treatment of moderate to severe plaque psoriasis in adults who failed to respond to, or who have a contraindication to, or are intolerant to other systemic therapies including ciclosporin, methotrexate (MTX) or PUVA (psoralen and ultraviolet A) (see section 5.1).

Paediatric plaque psoriasis

Usrenty is indicated for the treatment of moderate to severe plaque psoriasis in children and adolescent patients from the age of 6 years and older, who are inadequately controlled by, or are intolerant to, other systemic therapies or phototherapies (see section 5.1).

Psoriatic arthritis (PsA)

Usrenty, alone or in combination with MTX, is indicated for the treatment of active psoriatic arthritis in adult patients when the response to previous non-biological disease-modifying anti-rheumatic drug (DMARD) therapy has been inadequate (see section 5.1).

Crohn's Disease

Usrenty is indicated for the treatment of adult patients with moderately to severely active Crohn's disease who have had an inadequate response with, lost response to, or were intolerant to either conventional therapy or a TNFα antagonist.

The CHMP, therefore, recommend the granting of the marketing authorisation subject to the conditions described in the following sections.

2.8.3. Conclusions on biosimilarity and benefit risk balance

Based on the review of the submitted data, Usrenty is considered biosimilar to Stelara (ustekinumab). Therefore, a benefit/risk balance comparable to the reference product can be concluded.

2.8.4. Conditions or restrictions regarding supply and use

Medicinal product subject to restricted medical prescription (See Annex I: Summary of Product Characteristics, section 4.2).

2.8.5. Other conditions and requirements of the marketing authorisation

2.8.5.1. Periodic safety update reports

The requirements for submission of periodic safety update reports for this medicinal product are set out in the list of Union reference dates (EURD list) provided for under Article 107c(7) of Directive 2001/83/EC and any subsequent updates published on the European medicines web-portal.

2.8.6. Conditions or restrictions with regard to the safe and effective use of the medicinal product

2.8.6.1. Risk management plan (RMP)

The marketing authorisation holder (MAH) shall perform the required pharmacovigilance activities and interventions detailed in the agreed RMP presented in Module 1.8.2 of the marketing authorisation and any agreed subsequent updates of the RMP.

An updated RMP should be submitted:

- At the request of the European Medicines Agency;
- Whenever the risk management system is modified, especially as the result of new information being received that may lead to a significant change to the benefit/risk profile or as the result of an important (pharmacovigilance or risk minimisation) milestone being reached.

2.8.7. Conditions or restrictions with regard to the safe and effective use of the medicinal product to be implemented by the Member States

Not applicable.

3. Introduction

3.1. Therapeutic context

Usrenty (ustekinumab), a multiple of Yesintek (EMEA/H/C/006444 marketing authorisation granted on 14-February-2025), was approved as a similar product to Stelara (ustekinumab) which was granted a marketing authorisation on 15-January-2009.

The proposed indications for Usrenty are the same as the indications approved for Yesintek.

3.2. Aspects of development

According to Article 82(1) of Regulation (EC) No 726/2004, Biosimilar Collaborations Ireland Limited (BCIL), the current marketing authorisation holder (MAH) for Yesintek EMEA/H/C/006444 is hereby submitting a duplicate marketing authorisation application (MAA) for the same pharmaceutical product; same qualitative and quantitative composition in active substance, forms and strength as Yesintek EMEA/H/C/006444 under a different invented name.

It is confirmed that BCIL, the MAH for the original marketing authorisation will also be the same applicant/MAH for the duplicate MAA and that the original marketing authorisation is still valid.

This duplicate MA application is intended for co-marketing purposes.

Biosimilar Collaborations Ireland Limited is submitting a duplicate marketing authorisation application (MAA) for the same pharmaceutical product; same qualitative and quantitative composition in active substance, forms and strength as Yesintek EMEA/H/C/006444 under a different invented name.

Yesintek was approved in the EU by the European Commission with letter dated 14 February 2025. No further post-approval submissions were received yet. Thus, the status of the dossier for the new application reflects the finally agreed status of the dossier for Yesintek.

In the cover letter the applicant confirmed that the duplicate MAA remains identical to the original approved MAA of Yesintek (EMEA/H/C/006444) and all currently approved sections of Module 2, Module 3, Module 4 and Module 5 from Yesintek's approved MAA are replicated in this duplicate MAA submission.

The assessment report below therefore also reflects this status.

3.3. Description of the product

(BCIL) is submitting a duplicate marketing authorisation application (MAA) for Usrenty containing the same pharmaceutical product; same qualitative and quantitative composition in active substance ustekinumab, the same forms and strength as Yesintek EMEA/H/C/006444 under a different invented name.

Ustekinumab is a fully human monoclonal antibody composed of an IgG1 heavy chain isotype and a kappa light chain isotype with an approximate molecular weight of 148,600 Daltons.

Ustekinumab binds with high affinity and specificity to a 40 kilodalton (kDa) human protein that is a subunit of both interleukin (IL)-12 and IL-23 heterodimeric cytokines. This subunit is called IL-12/23p40.

Ustekinumab neutralises IL-12 and IL-23 bioactivity by binding to IL-12/23p40 and preventing IL-12 and IL-23 binding to the IL-12Rβ1 receptor protein expressed on the surface of natural killer (NK) or T cells. Through this mechanism of action, Ustekinumab neutralises IL-12 (Th1) and IL- 23 (Th17) mediated cellular responses.

Biocon Biologics has developed Bmab1200 45 mg/0.5 mL and 90 mg/mL Injection (Subcutaneous) in Pre-Filled Syringes, 45 mg/0.5 mL Injection (subcutaneous) in Vial (referred as Bmab1200 SC DP) and Bmab1200 130 mg/26 mL Solution for Intravenous Infusion (referred as Bmab1200 IV DP).

3.4. Inspection issues

3.4.1. Good manufacturing practice (GMP) inspection(s)

No inspection required.

3.4.2. Good laboratory practice (GLP) inspection(s)

No inspection required.

3.4.3. Good clinical practice (GCP) inspection(s)

No inspection required.

4. Quality aspects

4.1. Introduction

Bmab1200 (also referred to as Usrenty) is being developed as a biosimilar candidate to Stelara (ustekinumab). Both Bmab1200 and Stelara are recombinant human immunoglobulin isotype class G subclass 1 kappa (IgG1κ) monoclonal antibodies that bind with specificity to the p40 protein subunit of the interleukin (IL)-23 and IL-12 cytokines to neutralize IL-23- and IL-12-mediated cellular responses. Bmab1200 has a primary amino acid sequence that is identical to Stelara. Both, Bmab1200 and Stelara, are manufactured by recombinant DNA technology. Thereby, Bmab1200 and Stelara are both expressed in a murine cell line.

The indications and dosing regimens for Bmab1200 are the same as those for Stelara (ustekinumab). Bmab1200 drug product (DP) has the same formulation, route of administration, dosage form, and product strength as the reference product.

The DP intended for subcutaneous (SC) injection is supplied in a prefilled syringe (PFS) or a vial as a sterile, single-use, preservative-free, clear, and colourless to pale yellow solution. The presentations deliver 90 mg (1.0 mL, PFS only) or 45 mg (0.5 mL, PFS and vial) of Bmab1200 formulated in L-Histidine, L-Histidine hydrochloride monohydrate, sucrose and polysorbate 80, pH 6.0.

Each PFS consists of a 1 mL USP Type-I glass syringe with fixed stainless steel needle and rigid needle shield. It is stoppered with an elastomeric stopper. The PFS is also fitted with a plunger rod that facilitates passive actuation of the needle guard after dose administration.

The container closure system of the SC DP 45 mg vial presentation consists of a USP Type-I 2 mL glass vial. It is stoppered using with an elastomeric stopper and sealed with an overseal with plastic flip-off cap component.

The DP intended for intravenous (IV) infusion is supplied as a sterile concentrate for solution for infusion in a single-use vial containing 26 mL deliverable volume of 130 mg of Bmab1200 formulated in sucrose, L-histidine, L-histidine hydrochloride monohydrate, L-methionine, polysorbate 80, EDTA disodium salt dehydrate, pH 6.0. The IV DP 130 mg is intended for dilution in 0.9% or 0.45% saline.

The Applicant is seeking marketing authorisation for Bmab1200 in accordance with Article 10(4) of Directive 2001/83/EC, as amended. The reference biological medicinal product Stelara was originally approved in the EU on 16 January 2009 (EMEA/H/C/000958).

4.2. Active substance

4.2.1. General information

Bmab1200 is a monoclonal antibody expressed in recombinant Sp2/0 Ag14 cell line.

Bmab1200 is a fully human IgG1k monoclonal antibody that binds with specificity to the p40 protein subunit of the interleukin IL-12 and IL-23 cytokines. When bound to the p40 subunit of lL-12 and IL-23, Ustekinumab prevents p40 from binding to the IL-12Rb 1 (Interleukin-12 Receptor beta 1) receptor protein expressed on the surface of immune cells. This causes an interruption of the downstream Th1 and Th17 cytokine pathways, which are central to the pathology of inflammatory diseases such as psoriasis and Crohn's disease.

Bmab1200 is composed of 1326 amino acids, comprising two identical heavy chains (HC) each consisting of 449 amino acids and two identical light chains (LC) each consisting of 214 amino acid residues linked by covalent disulphide bonds and non-covalent heavy-heavy and heavy-light chain interactions. All cysteine residues are involved in disulphide bonds resulting in a total of 16 disulphide bonds with 12 intra-chain and 4 inter-chain disulphide bonds connecting heavy and light chains.

Bmab1200 HCs are fully glycosylated at Asn-299. The primary glycan structure is core fucosylated bi-antennary complex type structure having zero galactose (G0F), one galactose (G1F), or two galactose (G2F) as terminal residues. The G0F structures (terminating with 2 N-acetyl glucosamine residue) predominates. Glycan heterogeneity is also contributed by the presence of zero to two N-glycolylneuraminic acid (NGNA, Neu5Gc) residues. Neu5Gc is the main sialic acid in Bmab1200. Bmab1200 has no O-linked glycosylation sites.

4.2.2. Manufacture, process controls and characterisation

Manufacture

The Bmab1200 DS is manufactured at Biocon Biologics Limited, Special Economic Zone, Plot No. 2,3,4 & 5, Phase IV, Bommasandra-Jigani Link Road, Bengaluru-560099, Karnataka, India.

Recombinant murine myeloma cells are used for expression of the Bmab1200 DS, followed by an upstream cell culture and a downstream harvest and purification process typical of a monoclonal antibody production process. The upstream process begins with a working cell bank (WCB) vial and includes cell expansion steps, seed and production bioreactor steps, end with a harvest step leading to a harvest of the cell culture fluid (bulk harvest). The bulk harvest is then purified through series of chromatographic purification steps and additional steps for virus removal/inactivation and formulation

of bulk active substance. The manufacturing process, operating ranges and in process controls are well described. Acceptance criteria, ranges or limits are provided for critical and non-critical parameters. A distinct batch numbering system is used and described sufficiently.

The FBDS is filtered through a 0.22 µm filter to get formulated DS. The FBDS after filtration is termed as formulated DS or DS. The formulated DS is aliquoted in appropriate amounts into sterile single use bags. The filled bags are then frozen using a controlled freeze-thaw system. For DP manufacture, the frozen DS bag is thawed with a controlled freeze-thaw module and the thawed bags are transported to the DP facility which is present within the same premises as the DS facility. Reprocessing is not foreseen within the DS manufacturing process.

Control of material

The host cell line employed for expressing Bmab1200 is developed from Sp2/0, mouse myeloma cells. Bmab1200 drug substance amino acid sequence for the heavy and light chain was confirmed by peptide mass fingerprinting in comparison with that of the innovator molecule Reference Product Stelara®. The construction of plasmid vectors for the Bmab1200 expression is adequately described. The cell bank system for Bmab1200 consists of a RCB, a MCB, and a WCB and comprises further an end of production cell bank and a post-production cell bank. Adequate testing of cell banks was performed to maintain sterility and cell banks were demonstrated to be contamination free and also identity and purity was confirmed. Stability results of the MCB are also provided. The LIVCA of Bmab1200 was established using EPCB basis to comparable process performance, product quality attribute, genetic stability, and absence of adventitious agents. Preparation of the EPCB is described in sufficient detail. Characterisation studies were conducted for the EPCB in accordance with the ICH Q5A and ICH Q5D and results are presented. A post-production cell bank (PPCB) is further prepared and characterized. All outcoming results complied with pre-defined acceptance criteria. Analytical methods that are used for cell bank characterisation are described in sufficient detail.

Sufficient information on raw materials used in the active substance manufacturing process has been submitted. A detailed list of compendial (Ph.Eur., USP) and non-compendial materials used in the upstream process for cell culture media and the downstream process for buffers and purification materials was provided. The specifications were provided for non-compendial materials, and examples of certificates of analysis (CoAs) from suppliers were included for both compendial and non-compendial materials. Compositions for the cell culture media and feed used in upstream process have been described in details.

Control of critical steps

In-process controls are implemented in the manufacturing process to ensure that the process is controlled and able to produce a consistent quality of AS and also that AS meets the predefined specification requirements. The acceptance criteria/action limits of IPCs at different stages of manufacturing along with the justifications are provided. Validation data and in-process data obtained from the process validation batches are further provided. IPCs are specified either by using Action Limit or Acceptance Criteria/Limit. Action Limits are defined as the limit when exceeded requires an immediate follow up and if necessary and feasible, a corrective action as well as root cause evaluation and assessment of potential impact on product quality. Acceptance Criteria/Limits are defined as numerical limits, ranges, or other suitable measures for acceptance of the results of analytical procedures which the AS, FP or other materials should meet. Failure of meeting the acceptance criteria results in an out of specifications (OOS) investigation and impact assessment as well as batch rejection. Overall, the active substance manufacturing process is well controlled.

Analytical procedures for Bmab1200 control are described precisely hereinafter.

Method validation summaries are provided for methods that are specifically used in-process testing.

Process validation

The process validation of Bmab1200 DS is conducted with the three Bmab1200 process validation (PV) batches, PV Batch 1, PV Batch 2 and PV Batch ,3 and subdivided into cell culture validation and process validation for the purification process. Consistency for all three PV batches is demonstrated at the cell culture process, meaning that all three PV batches of the unprocessed harvest cell culture met the predefined limits set for in-process controls. The conclusion that Bmab1200 cell culture process is consistent, reproducible and thereby validated can be supported.

Validation of the Bmab1200 purification process includes assessment for all downstream unit operations. Unit operations capability to remove process related impurities and to control product related impurities/substances and to monitor microbial load.

For the cell culture process PV results are provided for inoculum expansion in shake flasks, inoculum expansion in seed bioreactors and production process in the production bioreactor. Additionally, testing results of cell culture media preparation are also provided to support consistency in the manufacturing process from the three Process Validation batches. PV results are further provided for each purification stage for all three PV batches from the corresponding cell culture runs. Process parameter details for inoculum preparation at seed bioreactors are described. The process parameters and their criticality are indicated and results demonstrate that all three PV batches were consistent and well within the acceptable range. Critical controls revealed that lots are contamination free, MVM DNA is absent and mycoplasma and adventitious virus are well within defined limits. Therefore, the results of process parameters and IPCs for production stage demonstrate process consistency and are considered as validated, what is supported. In Process controls for the upstream process are further presented and values are within the predefined acceptable range.

The purification process for Bmab1200 includes several stages: harvest and clarification chromatographic step for capture, viral inactivation as well as multiple chromatographic steps and filtration steps. Process parameters and IPCs results are presented for all three PV batches and values are well within the predefined ranges and also the step yield for each downstream unit operation is within a specified limit for all three batches. Based on data that are provided, it is concluded that Bmab1200 purification process is validated sufficiently. This is endorsed.

The conclusion from overall data of process validation studies with the three PV batches, that commercial Bmab1200 DS manufacturing process, when operated within the specified range, consistently produces DS that meets predefined specification is supported.

Further provided in section S.2.5 are process validation results of process related impurity clearance studies. Impurities of Bmab1200 are thereby divided into (1) process related impurities from host cells such as HCDNA and HCP or impurities generated during chromatographic steps, as well as (2) process additives that are used for optimisation. The capability of the manufacturing process to remove impurities sufficiently has been demonstrated adequately.

Furthermore, an extensive hold time study was carried out at manufacturing scale and evaluated hold time and storage conditions for various process intermediates during the routine manufacturing process.

The manufacturing process of Bmab1200 consist of multiple chromatographic stages. In order to evaluate reusability of these chromatographic resins, a small-scale resin lifetime study was performed. Reusability and carry over studies were further conducted and on the basis of obtained results resin lifetimes within the different unit operation were established.

Manufacturing process development

The manufacturing process development comprises the process characterisation and formulation. A risk assessment based on Failure Mode Effect Analysis (FMEA) was used for the categorisation of process parameters with identification of critical quality attributes (CQA).

Scale down models (SDM) are used to simulate manufacturing at laboratory scale and to characterize and qualify the DS manufacturing process. For Bmab1200 upstream production process (small scale bioreactors) were selected to mimic the production bioreactor. Input and output process parameters were determined. Trend analysis and statistical analysis were used for scale-down model qualification and results are presented for the Process 1A at production stage and Process 1B as commercial production process. Failure Mode Effect Analysis (FMEA) was used during upstream process at inoculum stages (vial thaw to seed bioreactor unit operations) and at production stage to create a list of pCPP. All identified pCPPs were further assessed during process characterisation studies using qualified SDM to confirm their criticality. Differences were observed in glycosylation at pilot scale in comparison to reference product target range. Therefore, a 2nd development batch was planned and executed to improve the glycosylation. Two major changes were introduced for the 2nd development batch: 1) Elimination of Seed bioreactor (with associated change in process flow and parameters at different inoculum propagation steps to enable this), and 2) Change in Feeding regime in production bioreactor to improve Process performance.

The purification process for Bmab1200 was developed at laboratory-scale followed by evaluation of process at pilot scale. The process was further linearly scale-up to the manufacturing scale. At scale, filtration and chromatography unit operations were optimized for the facility fit. The process development for downstream was initiated by defining goals (or targets) based on the quality target product profile (QTPP) data set. QTPP was derived by analysing multiple reference product batches for key product quality attributes and a range was defined. The downstream target for product quality attributes was to match the reference product TPP and biosimilarity.

Early phase development was initiated by optimizing clarification step for removal of cell debris followed by selective Bmab1200 capture by affinity chromatography. The downstream process development targeted to remove charge variants and size variants through multiple chromatographic steps. After incorporating all these changes from the platform process and developmental studies, the final process flow established for Bmab1200 purification process includes Clarification capture Chromatography Viral Inactivation, series of chromatographic steps, Viral Filtration (VF) and Ultrafiltration/Diafiltration (UF/DF).

Formulation development activities comprised pre-formulation development i.e. establishing the target composition as well as testing and optimizing operations including the establishment of a minimum target concentration of tangential flow filtration retentate (TFFR), optimisation of formulation buffer concentration and preparation and development of specifications for the in-process tests. The detailed information of formulation development process is provided in the Drug Product section.

Prior to start process validation the Bmab1200 DS manufacturing process was modified to reduce aggregate levels and the improved process was termed as "Process 1B" and is the intended commercial scale process. The impact of changes between Process 1A and Process 1B was assessed by using International Conference on Harmonization (ICH) Q5E. In line with details described in guideline, DS material generated from each process (Process 1A and Process 1B) was compared based on upstream process performance and downstream process quality as well as long-term stability outcome.

For three Process validation batches, all in-process tests and performance parameters of upstream, downstream and formulation stages met the comparability assessment criteria derived from the

historical batches of Process 1A.. The DS release data met both the release specifications and the comparability assessment criteria.

Long term and accelerated stability data were checked against the respective comparability assessment and found comparable up to 6 month time point. Stress stability (up to 3 months) and additional DS characterisation tests found to be comparable. Therefore, this demonstrates no impact due to process change on Bmab1200 DS product quality attribute.

Characterisation

Comparison of Bmab1200 DS batches from the proposed commercial process by Process 1B to Bmab1200 IRS EU-Approved and US-Licensed Stelara® batches is presented in the Characterisation section S.3. The characterisation data package comprises an extensive evaluation of physicochemical and functional components of Bmab1200 DP in PFS and vial presentations against US-Licensed Stelara and EU-Approved Stelara as part of an analytical similarity assessment. Qualified analytical techniques are utilized to evaluate the primary, secondary, higher order structures, post translational modifications, product related variants and functional attributes. The molecular mass was observed to be consistent within the three Bmab1200 DS batches and also comparable with Bmab1200 IRS and US-licensed Stelara and EU-approved Stelara batches. In addition, the observed molecular intact mass of all the batches were within the expected theoretical mass range. Observed mass for heavy chain and light chain closely matches with the theoretical mass and heavy chain and light chain mass obtained for Bmab1200 PV DS batches from Process 1B were comparable to those obtained for US-licensed and EU-approved Stelara.

Evaluation of higher order structure confirmed the expected antibody spectra and demonstrate consistency of the tertiary structure. Thermodynamic stability of Bmab1200 PV DS batches was further demonstrated to be comparable with the transition temperatures of US-licensed and EU-approved Stelara®.

Glycoforms for Bmab1200 PV DS batches, US-Licensed Stelara and EU-Approved Stelara were evaluated using Normal Phase Chromatography with Fluorescence detector (NP-UPLC-FLD) and it could be demonstrated that N-Glycan profiles for Bmab1200 PV DS batches were comparable to that of US-licensed and EU-approved Stelara®.

The protein content for Bmab1200 DS from PV batches were further found to be within defined acceptable limits and are comparable to US-Licensed and EU-Approved Stelara additionally. Aggregates, charge variant, hydrophobic variant profiles were observed to be consistent within three AS PV batches and were comparable with that of Bmab1200 IRS and EU Approved and US Licensed Stelara. In terms of fragments slightly higher purity and monomer content in Bmab1200 AS PV batches was observed in comparison to Stelara EURP and USRLD batches.

Ustekinumab binds to the p40 subunit of IL12 and IL23, preventing the two cytokines from binding to their receptor, IL12Rβ1 (IL12 receptor beta 1) and neutralizing their biological activity. Binding of IL23 to its receptor predominantly present on NK and T cells, triggers a signalling pathway involving TyK2 (tyrosine kinase 2), JAK2 (Janus kinase 2) and STAT3 (signal transducer and activator of transcription 3). In line with this mechanism of action, a cell based functional assay measuring the neutralisation of IL23 induced STAT3 activation by ustekinumab (Stelara® /Bmab1200) using appropriate IL23 cell line was developed. The functional characterisation of Bmab1200 comprises a Fab mediated assay and a Fc mediated assay that both leads to similar results in the capacity of three Bmab1200 batches and one Stelara® USRLD batch to neutralize IL-23 induced STAT3 activation and to bind to the FcRn.

Intact and reduced mass data and profiles of Bmab1200 DS PV batches are consistent, within the theoretical mass range and are comparable to Bmab1200 IRS and EU-Approved and US-Licensed Stelara® along with 100% sequence coverage, when analysed by LC-ESI-MS using samples digested

with proteolytic enzymes. Additionally, N-terminal and C-terminal sequences were also confirmed through MS/MS analysis of terminal peptides.

Impurities

Adequate removal of product related and process related impurities could be demonstrated. Thereby, product related impurities are defined as aggregate/high molecular weight proteins (HMWP), fragments/low molecular weight impurities (LMWP) and charge variants and process related impurities as cells, HCPs and their DNA and LPA as well as process additives.

Characterisation data are further included in the impurities section showing results for aggregates (HMWPs) and fragments (LMWPs), primary structure, higher order structure, heterogeneity with charge variants, N-glycan profile, purity, posttranslational modifications and sequence variants as well as functional and biological activity analysis. Values are provided that demonstrate adequate reduction of media components process additives. Finally, nitrosamine and elemental impurities are also reduced on acceptable levels. A Nitrosamine impurities risk assessment for DS and DP is provided. The physicochemical characterisation of HMWP isolated from Bmab1200 and Stelara was analysed using multiple physico-chemical and functional techniques and it could be concluded that the HMWP are primarily dimer species with minor amounts of trimer and tetramer identified. The aggregate species for both Bmab1200 HMWP and Stelara are formed predominantly via disulfide linages and are found to be bonded through Fab-Fab, Fab-Fc and Fc-Fc domain. The species of HMWP observed in Bmab1200 HMWP is similar to that observed in US-Licensed Stelara.

The isolated charge variants from Bmab1200 and US-Licensed Stelara were extensively characterized with different analytical techniques. The attributes of the isolated charge variants were mostly comparable across techniques used for analysis of Bmab1200 and US-Licensed Stelara®. Based on the characterisation results it can be concluded that, when compared to the main variant all the other charge variants (acidic and basic) present in Bmab1200 and Stelara retain the same primary and higher order structure, similar charge profiles, size distribution and significant potency.

PTMs that have been identified and quantitated includes oxidation, C-Terminal lysine variants, N-Terminal pyroglutamate, Glycation and deamidation. Results showed comparable levels between Bmab1200 and US-Licensed Stelara. Minor Differences observed in certain PTM’s does not present a safety risk to patients as those PTM’s were ranked moderate in critical risk ranking.

4.2.3. Specification, analytical procedures, reference standards, batch analysis, and container closure

Specification, batch analysis and justification

The following tests are included in the active substance specification: general tests (appearance, colour, clarity), solution properties (pH, osmolality), quantity, identity, purity and impurities, glycosylation, microbial safety (bacterial endotoxins, bioburden), process related impurities, excipient quantity and potency.

The DS specification is adequate and analytical procedures are described sufficiently. Methods verification and validation data have been further provided.

The batch analyses release data demonstrate consistent and comparable quality of Bmab1200 DS manufactured across all batches of early process development, Process 1A and Process 1B.

All DS batches comply with the pre-established specifications valid at the time of testing.

The release and shelf life specifications of Bmab1200 DS have been set in accordance with ICH Q6A, ICH Q6B, pharmacopeial guidelines (USP, Ph. Eur.) and based on overall data from all Bmab1200 DS process 1A and Process 1B batches. Release and shelf-life specification for the Bmab1200 DS comprises different control parameters with focus on physicochemical parameters, appearance, colour and clarity and further parameters pH, osmolality, quantity (protein concentration and excipient polysorbate 80), identity, purity, glycosylation, functional characterisation, impurities and parameters for microbial safety control. Analytical procedures are described adequately and in sufficient detail. Validation data are provided for analytical procedures demonstrating their suitability.

Reference standard

The reference standards for Bmab1200 (ustekinumab) are selected from either the development (pilot scale batch) or clinical batches and are qualified against the reference product Stelara® (EU-Approved and/or US-licensed) and/or against the previous reference standards. Three reference standards have been qualified for Bmab1200, and two reference standards have been used through development of Bmab1200.

The Primary Internal Reference Standard (Bmab1200 PRS or Bmab1200 IRS) was qualified against the Bmab1200 IRS as well as EU-approved Stelara® (for functional potency). Additional characterisation tests of Bmab1200 PRS were also performed using Bmab1200 IRS and US-licensed Stelara® This Bmab1200 PRS has been used for the in-process, release as well as stability testing of Process Validation (PV) and post PV batches. This PRS will further be used for subsequent secondary reference standard qualification.

In order to maintain a two-tier reference standard system, a Secondary Internal Reference Standard (Bmab1200 SRS) was qualified and characterized against Bmab1200 PRS and will be used for analyst qualifications, in-process testing, batch release, future and ongoing stability, method transfer, method verification and method validation testing. The Bmab1200 IRS or interim reference standard was the initial IRS that has been prepared from Pilot scale DS. The same has been used for the developmental activities, method transfer to QC, method validation activities and release of developmental batches including clinical batch. PRS was used for release of the PV and post PV batches and SRS will be used for the release of the commercial batches. The interim RS will no longer used in the commercial phase of the product. However, the stability is ongoing for the interim RS to support the shelf-life of the PRS.

Container closure system

The Bmab1200 formulated DS is filtered through 0.22 µm filter and stored in single-use, sterile, bag under frozen condition. The single-use bag and EVAM fluid contact layer are compliant with the compendial monographs and other quality standards.

4.2.4. Stability

Stability studies for the Bmab1200 drug substance are performed according to ICH Q1A (R2) and Q5C. The stability samples are stored in 30 mL single-use, sterile bag at their respective stability conditions.

The stability protocol is provided and information on DS batches is given with batch number, date of manufacture, process, and purpose and is adequate. Any out of specification result is coupled to an appropriate action plan.

As comparability between drug substance batches from process 1A (P1A) and process 1B (P1B) has been demonstrated, both, data from supportive stability studies together with the registration stability study were used to propose the shelf-life for Bmab1200 DS.

Based on available long term stability data a shelf life of 36 months is proposed when DS is stored at the recommended storage conditions in single use bag as the primary packaging container. The shelf life claim is supported.

4.3. Finished Medicinal Product

4.3.1. Description of the product and pharmaceutical development

In general, the pharmaceutical development of Bmab1200 DPs utilized principles described in the ICH Q8 Pharmaceutical Development guideline and was based on scientific knowledge and prior experience with similar protein products, as well as risk assessments and development studies.

Description and Composition

Bmab1200 DP is supplied in four presentations including PFS at two doses (45 mg and 90 mg) and 45 mg vial all of them intended for SC injection, and 130 mg vial for IV injection. The composition of each presentation is provided, and all excipients comply with Ph. Eur. / USP-NF. The compositions of final DPs are the same as compositions of reference medicinal product (RMP) Stelara. No formula overages are included but overfills ensure the respective nominal volumes. The components of DPs have been adequately reported. Excipients and their function are presented. These properties are clearly described in SmPC.

Formulation Development

During formulation development of SC DPs, the impact of variations in pH, protein concentration and excipient (sucrose, polysorbate 80) concentrations was studied through design of experiments (DoE). DP stability was monitored for colour, clarity, pH, osmolality, protein concentration, size variants and charge variants. The study was conducted with (i) 45 mg PFS, which is considered representative for 90 mg PFS as both presentations are similar in product contact surface area to volume ratio, and (ii) 45 mg vial because of headspace that is not present in PFS. DoE studies provide support that a pH 6.0±0.3 is the optimal range for DS/DP. For excipient amounts and protein concentration the wide ranges tested did not seem to impact the DP stability. Respective limits were established and justified, which is accepted.

Overall, the provided formulation development data was adequate and it can be agreed with the Applicant that based on formulation development data the formulations showed appropriate robustness.

Manufacturing Process Development

The manufacturing process of SC DP (PFS and Vial) and IV DP (Vial) is very similar, except for the DS dilution step in the IV DP process. All presentations use the same DS and no differences in product quality attributes are expected. Consequently, the same release and shelf-life specifications are applied across SC DP and IV DP except for: osmolality, extractable volume, protein and PS80 concentration. To ensure that shelf-life specifications are similar, stability trends were assessed and comparability data provided. No major changes were implemented in the DP process between clinical campaign and process validation except those that facilitated operational feasibility for commercial manufacture. As none of these changes affected the DP process, a process comparability exercise was not performed, which is accepted.

The manufacturing process comprises of preparation and filtration of formulation buffer (only 130 mg vial), active substance thawing and pooling, dilution of the active substance (only 130 mg vial), mixing of bulk DS (in case of pooling), pre-filtration, sterile filtration, aseptic filling, plunger-stopper

placement (PFS)/stoppering and sealing (vials), visual inspection, labelling and packing and storage. There is no reprocessing for the finished product process. A process flow chart with process parameters, including hold times, and in-process testing has been provided.

Process characterisation was performed in parallel to DP process development at the intended manufacturing scale. Process characterisation experiments were designed and executed to understand the relationship between input process parameters and output process performance as well as product quality. The process parameters were identified as critical (CPP) and non-critical (NCPP) in both, SC DP and IV DP, processes. Based on gained process understanding, process parameters and controls have been established that ensure process consistency resulting in a reliable product quality.

Overall, the applicant describes results of manufacturing process development activities in sufficient detail. The provided explanations and drawn conclusions are plausible.

Container Closure System

The selection of the commercial primary container closure systems (CCS) is based on the results of physical, chemical, and functional tests. The primary CCS for Bmab1200 SC DP PFS (45/90 mg) presentation is composed of a 1 mL USP Type-I glass syringe fitted with a staked needle and stoppered with a Flurotec® coated butyl plunger stopper. The primary CCS for Bmab1200 SC DP vial (45 mg) consists of a 2 mL, USP Type-I clear glass vial, stoppered with coated, butyl rubber stoppers and sealed with ready to use flip-off seal containing a plastic component. The primary CCS for Bmab1200 IV DP vial (130 mg) consists of a 30 mL, Type-I clear glass vial, stoppered with coated butyl rubber stoppers and sealed with ready to use flip-off seal containing a plastic component. The CCSs are composed of components that are standard for parenteral use. The glass syringe barrel of PFS and vials met the Ph. Eur. 3.2.1 requirements and needle shield and plunger-stopper of PFS and stopper of vials met the requirements of Ph. Eur. 3.2.9. The container closure integrity has been tested using seal integrity test (dye ingress) as per Ph. Eur.3.2.9. Container integrity was found to be intact. Controlled extraction studies were conducted and the origin of detected compounds (extractables) discussed. The recommended storage temperature for DP is 2-8 °C. Leachable screening study was performed for DP in contact with primary container closure after storage under stress condition for 1 month in inverted orientation to enhance release of compounds from the container and closure. No volatile, semi-volatile or non-volatile compounds were found at or above the respective Analytical Evaluation Threshold (AET) levels in DPs stored in PFS and Vials. The results demonstrate that the risks to patient safety from leachables originating from the manufacturing process and the SC DP PFS and vial CCSs is low. The applicant commits to perform additionally leachable shelf life studies for DP generated from process validation batches, which is encouraged. Additional spiking studies showed that silicon oil and tungsten do not have an impact on the product quality attributes of Bmab1200, tungsten does not have an impact on DP quality. Overall, the applicant has demonstrated that primary CCSs are compatible for storing Bmab1200 SC DP and IV DP.

Microbiological Attributes

Bacterial Endotoxin test (BET), Sterility test, and Seal Integrity tests are performed as a part of the batch release testing and during stability testing to confirm sterility of the final product and integrity of the container closure system. All DP batches tested met the pre-defined acceptance limit for bacterial endotoxin BET and the compendial requirements of the sterility test. Container closure integrity was confirmed by dye ingress and microbial ingress tests, which have been both validated/qualified using compromised positive controls.

Compatibility

SC DP Vial 45 mg and SC DP PFS 45/90 mg are administered by subcutaneous injection, directly from vial or PFS without requirement of diluents or reconstitution. Therefore, compatibility studies are not

applicable. In addition, SC DP compatibility with respective primary CCS (vial or PFS) is supported by batch release testing and on-going stability studies. Compatibility studies were performed with IV DP Vial 130 mg presentation. The Applicant performed physical and chemical studies of Bmab1200 at two different doses in PVC and PO bags at minimum dosage of 1.04 mg/mL and maximum dosage of 2.08 mg/mL in 0.9% saline, which corresponds to the lowest and highest doses in a clinical setting. The experiments demonstrated that Bmab1200 is stable and compatible with representative materials and conditions of IV administration. Based on these studies the Applicant claims a shelf life (in use stability) of 12 hours at RT (+15°C to +25°C) for 0.9% saline diluted IV bags. The applicant outlines (in SmPC) that Bmab1200 should only be diluted with sodium chloride 9 mg/mL (0.9%) solution.

4.3.2. Manufacture of the product and process controls

Manufacturers

Bmab1200 DP manufacturing (including PFS assembly), (in-process) quality control and stability testing, storage, packaging, labelling, and shipping are performed at Block No. B1 at Biocon Biologics Limited (BBL, India).

Valid proof of GMP compliance is provided for all sites involved in manufacturing, storage and testing of drug product. The new building Block No. B5 at Biocon Biologics Limited (India) for manufacturing of the drug substance is not covered by the current EU GMP Certificate (no. 33100), but a post-approval inspection in 2025 is proposed.

Batch Formula

With respect to SC DP presentations, PFS 45 mg, PFS 90 mg, and Vial 45 mg, DS is fully formulated and no further formulation steps are conducted during DP manufacture. The three SC DP presentations are identical in all aspects except for the fill volume and primary CCS.

Description of Manufacturing Process and Process Controls

The manufacturing process comprises of preparation and filtration of IV spiking buffer (IV DP only), DS thawing and pooling (as required), dilution of DS and mixing of IV bulk DP (IV DP only), pre-filtration (offline) for bioburden reduction, sterile filtration (online), aseptic filling, plunger-stopper placement (PFS only), stoppering and capping (vials only), visual inspection, labelling, packing, and storage. Both container closure systems, PFS and vials, are purged with nitrogen before and after filling. The manufacturing process steps have been described with sufficient detail. There are no reprocessing steps in the manufacture of DPs.

Controls of Critical Steps and Intermediates

Critical in-process controls are presented for formulation, bioburden reduction and sterile filtration (bioburden and filter integrity) and filling (CCIT) steps with action limits or acceptance criteria. References for description and validation/verification of analytical methods used are provided. In addition, a method validation report for Bioburden (IV DP Vial) is provided. Critical process parameters are described in CTD section P.3.5, which is acceptable.

Process Validation and/or Evaluation

The DP manufacturing processes were validated by producing at least three DP batches for each presentation at commercial scale at the intended commercial production site (BBL, India). Manufacturing process validation included steps for DS thawing and mixing of DS, pooling and mixing of DS, dilution of pooled DS with IV spiking buffer (IV DP only), pre-filtration of DS or IV bulk DP,

sterile filtration of DS or IV bulk DP, aseptic filling, stoppering of PFS or Vials, inspection, plunger rod and needle guard assembly (PFS only), and storage.

Overall, process parameters were adequately controlled within pre-defined ranges during PV studies. All PV DP batches were successfully validated, presented data met acceptance criteria for in-process and DP quality attributes, demonstrating consistency and reproducibility/reliability of the DP manufacturing processes. All PV DP batches met the release results of the proposed commercial specification acceptance criteria. Routine monitoring of the manufacturing process is undertaken as Continued Process Verification (CPV) to ensure product quality and to gain ongoing assurance that the manufacturing process remains in a state of control. A CPV protocol was provided, which is acceptable.

All (100%) filled PFS and Vials were visually inspected for defects (categorized as critical, major, and minor). The sponsor claimed that all defects were found consistent and well within the limits defined. Certain defects that were above the pre-defined action limits/ acceptance criteria were investigated and the root cause were identified. No quality concerns are raised and visual inspection AQL testing is considered to fall under the remit of GMP.

Hold times during the manufacturing processes have been validated and results are presented in respective PV reports. Overall, hold times are considered to be appropriately validated. Comparative assessment of product quality attributes for source DS batches and released PV DP batches showed no significant change in product quality attributes which demonstrates reliable DP manufacturing within the recommended (cumulative) hold times. The recommended hold times are summarized for relevant process stages of each DP formulation.

Filter validation studies comprised establishment of product specific bubble point (filter integrity test), membrane/device compatibility, and bacterial retention studies. The bacterial retention test was performed based on the filter size recommendation from Filter sizing study (Vmax study).

Extractables information on the filters used in the Bmab1200 SC and IV DP manufacture was procured from studies performed by the vendor. Only in the IV presentation, few compounds had potential leachable levels above the safety concern threshold (SCT). However, the levels of all compounds fall within the ICH M7 less than lifetime (LTL) limit. Hence, no leachable risk is foreseen from the filters and a separate leachables assessment is not required.

The aseptic process simulation (medial fill) of each DP presentation represented the commercial configuration. Based on the provided qualification/requalification data, media fill batches for 1 mL PFS, 2 mL vial (45 mg SC DP), and 30 mL vial (130 mg IV DP) were successfully validated for aseptic process.

Materials and equipment that will be in contact with the sterile DP are sterilized, irradiated, or depyrogenated prior to introduction into the manufacturing process.

Shipping validation of SC DP PFS, SC DP Vial and IV DP Vial is performed and respective protocols and shipping validation reports are provided. The quality control testing for physicochemical (stability indicating) parameters on PFS and vials after shipping show that the specifications are met for all parameters and for all products.

In addition, plunger-stopper movement of PFS DPs during typical air shipment was evaluated by an air transportation simulation study. This study demonstrated that the product sterility is not compromised during air transportation.

Control of Excipients

The excipients used in the finished Bmab1200 DPs are of Ph. Eur. quality and controlled in line with the current version of the respective Ph. Eur. monographs.

The applicant has provided the certificate of analysis (COA) for each excipient used in Bmab1200 DPs but they have been left out of assessment. Excipients are tested with compendial methods and no validation of the methods are required. No novel excipients nor excipients originated from human or animal source are used.

4.3.3. Product specification, analytical procedures, batch analysis and container closure system

Specification

Specifications are set in accordance with ICH Q6B principles and cover all relevant characteristics of Bmab1200 DPs. Comprehensive panel of specification are set for Bmab1200 DPs including tests for appearance (appearance, clarity, colour), identity and impurities, adventitious agents (microbial safety in general) including bacterial endotoxins (BET), sterility, and container closure integrity (CCI), product potency and biological activity, quantity (protein concentration), polysorbate 80 concentration as well as general properties including pH, osmolality, visible and subvisible particles, uniformity of dosage units, and extractable volume.

Analytical Procedures and Validation of Analytical Procedures

Analytical procedures utilized in the specification determination of DPs are described and discussed both in the DS and DP sections. Most of the methods including appearance, colour, clarity, protein concentration, pH, osmolality, visible particles, subvisible particles, uniformity of dosage units, extractable volume, bacterial endotoxins, sterility, and container closure integrity were based on respective Ph. Eur./USP monographs.

Based on the method validation results obtained for Microbial Safety Testing (bacterial endotoxin testing, sterility, and container closure integrity test) these methods are considered to be suitable for routine release and stability testing of DP samples.

Low endotoxin recovery (LER) studies were performed to evaluate the masking effect of undiluted DP on endotoxin recovery by gel clot method.

An evaluation process to switch from gel clot method to Ph. Eur. 2.6.32 Test for bacterial endotoxins using recombinant factor C (rFC) has been initiated by the applicant and implementation of the rFC test method for routine analysis is foreseen by December 2026.

Based on the method verification results obtained for Syringe Functionality Tests Friction force testing, Extractable Volume, and Actuation of Safety device) these methods are considered to be suitable/verified for its intended purpose. The verified methods can be adopted for routine analysis and stability testing of PFS.

Analytical methods for determination of quantity (Protein Concentration), identity, purity/impurity, and potency/biological activity are in-house methods. These methods have been validated according to the principles of ICH Q2 (R1) guideline and are confirmed to be suitable for their intended purpose. The assessment of validation data for these methods is presented in CTD section S.4.3.

Batch Analysis

Batch analytical data was provided for development, clinical campaign, global phase 1/Phase 3 clinical batches, process validation batches and post process validation batches as applicable for SC FP 45 mg PFS, SC PF 90 mg PFS, SC FP 45 mg vial and IV FP 130 mg vial.

All presented batches met the acceptance criteria of release in place at the time indicating adequate batch-to-batch consistency and controlled manufacturing process.

Characterisation of Impurities

The Applicant has performed risk assessments of elemental and nitrosamine impurities.

Elemental impurity analysis was performed for all PV batches of SC DP PFS, SC DP Vial and IV DP Vial. The results showed that elemental impurities in all tested DP presentations were within the ICH Q3D guidelines, i.e. test results were clearly below PDE limits. The risk assessment regarding nitrosamine impurities conducted in accordance with principles from ICH Q9 and M7 was designed to evaluate all potential sources of nitrosamine formation or contamination during manufacture of the DP including the DS, excipients, manufacturing process, equipment, utilities, and packaging. Overall, no significant risk of elemental or nitrosamine impurities were identified. This can be agreed. Other process and product related impurities are not introduced during the manufacturing process of Bmab1200 DPs.

Justification of Specifications

The approach to setting acceptance criteria for each quality attribute in the Bmab1200 DP specification included manufacturing experience and knowledge of process capability and consistency, experience with the analytical procedures and knowledge of the method capabilities and dataset consisting of analytical test results. SC DP PFS and SC DP Vial share identical DP manufacturing processes and only difference is the container closure system. Consequently, justification of specifications for SC DP Vial 45 mg are the same as that of SC DP PFS 45 mg/90 mg except for PFS specific functionality and safety device testing. The test for extractable volume for the vial and its specification follows Ph. Eur. 2.9.17. The stability trends and degradation kinetics between SC DP and IV DP were found to be similar. Therefore, IV DP specifications were established for product quality attributes by considering SC DP batches stability trends. As a result, the majority of specifications are common between SC DP and IV DP presentations. However, specific differences are noted for the attributes such as protein concentration, osmolality, excipient Polysorbate 80, extractable volume, and bacterial endotoxin based on the requirements of IV presentation.

The acceptance limits for endotoxins have been calculated correctly by using the highest drug dose. In case of IV DP Vial 130 mg presentation, the product is diluted with 0.9% NaCl solution before IV administration. The effect of endotoxin burden originating from 0.9% NaCl-solution is expected to be minor and can be ignored for calculation of limits.

The acceptance range for potency/biological activity is the same for DS and DP release and shelf-life specifications, which is accepted.

Different acceptance criteria are set for release and stability specifications of purity/impurity parameters, which is accepted.

Overall, a sufficient panel of quality attributes is proposed for release and shelf-life specifications of Bmab1200 finished DPs. Set specification limits are accepted.

Container Closure System

The primary CCS for Bmab1200 SC DP PFS (45/90 mg) presentation is composed of a 1 mL USP Type-I glass syringe fitted with a staked needle and stoppered with a coated butyl plunger stopper. The PFS is configured with Plunger Rod (White), Plunger Stopper and Passive Needle Guard. SC DP PFS is available in two variants: 0.5 ml and 1.0 ml of fill volumes. The device configuration is the same for both fill volumes. The conformity of the device part with the relevant general safety and performance requirements (GSPR) set out in Annex I Regulation (EU) 2017/745 was evaluated and approved by notified body.

The primary CCS for Bmab1200 SC DP vial (45 mg) consists of a 2 mL, USP Type-I clear glass vial, stoppered with coated butyl rubber stoppers and sealed with ready to use flip-off seal with flip top plastic part.

The primary CCS for Bmab1200 IV DP vial (130 mg) consists of a 30 mL, Type-I clear glass vial, stoppered with coated butyl rubber stoppers and sealed with ready to use flip-off seal with flip top plastic part.

All components of primary and secondary container closure systems are listed and representative technical drawings are provided. Specifications for primary and secondary container closure systems are provided. Apart from testing by the vendor, as a part of incoming material testing applicant also performs testing for individual components. Testing is performed according to compendial methods or validated in-house methods. Method description and validation summary are provided for non-compendial, in-house methods. Representative certificates of conformance form vendor and applicant are provided.

Compatibility of primary components of container closure systems with DP was addressed during pharmaceutical development (CTD section P.2.4) and suitability of container closure systems was further confirmed by container closure integrity (CTD section P.2.5) and stability tests (CTD section P.8.3).

4.3.4. Stability of the product

The Applicant has designed DP stability programmes for all presentations (SC DP PFS 45/90 mg PFS, SC DP Vial 45 mg, and IV DP Vial 130 mg) following ICH Q1A (R2) and ICH Q5C guidelines.

The stability programmes for all DP presentations are currently still ongoing and include commercial scale process validation (PV) and development batches (manufactured using commercial scale DS batches).

The Applicant has provided stability data at long-term storage condition (5°C ± 3°C), accelerated storage condition (25°C ± 2°C), and stress storage condition (40°C±2°C). For all DP presentations sample batches stored at the recommended long-term storage condition met the stability acceptance criteria. The applicant proposed a shelf-life of 36 months (3 years) when stored at 5ºC±3ºC, protected from light for the SC DP PFS 45/90 mg presentations, which is endorsed. A shelf-life of 18 months when stored at 5ºC±3ºC, protected from light is proposed for the SC DP 45 mg vial and IV DP 130 mg vial presentation, which is accepted.

The results of comparative forced degradation study of Bmab1200 DP were similar with EU-approved and US-Licenced Stelara® The behaviour of Bmab1200 DP was comparable to EU-approved and US-Licenced Stelara® under various stress conditions such as temperature, pH, oxidative chemical, photo exposure, and mechanical stress. Upon light exposure (1.2 million lux hours), a significant amount of degradation was observed for Bmab1200 DP, EU-Approved and US-Licensed Stelara® batches, indicating that the molecules are sensitive to light. These results are considered sufficient to demonstrate that protection from light is justified.

Additionally, to enhance convenience and facilitate dosing of SC DP PFS, in-use stability studies were performed to confirm that the product is stable at 30°C ±2°C (65±5% RH) for a period of 30 days once removed out of refrigeration (2ºC-8ºC). This study was performed based on Stelara® label that includes a provision to store PFS at room temperature up to 30°C (86°F) for a maximum single period of up to 30 days in the original carton to protect from light. As stability data was within specification individual PFS may also be stored at room temperature up to 30°C (86°F) for a maximum single period of up to 30 days in the original carton to protect from light.

Furthermore, the Applicant commits to complete the ongoing stability studies of commercial scale (PV) batches for each DP presentation packed in the intended commercial primary CCS. Appropriate post-approval stability protocols were provided by the applicant for all DP presentations. Stability will be tested against respective shelf life specifications. Overall, the provided post-approval stability protocols are considered acceptable.

4.3.5. Biosimilarity

Bmab1200 has been developed as proposed biosimilar to the reference product Stelara (ustekinumab) with subcutaneous (SC) and intravenous (IV) DP presentations. Comparative analytical assessments was performed for the SC and for the IV presentation. The overall approach to demonstrate similarity to Stelara is in line with EMA/CHMP/BWP/247713/2012 guidance.

All product quality attributes that are relevant towards impact on clinical safety, efficacy, PK, and immunogenicity were ranked thorough a criticality risk assessment and categorized into very high, high, moderate, low and none/very low risk. A comprehensive list of analytical methods was developed and qualified or validated to be appropriate to assess the different quality attributes.

Multiple DS and DP batches were manufactured and considered for comparative analytical assessment over 5 to 6 years with reference products of US-licensed and EU-approved Stelara batches.

A three-way comparative PK study has been completed with US-licensed Stelara, EU-approved Stelara and Bmab1200 subcutaneous PFS presentation to support the development of Bmab1200 as a biosimilar to Stelara. A detailed risk assessment based on formulation, container closure, DP manufacturing process etc. was performed and a product quality comparison between the different SC presentations was conducted for US-licensed Stelara® and EU-approved Stelara® separately. Based on the outcome of this risk assessment, it was concluded that a single Comparative analytical assessment (CAA) for all three Bmab1200 SC DP presentations would be sufficient.

For Bmab1200, the DS process was modified from process 1A (used for the clinical trial) to 1B (commercial process) to reduce the level of HMWP. As part of this change, few other product quality attributes were also marginally changed. A comprehensive development was undertaken to assess the risks and upon confirming that the change in the product quality would not pose any risk to clinical safety, efficacy, PK, and immunogenicity, this change was implemented in the cGMP batches and the DS process was validated (process 1B). An at-scale cGMP DS process comparability was executed demonstrating that process 1A and 1B are comparable. Bmab1200 DP batches have been manufactured from both process 1A and 1B and has been subjected to the comparative analytical assessment. An assessment on all quality attributes towards establishing comparability between process 1A and 1B was also completed.

The comparative testing included analysis of biological activity, primary structure, higher order structure, particles and aggregates, product-related substances and impurities, general properties and thermal stability studies. Appropriate analytical methods have been utilized to ensure an understanding of Stelara (EU/US) product profile and Bmab1200 DP.

Table 2. Summary of biosimilarity assessment (composed by the Rapporteur)

Molecular parameter	Analytical method	Quality attribute	Key findings / Conclusion on biosimilarity with Stelara (EU/US)
General properties	Protein concentration by Solo VPE	Protein concentration	Similar protein concentration; 3-way comparability
Primary structure	Electrospray ionisation (ESI) / molecular mass (MM)	Intact molecular mass	Similar molecular mass; 3-way comparability
	ESI /MM	Reduced molecular mass	Similar reduced (HC and LC) molecular mass; 3-way comparability
	peptide mapping fingerprint (UV)	reduced peptide map (identity)	Profiles comparable (including ustekinumab-specific signature peptides)
	LC-MS / MAM including N- and C-Terminus	amino acid sequence (confirmation)	100% sequence coverage, no sequence variants; Identical primary amino acid sequence
	Extinction coefficient determination by Edelhoch method	Extinction Coefficient	Extinction coefficients were determined to be similar between Bmab1200 and Stelara and comparable to theoretical extinction coefficient.
	Disulfide mapping by non-reduced peptide mapping	Sites of disulphide linkages (Disulphide linked peptide mass)	all 8 disulphide linked peptides have been identified for all sample groups; 3-way comparability
	Estimation of free cysteine by Ellman's Test	Free Cysteine	Free Cysteine levels were below quantification limits for all samples
	N-Glycan analysis by HILIC-UPLC	Total High Mannose(%)	Similar high mannose (SC DP) Lower high mannose (IV DP)
		Total Sialylation(%)	SC DP (same trends for IV DP): Lower Sialic acidic (sialylation)
		Total Terminal Galactose	Lower terminal galactose (galactosylation)
		Total Terminal GlcNAc	Higher Terminal GlcNAc

Molecular parameter	Analytical method	Quality attribute	Key findings / Conclusion on biosimilarity with Stelara (EU/US)
			Fc linked GlcNAc has not been reported to impact PK Functional similarity shown between Bmab1200 and Stelara
		Total Afucosylation(%)	Lower Afucosylation (=more fucose) afucosylation effects Fc binding (see FcγR binding in table below)
		Total Alpha 1, 3 Gal(%)	Lower Alpha 1,3 galactose
	Post-translational modification using Multi-Attribute Monitoring (MAM)	N terminal Pyroglutamate Asparagine Deamidation Methionine oxidation (CDR and Framework region)	Similar; 3-way comparability
		C terminal Lysine	Lower C-terminal Lysine content
		Methionine oxidation (Fc region)	Higher oxidation level of oxidation is <1% in all samples, except for one (SC DP)
		(Non-enzymatic) lysine glycation	Minimal Lysine glycation observed in Bmab1200 batches but not in Stelara.
Higher Order structure	Secondary structure by Far UV CD Spectroscopy	Profile overlays, Ellipticity ratio	The secondary and tertiary structures were similar; 3-way comparability
	Secondary structure by FTIR	Profile overlays, Amide I band	

Molecular parameter	Analytical method	Quality attribute	Key findings / Conclusion on biosimilarity with Stelara (EU/US)
	(orthogonal method)	peak position (cm-1)	
	Tertiary Structure by Near UV CD Spectroscopy	Profile overlays	
	Tertiary Structure by Intrinsic Fluorescence Spectroscopy	Profile overlays, emission maximum (λmax)	
	Protein tertiary structure/ Conformation and conformational dynamics by HDX-MS	Profile similarity	
	Differential Scanning Colorimetry (DSC)	Thermal stability, Profile overlays, Tm °C values	*Overall, similar thermal stability was demonstrated.*
Product-related Substances and Impurities	Charge variants by iCIEF	Acidic (%), Main (%), Basic (%), Main peak pI (with and w/o carboxypeptidase B (CpB) treatment)	IV DP: acidic variants higher than RMP SC/IV DP: Basic/Main variants: Lower basic variants attributed to lower C-terminal lysine variant. *Marginally higher main variant due to lower C terminal lysine variant in Bmab1200*
	Charge variants by IEX HPLC	Acidic (%), Main (%), Basic	similar observations and conclusions as for iCIEF analysis
	Size variants by SEC HPLC	HMWP (%), Main (%),	SC DP: Process 1B (intended commercial process): all batches are comparable in HMWP content to Stelara (EU/US); 3-way comparability for 1B batches

Molecular parameter	Analytical method	Quality attribute	Key findings / Conclusion on biosimilarity with Stelara (EU/US)
			IV DP: Lower HMWP and concomitant higher main peak in Bmab1200 in comparison to Stelara *HMWP is an impurity. Marginally lower HMWP and higher main peak are not expected to have any meaningful impact to clinical safety, efficacy, PK and immunogenicity.*
	Size variant analysis by AUC	Sedimentation coefficient	Similar sedimentation coefficients; 3- way comparability
	Purity and Impurity by CE-SDS NR	Monomer (%), Total Fragments (%), 2H1L (%)	SC DP: For Process 1B (intended commercial process): Monomer/fragments: Marginally higher monomers and lower fragments IV DP: Monomer/fragments: significant higher monomers and lower fragments
	Purity and Impurity by CE-SDS R	LC+HC (%), Total Other species, Nonglycosylated heavy chain (NgHC) (%)	NgHC is less than 1% in all test sample groups Marginally higher NgHC in Bmab1200
	Hydrophobic variants analysis by HIC	Profile overlays, Total Less hydrophobic species (LHS) (%), Main (%), More Hydrophobic species (MHS)(%)	No MHS species Marginally higher LHS post CpB treatment in Bmab1200
Biological activity	Target binding p40	Relative Binding	Marginally higher levels of P40 relative binding for Bmab1200 SC DP. *Not seen in IL12/23 binding studies and neutralisation (STAT) assays. Hence, considered similar as no clinical meaningful effect is expected.*

Molecular parameter	Analytical method	Quality attribute	Key findings / Conclusion on biosimilarity with Stelara (EU/US)
			Similar; 3-way comparability seen in IV FP
	Target binding IL-12 ELISA	Relative Binding	Similar; 3-way comparability
	Target binding IL-23 ELISA		
	Neutralisation of IL-12 induced STAT-4 activation		
	Neutralisation of IL-23 induced STAT-3 activation		
	FcRn binding	Binding Kinetics (K_D)	Similar; 3-way comparability
	FcγRIa binding kinetics		
	FcγRIIa binding kinetics		
	FcγRIIb binding kinetics		
	FcγRIIIaV158 binding kinetics	Binding Kinetics (K_D)	Higher KD value (=lower affinity) for Bmab1200 attributed differences in glycosylation *Fc binding is not related to mechanism of action. Lack of ADCC/CDC also shown. Hence, no clinically meaningful effect is expected from difference*.
	FcγRIIIaF158 binding kinetics		
	FcγRIIIb binding kinetics		
	C1q Binding	Relative Binding	Similar; 3-way comparability
	IFN-γ release	Cell Based Assay	Similar; 3-way comparability
	IL-17 release	Cell Based Assay	Similar; 3-way comparability
	Lack of ADCC	Cell Based Assay	Similar; 3-way comparability
	Lack of CDC	Cell Based Assay	Similar; 3-way comparability
	(lack of)binding to IL-6	ELISA	Similar; 3-way comparability
	(lack of)binding to IL-10		

Molecular parameter	Analytical method	Quality attribute	Key findings / Conclusion on biosimilarity with Stelara (EU/US)
	Binding to receptor-bound IL- 12	Cell Based Assay	Similar; 3-way comparability
	Binding to receptor-bound IL- 23		
	IL-12 Affinity-SPR	SPR	Similar; 3-way comparability
	IL-23 Affinity-SPR	SPR	Similar; 3-way comparability

In the analytical similarity exercise minor differences were observed:

Minor differences in N-glycan profile were observed between Bmab1200 and RMP Stelara (EU/US). Similar to Stelara, Bmab1200 is also expressed in murine mouse myeloma cell line. Therefore, observed differences in N-glycans cannot be attributed to a different expression cell line. However, N-glycans in Bmab1200 are located in the Fc region only. As Bmab1200 does not comprise any Fc effector function such as ADCC or CDC, observed differences in N-glycans are not expected to have any clinically meaningful effect. No difference in PK profile was observed in clinical study BM12H-NHV-01-G-01 (EudraCT:2021-006630-39).

Due to the murine expression cell line, Bmab1200 contains non-human glycans, such as N-glycolylneuraminic acid (NGNA) and alpha 1,3 Galactose. However, no risk to safety or immunogenicity is perceived because levels of both glycan species are lower in Bmab1200 compared to RMP Stelara and enclosed in a cavity in the Fc region.

Further differences between Bmab1200 and RMP Stelara have been observed in C-terminal lysine content and size variants. However, differences are rather small and not shown to impact biological function related to the mechanism of action and are therefore likely not to be clinically meaningful.

A lower binding activity of Bmab1200 to FcγRIIIa (V158 and F158) and FcγRIIIb compared to RMP Stelara (EU/US) was observed, which is attributed to differences in glycans in Bmab1200. No clinical impact is expected. Bmab1200 does not induce Fc effector functions such as ADCC and CDC, since its target, IL-23 and IL-12, only exist as soluble secreted proteins, and Bmab1200 does not bind to receptor-bound IL-23 or IL-12.

. The experimentally determined extinction coefficient was for both EU-approved Stelara and US-licensed Stelara, as well as for Bmab1200 were similar. The average values were highly comparable to theoretical extinction coefficient for all 3 products. Therefore, the usage of the theoretical extinction coefficient is justified for the determination of protein concentration.

After the analytical assessment conducted, the following conclusions are drawn:

- The primary structure of Bmab1200, US-licensed Stelara® and EU-approved Stelara® are identical. 100% sequence coverage has been demonstrated.

- The secondary, tertiary, and higher order structure for Bmab1200, US-licensed Stelara® and EU approved Stelara® have been assessed by multiple state-of-the-art, orthogonal techniques that demonstrate, high degree of similarity between all three products.
- Bmab1200 and Stelara are manufactured using the same host cell system. While there is high similarity in the type of glycosylation between the proposed biosimilar and reference product, minor differences in relative abundance of few glycosylation species were observed. Additionally, certain minor difference in oxidation have been observed. However, the extent of these differences is minor and is not anticipated to have meaningful impact on clinical outcomes. This conclusion is supported by the successful outcome of the comparative PK and efficacy studies.
- Other physicochemical attributes that are observed to have minor differences include charge and hydrophobic variants, both influenced by lower C-terminal lysine variant content in Bmab1200 compared to Stelara. However, the extent of these differences is minor and is not anticipated to have meaningful impact on clinical outcomes. This conclusion is supported by the successful outcome of the comparative PK and efficacy studies.
- The comparative analytical assessment included a comprehensive array of in-vitro functional bioassays that are designed to demonstrate the mechanism of action of ustekinumab. Functional similarity has been unequivocally established for Fab and Fc mediated functions.

Overall conclusion

A comprehensive assessment of biosimilarity between Bmab1200 and US licensed Stelara® and EU-approved Stelara® has been presented. In general, observed differences have been adequately discussed and shown not to impact biological function related to the mechanism of action and thus are justified not to be clinically meaningful. Based on the analytical comparative results provided in the biosimilarity studies (SC and IV), the primary and higher order structure are considered similar. It is noted that minor differences have been observed in purity by SE-HPLC and CE-SDS (NR and R), charge variants by icIEF and IEX-HPLC, hydrophobic variants by HIC, glycosylation by HILIC-UPLC-FLD, and post-translational modifications. However, these differences have been sufficiently justified by the Applicant and demonstrated to have no impact on functionality assays, since all results obtained for all Fab-mediated functionality tests were demonstrated to be similar (i.e. target p40 binding, target IL-12 binding, target IL-23 binding, neutralisation of IL-12 induced STAT4 activation, neutralisation of IL-23 induced STAT3 activation, neutralisation of IL-12 induced IFNγ production, neutralisation of IL-23 induced IL-17 production, lack of binding to IL-6 and IL-10, and lack of binding to IL-12 and IL-23 already bound to receptors). In addition, similar results between Bmab1200 and EU-/US-Stelara were also obtained for Fc-mediated functionality tests (i.e. FcRn binding, FcyRIa binding, FcyRIIa/b binding, C1q binding, lack of ADCC and CDC activity), except for lower binding affinity to FcyRIIIa/b, which is attributed to difference in glycosylation in Bmab1200. Nevertheless, this is considered to have no impact since ustekinumab does not display Fc-mediated effector functions.

In conclusion, based on the biosimilarity results provided, Bmab1200 can be considered biosimilar to EU-/US-Stelara.

4.3.6. Adventitious agents

TSE compliance

No animal- or human-derived substances are used during the production of the Bmab1200 drug substance and drug product except the murine myeloma expression cell line and one material in cell culture media at all cell stages. Cells are murine-derived and as such not derived from a TSE-relevant

species. The cell culture material that is sourced from healthy animals in EU countries.. Furthermore, no human- and animal-origin material was used during cell bank preparation. None of the excipients is of animal or human origin. Thus, compliance with the TSE Guideline (EMEA/410/01 – rev. 3) has been sufficiently demonstrated.

Virus safety

The safety strategy for adventitious viruses includes the use of the well-known murine myeloma host cell line, establishment of a two-tiered cell bank system, testing for potential virus contaminants in the cell banks, testing of production cultures for potential viral contaminants, development and use of a chemically-defined cell culture medium, purification process, formulation that are as most as possible devoid of human or animal proteins, employment of dedicated virus removal steps in the purification process, and a rational evaluation of the overall ability of the purification process to remove/inactivate viruses.

In detail, no animal or human derived raw materials are used during the production of Bmab1200, or have been used in the preparation of the cell banks, except for one raw material used in the culture medium during drug substance manufacture. The raw material has been derived from healthy animals. The processing and treatment of this raw material for virus inactivation has been sufficiently demonstrated prior to use in cell culture medium. The excipients are not of animal or human origin. The cells used for production of Bmab1200 are suspension-adapted murine cells. The MCB, WCB, post-production cells (PPCB) and end-of-production cells (EPCB) were screened sufficiently for endogenous and adventitious viruses (including specific tests for bovine, porcine, murine, human and simian viruses) and found to be negative with the exception of A-type and C-type retrovirus-like particles (RVLP). The testing scheme is in compliance with ICH Q5A. Testing reports, certificates of analysis and validation reports are provided. Further, the preparation and viral testing strategy of future WCBs will follow the same strategy as for the current WCB and is as such acceptable. The unprocessed bulks of the antibody are screened for adventitious viruses by *in vitro* assays and qPCR assay. The specification for these assays) is included in the dossier. The assays are sufficiently qualified. Results for adventitious viruses from three process performance runs are presented demonstrating absence of viruses. Five steps in the manufacturing process have been validated for virus reduction. The virus reduction capacity of the downstream purification process has been investigated using model viruses which is an adequate selection, because they are either specific model virus or unspecific with different physicochemical properties and resistance to physicochemical agents. The overall virus clearance has been sufficiently demonstrated. Details on the down scaling (load material, parameters applied for each step, appropriate controls) and study reports are provided. Furthermore, the representativeness of the down scale performance to the manufacturing scale has been shown by appropriate data.

In summary, the purification process seems to be suitable for reducing potential viral contaminants with different physicochemical attributes from the process, provided the missing information on down scaling and controls can be adequately answered.

4.3.7. GMO

N/A

4.4. Discussion and conclusions on chemical, pharmaceutical and biological aspects

Overall, the provided Module 3 for Bmab1200 is of good quality, and relevant aspects of Bmab1200 manufacturing are, in general, appropriately addressed. In addition, the presented quality data support the biosimilarity between Bmab1200 and Stelara (EU/US).

From the quality perspective the application can be approved.

4.5. Recommendations for future quality development

None

5. Non-clinical aspects

5.1.1. Introduction

The abnormal regulation of IL-12 and IL-23 has been associated with a variety of immune mediated human diseases, including psoriasis, Crohn's disease.

Ustekinumab is a fully human monoclonal antibody composed of an IgG1 heavy chain isotype and a kappa light chain isotype with an approximate molecular weight of 148,600 Daltons. Ustekinumab binds with high affinity and specificity to p40 protein, which is a subunit of cytokines IL-12 and IL-23. Ustekinumab neutralizes bioactivity of IL-12 and IL-23 by binding to IL-12/23p40 and preventing IL-12 and IL-23 binding to the IL-12Rβ1 receptor protein expressed on the surface of natural killer or T cells. Through this mechanism of action, ustekinumab neutralizes IL-12 (Th1) and IL-23 (Th17) mediated cellular responses.

Based on the mechanism of action, the pharmacology of Bmab1200 was evaluated *in vitro* side by side with US-Licensed Stelara and EU-Approved Stelara to demonstrate functional similarity. A comprehensive battery of *in vitro* pharmacodynamic characterisation studies were performed to compare the key biological activities of Bmab1200 DP, US-Licensed Stelara and EU-Approved Stelara.

5.1.2. Pharmacology

5.1.2.1. Primary pharmacodynamic studies

The assays assessed the primary pharmacodynamics of ustekinumab that directly impact clinical effects, including binding to p40 subunit, binding to IL-12 and IL-23, neutralisation of IL-12 induced STAT4 activation, neutralisation of IL-23 induced STAT3 activation, neutralisation of IL-12 induced IFNγ release, neutralisation of IL23 induced IL-17 release, and binding to various Fc receptors (including FcRn) and complement factor C1q. In vivo pharmacology studies were not conducted which is in agreement with relevant guidelines.

All methods used in the functional similarity exercise were qualified or validated and suitable for the intended purpose. No explicit information on the analytical sensitivity of the methods was provided.

The formulations of Bmab1200 DP that were used in the pharmacology studies are representative of Bmab1200 clinical formulations and identical with RMP Stelara formulations.

Generally, the results of these *in vitro* pharmacodynamic studies demonstrated similar functional/biological effects and binding properties between Bmab1200 and RMP Stelara. The results further demonstrated that by preventing IL-12 and IL-23 from binding to the IL-12Rβ1 receptor, Bmab1200 (ustekinumab) can effectively neutralise human IL-12- and IL-23-mediated cell signalling, activation, and cytokine production.

Fc receptors mediate antibody physiology by binding the common Fc region of monoclonal antibodies. These receptors often play important roles in immunomodulation. For example, FcγRIIa is a phagocytic leukocyte receptor while FcγRIIIa is a glycoprotein with affinity for the Fc portion of monoclonal antibodies and a mediator of antibody dependent cell cytotoxicity. FcγRIIIb is selectively expressed in neutrophils and eosinophils and is a decoy receptor that binds IgG complexes. Therefore, FcR binding was carefully evaluated for Bmab1200 and RMP Stelara. For most FcRs including FcRn, which is known to play an important role in antibody pharmacokinetics, Bmab1200 DP demonstrated comparable binding affinity to RMP Stelara. However, a lower binding affinity of Bmab1200 to FcγRIIIa (V158 and F158) and FcγRIIIb compared to RMP Stelara (EU/US) was observed, which is attributed to lower levels of afucosylated glycans in Bmab1200. Generally, no clinical impact is expected as Bmab1200 (ustekinumab) does not induce Fc effector functions such as ADCC and CDC (see also discussion below).

Furthermore, it was shown that Bmab1200 (ustekinumab) cannot bind to receptor-bound IL-12 or IL-23. Thus, Bmab1200 (ustekinumab) is unlikely to mediate Fc effector functions such as ADCC or CDC. Despite the fact that ustekinumab does not act through either of these mechanisms, ADCC and CDC assays were included as part of the comparability exercise. Results confirmed that Bmab1200 and RMS Stelara have no ADCC and CDC activity.

In summary, results obtained across the various comparative assays demonstrate that Bmab1200 DP and RMP Stelara are highly similar in terms of primary pharmacodynamics.

No major issues were identified on the biological/functional similarity assessment. The pharmacology package was considered to sufficiently demonstrate similarity of Bmab1200 and RMP Stelara (EU and US).

5.1.2.2. Secondary pharmacodynamic studies

Comparative secondary pharmacodynamics studies with Bmab1200 and Stelara (ustekinumab) were not conducted. During the analytical similarity exercise no uncertainties are identified that need to be addressed by secondary pharmacodynamics testing.

5.1.2.3. Safety pharmacology programmeme

Safety pharmacology studies comparing Bmab1200 and Stelara (ustekinumab) were not conducted.

According to EMA "Guideline on similar biological medicinal products containing biotechnology-derived proteins as active substance: non-clinical and clinical issues EMEA/CHMP/BMWP/42832/2005 Rev1" studies regarding safety pharmacology are not required for non-clinical testing of biosimilars.

5.1.2.4. Pharmacodynamic drug interactions

No pharmacodynamic drug interaction studies comparing Bmab1200 and Stelara (ustekinumab) were conducted.

5.1.3. Pharmacokinetics

Non-clinical pharmacokinetic (PK) studies comparing Bmab1200 and RMP Stelara (ustekinumab) were not conducted.

Data from the comparative analytical assessment in module 3/4 appear to demonstrate biosimilarity between Bmab1200 and RMP Stelara and no further non-clinical PK studies are deemed necessary.

The absence of PK studies is acceptable and in agreement with the stepwise approach mentioned in EMA "Guideline on similar biological medicinal products CHMP/437/04 Rev 1" and EMA "Guideline on similar biological medicinal products containing biotechnology-derived proteins as active substance: non-clinical and clinical issues EMEA/CHMP/BMWP/42832/2005 Rev1".

In addition, according to "ICH guideline S6 (R1) – preclinical safety evaluation of biotechnology-derived pharmaceuticals", no standard absorption, distribution, metabolism, and excretion (ADME) studies are warranted for biopharmaceuticals.

5.1.4. Toxicology

Comparative toxicology studies were not conducted with Bmab1200 and RMP Stelara. The waiving of such studies is in line with relevant guidelines.

5.1.4.1. Single dose toxicity

Comparative single-dose toxicity studies with Bmab1200 and Stelara (ustekinumab) were not conducted. The waiving of such studies is in line with relevant guidelines.

5.1.4.2. Repeat dose toxicity

Comparative repeat-dose toxicity studies with Bmab1200 and Stelara (ustekinumab) were not conducted. The waiving of such studies is in line with relevant guidelines.

5.1.4.3. Genotoxicity

No genotoxicity studies have been conducted. The waiving of such studies is in line with relevant guidelines.

In general, according to "ICH guideline S6 (R1) – preclinical safety evaluation of biotechnology-derived pharmaceuticals" routine genotoxicity studies are not applicable to biotechnology-derived pharmaceuticals and therefore are not needed.

5.1.4.4. Carcinogenicity

Carcinogenicity studies comparing Bmab1200 and Stelara (ustekinumab) were not conducted. The waiving of carcinogenicity studies is in line with relevant guidelines.

According to EMA "Guideline on similar biological medicinal products containing biotechnology-derived proteins as active substance: non-clinical and clinical issues EMEA/CHMP/BMWP/42832/2005 Rev1" studies regarding carcinogenicity are not required for non-clinical testing of biosimilars.

Furthermore, according to "ICH guideline S6 (R1) – preclinical safety evaluation of biotechnology-derived pharmaceuticals" standard carcinogenicity bioassays are generally inappropriate for biotechnology-derived pharmaceuticals.

5.1.4.5. Reproductive and developmental toxicity

Reproductive and developmental toxicity studies comparing Bmab1200 and Stelara (ustekinumab) were not conducted.

According to EMA "Guideline on similar biological medicinal products containing biotechnology-derived proteins as active substance: non-clinical and clinical issues EMEA/CHMP/BMWP/42832/2005 Rev1" studies regarding reproduction toxicology are not required for non-clinical testing of biosimilars.

5.1.4.6. Toxicokinetic data

N/A

5.1.4.7. Tolerance

Local tolerance studies comparing Bmab1200 and Stelara (ustekinumab) were not conducted. The waiving of these studies is acceptable and in line with relevant guidelines.

According to EMA "Guideline on similar biological medicinal products containing biotechnology-derived proteins as active substance: non-clinical and clinical issues EMEA/CHMP/BMWP/42832/2005 Rev1" studies on local tolerance are usually not required for non-clinical testing of biosimilars.

Bmab1200 has the same formulations, dosage forms, presentations, and product strengths as the reference medicinal product. In addition, the excipients used (L-histidine, L-histidine monohydrochloride monohydrate, L-methionine, ethylenediaminetetraacetic acid disodium salt dihydrate, Polysorbate 80, Sucrose) are standard excipients for monoclonal antibodies and sufficient experience with the excipients is available.

5.1.4.8. Other toxicity studies

Not applicable. No other toxicity studies were conducted.

5.1.5. Ecotoxicity/environmental risk assessment

Bmab1200 is a proposed biosimilar to the reference medicinal product Stelara. The approval of Bmab1200 is not expected to cause increase in environmental exposure and any additional hazards to the environment. An environmental risk assessment is therefore not deemed necessary.

In addition, ustekinumab is a protein, which is expected to biodegrade in the environment and not to be a significant risk to the environment. Thus, according to the 'Guideline on the Environmental Risk Assessment of Medicinal Products for Human Use (EMEA/CHMP/SWP/4447/00 corr 2)', ustekinumab is exempted from preparation of an Environmental Risk Assessment as the product and excipients do not pose a significant risk to the environment.

Furthermore, ustekinumab is already used in existing marketed products (e.g. Stelara) and no significant increase in environmental exposure is anticipated.

5.1.6. Discussion on non-clinical aspects

Bmab1200 has the same amino acid sequence, formulations, dosage forms, presentations, and product strengths as RMP Stelara. In addition, data from the comparative analytical assessment in Module 3/4 appear to demonstrate biosimilarity between Bmab1200 and RMP Stelara. In the analytical similarity exercise minor differences (for details see sections 4.3.5. Biosimilarity) were observed, which are not considered clinically meaningful.

From the provided similarity exercise no uncertainties arise which could be addressed in non-clinical in vivo toxicology studies. Observed differences in the analytical similarity exercise are small and non-clinical in vivo studies are not considered sensitive enough to further evaluate these differences. Observed differences do not preclude biosimilarity.

The biological activity (functional) studies of Bmab1200 were included in module 4 and are also part of the comparative analytical assessment presented in module 3. Analysis of *in vitro* pharmacodynamic (PD) included binding to p40, free and receptor bound IL-12 and IL-23, and IL-6 and IL-10. For functional comparison, neutralisation of IL-12 induced STAT-4 activation and IFNγ release as well as neutralisation of IL-23 induced STAT-3 activation and IL-17 release were studied. Furthermore, potential binding of Bmab1200 to Fc receptors (FcR) and complement factor were analysed via binding to FcRn, C1q, FcγRIa, FcγRIIa, FcγRIIb, FcγRIIIa (V158 and F158), and FcγRIIIb. The comparability exercise also included analysis of antibody dependent cellular cytotoxicity (ADCC) and complement dependent cytotoxicity (CDC) despite that fact that ustekinumab is not known to act through either of these mechanisms.

The results from the *in vitro* PD characterisation studies demonstrated functional similarity between Bmab1200 and RMP Stelara (EU/US), which also provides support for the claimed therapeutic indications of Bmab1200. The analytical methods used were scientifically valid and fit for purpose.

Comparative *in vivo* pharmacology, secondary PD, safety pharmacology, and PD drug interaction studies as well as *in vivo* pharmacokinetics (PK) and toxicology (or toxicokinetic) studies were not conducted. The absence of these studies is considered justified because (i) animal models are not considered sensitive enough to determine pharmacological differences and (ii) comparability exercise revealed no uncertainties, which could be addressed in non-clinical *in vivo* pharmacokinetics and toxicology studies. The waiving of such studies is in line with relevant guidelines.

Labelling of Bmab1200 is based on product labelling for Stelara (ustekinumab) and addresses the following PK aspects based on human data:

- Concomitant use of immunosuppressants or corticosteroids did not appear to influence the safety or efficacy of ustekinumab (section 4.4 SmPC),
- Ustekinumab crosses the placenta and has been detected in the serum of infants born to female patients treated with ustekinumab during pregnancy (section 4.6 SmPC),
- Data from published literature suggests that ustekinumab is excreted in human breast milk in very small amounts (section 4.6 SmPC),
- Distribution, elimination etc. was addressed in human subjects (section 5.2 SmPC),
- CYP450 enzyme activities are not altered by ustekinumab (section 5.2 SmPC).

Additionally, given the results of the analytical similarity exercise, pharmacodynamic drug interactions for Bmab1200 are expected to be similar to those of Stelara. Reference has been made to the Summary of Product Characteristics for the reference medicinal product Stelara. The reference medicinal product is used in patients with plaque psoriasis, psoriatic arthritis, Crohn's disease, and

ulcerative colitis. Concomitant use of immunosuppressants or corticosteroids did not appear to influence the safety or efficacy of ustekinumab.

The active substance is a natural substance, the use of which will not alter the concentration or distribution of the substance in the environment. Therefore, ustekinumab is not expected to pose a risk to the environment.

5.2. Conclusion on non-clinical aspects

In general, the provided Module 4 for Bmab1200 is of good quality, and relevant aspects of Bmab1200 in vitro functional activity compared to RMP Stelara (EU/US) are appropriately addressed. Overall, the presented non-clinical in vitro functional activity data support the biosimilarity of Bmab1200 to Stelara (EU/US).

6. Clinical aspects

6.1. Introduction

6.1.1. Good Clinical Practice (GCP) aspects

The Clinical trials were performed in accordance with GCP as claimed by the applicant.

The applicant has provided a statement to the effect that clinical trials conducted outside the Community were carried out in accordance with the ethical standards of Directive 2001/20/EC.

6.1.2. Tabular overview of clinical trials

- **Tabular overview of clinical studies**

Study No. and Treatments	**Study design**	**Country /Region & No of centres** **No. of patients**	**Primary Objective and Endpoint**
BM12H-NHV-01-G-01 Bmab1200, US-Stelara and EU-Stelara	Randomized, Double-blind, 3-arm, Parallel Design Study in Healthy Subjects to Evaluate Pharmacokinetics, Safety, Tolerability, and Immunogenicity of Bmab1200 After Single Subcutaneous Injection in Comparison with EU-approved Stelara and US-licensed Stelara.	United Kingdom/ 02 258	Primary Objective: To establish PK equivalence between Bmab1200 and US Stelara, Bmab1200 and EU Stelara, and EU Stelara and US Stelara after single 45 mg subcutaneous injection in healthy subjects. Primary Endpoint: AUC_{0-inf} and C_{max} of study drugs following a single 45 mg subcutaneous injection.
BM12H-PSO-03-G-02 Bmab1200 and EU-Stelara	Randomized, double-blind, active-controlled, parallel group, multicentre study to compare efficacy, safety, immunogenicity, and PK of Bmab1200 with EU-Stelara in adult patients with moderate to severe chronic plaque psoriasis.	United States and Europe/ 41 384	Primary Objective: To demonstrate equivalent efficacy between Bmab1200 and Stelara in patients with moderate to severe chronic plaque psoriasis. Primary Endpoint: Percentage change from baseline in the Psoriasis Area and Severity Index (PASI) score at Week 12 (Time Frame: Baseline [Day 1] to Week 12).

6.1.3. Clinical pharmacology

6.1.3.1. Pharmacokinetics

Bioanalytical methods

A summary of the bioanalytical methods and validated assay performance used to compare the pharmacokinetics (PK) and immunogenicity [anti-drug antibodies (ADA) and neutralising antibodies (NAb)] of Bmab 1200, EU-Stelara, and/or US-Stelara, is included in the Table 3 below.

The analytical methods have been validated in accordance the EMA guidelines on bioanalytical method validation (EMEA/CHMP/EWP/192217/2009 Rev. 1 Corr. 2), immunogenicity assessment of therapeutic proteins (EMEA/CHMP/BMWP/14327/2006 Rev 1) and immunogenicity assessment of monoclonal antibodies intended for in vivo clinical use (EMA/CHMP/BMWP/86289/2010). For the ADA and NAb assays, the statistical analysis methods used to determine the cut point are mostly consistent with the procedures recommended by Devanarayan, 2017 and Shankar, 2008.

Table 3. Summary of Bioanalytical Reports associated with PK, ADA and NAb

Description	Applicable Clinical Studies
Validation of an ECLIA (Electrochemiluminescence Immunoassay) method for the determination of ustekinumab in human serum	BM12H-NHV-01-G-01 BM12H-PSO-03-G-02
Validation of a bioanalytical method for the determination of anti-ustekinumab antibodies in human serum by ECLIA	BM12H-NHV-01-G-01 BM12H-PSO-03-G-02
Validation of a bioanalytical method for the determination of anti-ustekinumab neutralizing antibodies in human serum by ECLIA	BM12H-NHV-01-G-01 BM12H-PSO-03-G-02

Modified from Table 3 (2.7.1. Summary of Biopharmaceutic Studies and Associated Analytical Methods)

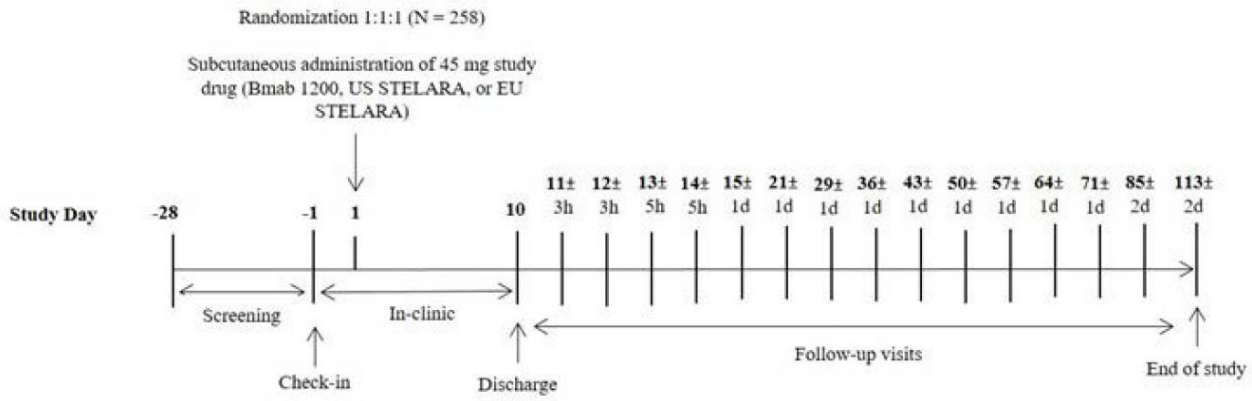
Bioequivalence

Study BM12H-NHV-01-G-01 (Pivotal PK Study)

Trial design

This was a Phase 1, multi-centre, randomized, double-blind, 3-arm, parallel group study in healthy male and female subjects. The study was conducted in the UK, initiated on 20 April 2022 and was completed (last subject's visit) on 13 Mar 2023. See Figure 1 for Study Schematic.

Figure *1*. Study Schematic



The primary objective was to establish PK equivalence between Bmab 1200 and US-Stelara, Bmab 1200 and EU-Stelara, and EU-Stelara and US-Stelara after a single 45 mg subcutaneous injection in terms of $AUC_{0\text{-}inf}$ and C_{max}. The secondary objectives were to further determine the PK of Bmab 1200, US-Stelara, and EU-Stelara ($AUC_{0\text{-}t}$, t_{max}, $t_{1/2}$, k_{el}, V_d/F, CL/F, and $\%AUC_{extrap}$), and to evaluate safety, tolerability, and immunogenicity of Bmab 1200 as compared to US-Stelara and EU-Stelara.

Eligible participants were randomised 1:1:1 to Bmab 1200, EU-Stelara or US-Stelara and dosed with a single therapeutic dose of 45 mg subcutaneously. Stratification factors were ethnic origin (Japanese or non-Japanese), weight range (60.0 to 79.9 kg or 80.0 to 100.0 kg, inclusive), sex and study site.

PK sampling was performed at Day 1 pre-dose, at 12 hours post-dose, on Day 2 (24 hours post dose), 3, 4, 5, 6, 7, 8, 9, 10, 11, 12, 13, 14, 15, 21, 29, 36, 43, 50, 57, 64, 71, 85, and 113. Blood samples for the immunogenicity assessment were collected at Day 1 pre-dose, and Days 7, 15, 29, 57, 85, and 113.

258 participants were randomised and dosed (Bmab 1200 n=86, US-Stelara n= 87, EU-Stelara n= 85). All participants completed the study except one subject who withdrew consent due to work commitments.

Pharmacokinetic evaluations

Three participants were excluded from the PK analysis set due to major protocol deviations: One participant in the US-Stelara group withdrew consent and discontinued the study prematurely on day 5, and one participant in the US-Stelara group and one participant in the EU-Stelara group had a mix-up of samples on three consecutive days due to an error in the sample identification badge. In addition, one subject experienced an important protocol deviation by not completing the PK sample visits on days 43, 50, and 57 due to COVID-19 infection. The subject was not excluded from the PK population. The PK analysis set included n=86 in the Bmab 1200 group, n=85 in the US-Stelara group and n=84 in the EU-Stelara group.

Following a single subcutaneous dose of 45 mg Bmab 1200, US Stelara, or EU Stelara on Day 1, the median t_{max} was approximately 9 days for all treatments with comparable mean C_{max} being attained between treatment arms (see Table 4). Geometric means for $AUC_{0\text{-}inf}$ and $AUC_{0\text{-}t}$ were a little higher after administration of Bmab 1200 compared to EU-Stelara or US-Stelara indicating a trend towards higher exposure with Bmab 1200 compared to the originator. After reaching C_{max}, serum concentrations of ustekinumab appeared to decline in a monophasic manner with a $t_{1/2}$ of 20.5 to 22.1 days. Ustekinumab levels remained quantifiable until the time of the last sample collected across all treatments (Day 113). The mean $\%AUC_{extrap}$ was less than or equal to 3.45% following administration of all 3 study treatments reflecting that the PK sampling duration taken in the study was adequate for reliable estimation of AUC.

Table 4. Summary of Pharmacokinetic Parameters (Pharmacokinetic Population)

Parameter	45 mg Bmab 1200 (N = 86)	45 mg US-Stelara (N = 85)	45 mg EU-Stelara (N = 84)
$AUC_{0\text{-}t}$ (day*ng/mL)	182402 (30.0)	167792 (34.5)	166404 (36.2)
$AUC_{0\text{-}inf}$ (day*ng/mL)	191504 (31.9)	175260 (36.1)	173381 (38.5)
$\%AUC_{extrap}$ (%)	3.45 (120.9)	2.90 (126.0)	2.71 (129.5)
C_{max} (ng/mL)	4459 (28.1)	4351 (29.9)	4494 (28.8)
t_{max} (day)	8.99 (2.97-21.1)	8.97 (0.500-21.0)	8.96 (3.00-21.1)
t_{last} (day)	112 (20.0-114)	112 (42.1-115)	112 (43.1-115)
k_{el} (1/day)	0.0314 (43.4)	0.0325 (36.0)	0.0338 (33.3)
$t_{1/2}$ (day)	22.1 (43.4)	21.3 (36.0)	20.5 (33.3)
CL/F (L/day)	0.235 (31.9)	0.257 (36.1)	0.260 (38.5)
V_d/F (L)	7.48 (30.4)	7.90 (28.8)	7.68 (24.6)
$AUC_{0\text{-}inf}/P$ ((day*ng/mL)/(mg/mL))	2135 (31.9)	1998 (36.1)	1935 (38.5)
C_{max}/P ((ng/mL)/(mg/mL))	49.7 (28.1)	49.6 (29.9)	50.2 (28.8)

Parameter	45 mg Bmab 1200 (N = 86)	45 mg US-Stelara (N = 85)	45 mg EU-Stelara (N = 84)

$AUC_{0\text{-}inf}$ = area under the concentration-time curve from time 0 extrapolated to infinity; $AUC_{0\text{-}inf}/P$ = investigational medicinal product protein-content adjusted area under the concentration-time curve from time 0 extrapolated to infinity; $AUC_{0\text{-}t}$ = area under the concentration-time curve from time 0 to the time of the last quantifiable concentration; CL/F = apparent total clearance; C_{max} = maximum observed concentration; C_{max}/P = investigational medicinal product protein-content adjusted maximum observed concentration; CV = coefficient of variation (%); k_{el} = apparent terminal elimination rate constant; N = number of subjects; $t_{1/2}$ = apparent terminal elimination half-life; t_{last} = time of the last quantifiable concentration; t_{max} = time of the maximum observed concentration; V_d/F = apparent volume of distribution during the terminal phase; $\%AUC_{extrap}$ = percentage of area under the concentration-time curve due to extrapolation from the last quantifiable concentration to infinity
Geometric mean (CV) statistics presented; for t_{max} and t_{last}, median (minimum-maximum) statistics presented.

For all the 3 pairwise comparisons (Bmab 1200 vs US-Stelara, Bmab 1200 vs EU-Stelara and US-Stelara vs EU-Stelara), the bioequivalence criterion was based on the geometric least squares mean (GLSM) ratios of the primary PK parameters ($AUC_{0\text{-}inf}$ and C_{max}). Statistical analysis demonstrated PK similarity as the 90% CIs of GLSMs ratio for both primary PK parameters ($AUC_{0\text{-}inf}$ and C_{max}), as well as $AUC_{0\text{-}t}$, were entirely contained within the predefined bioequivalence range of 0.8000 and 1.2500 for each of the three pairwise comparisons (see Table 5).

Table 5. Summary of Statistical Analysis of Pharmacokinetic Parameters

				Test vs Reference	
Parameter	**Treatment**	**n**	**GLSM**	**Ratio of GLSMs (90% CI)**	**Between -subject CV**
$AUC_{0\text{-}inf}$ (day*ng/mL)	45 mg US-Stelara (Reference)	85	165115	---	---
	45 mg Bmab 1200 (Test)	86	178047	1.0783 (0.9975, 1.1657)	31.5
	45 mg EU-Stelara (Reference)	84	158237	---	---
	45 mg Bmab 1200 (Test)	86	170698	1.0787 (0.9959, 1.1685)	32.2
	45 mg EU-Stelara (Reference)	84	164979	---	---
	45 mg US-Stelara (Test)	85	165574	1.0036 (0.9223, 1.0921)	34.1
C_{max} (ng/mL)	45 mg US-Stelara (Reference)	85	3967	---	---
	45 mg Bmab 1200 (Test)	86	4001	1.0085 (0.9478, 1.0732)	24.9
	45 mg EU-Stelara (Reference)	84	4185	---	---
	45 mg Bmab 1200 (Test)	86	4074	0.9736 (0.9136, 1.0376)	25.4
	45 mg EU-Stelara (Reference)	84	4224	---	---
	45 mg US-Stelara (Test)	85	4064	0.9619 (0.9012, 1.0267)	26.0
$AUC_{0\text{-}t}$ (day*ng/mL)[#]	45 mg US-Stelara (Reference)	85	158237	---	---
	45 mg Bmab 1200 (Test)	86	169784	1.0730 (0.9967, 1.1551)	29.7
	45 mg EU-Stelara (Reference)	84	153115	---	---
	45 mg Bmab 1200 (Test)	86	164157	1.0721 (0.9941, 1.1563)	30.3
	45 mg EU-Stelara (Reference)	84	158738	---	---
	45 mg US-Stelara (Test)	85	158951	1.0013 (0.9242, 1.0850)	32.3

				Test vs Reference	
Parameter	**Treatment**	**n**	**GLSM**	**Ratio of GLSMs (90% CI)**	**Between -subject CV**

AUC_{0-t} applicable for submission to BRDD (Health Canada)
AUC_{0-inf} = area under the concentration-time curve from time 0 extrapolated to infinity; AUC_{0-t} = area under the concentration-time curve from time 0 to the time of the last quantifiable concentration; CI = confidence interval; C_{max} = maximum observed concentration; CV = coefficient of variation (%); GLSM = geometric least squares mean; ln = natural log; LSM = least square mean; n = number of subjects with valid observations
Model: ln(parameter) = treatment + body weight + ethnic origin (Japanese/Non-Japanese) + sex + study site + random error
The GLSMs, ratios of GLSMs, and corresponding CIs were obtained by taking the exponential of the LSMs, differences in LSMs, and corresponding CIs on the ln scale.

Supportive statistical PK analyses

In a pre-specified supportive analysis, a correction for protein content of the primary parameters has been conducted by considering the protein concentration of the respective batch. Statistical analysis of AUC_{0-inf}/P and C_{max}/P supported the PK similarity of Bmab 1200 and Stelara, as 90% CIs of GLSMs ratios fell within the bioequivalence range of 0.8000 and 1.2500 for all pairwise comparisons.

Subgroup analysis of both primary PK parameters revealed PK similarity irrespective of ethnicity (Japanese/non-Japanese). No significant effects of the ADA status on the GLSMs of the primary PK parameters have been observed.

Partial AUC analyses

The median Tmax (minimum – maximum) observed in the phase-1 study was ~ 9 days (3 – 21 days). For the evaluation of partial AUCs, several time frames were selected to characterise both the absorption phase (starting after subcutaneous administration from Day 0; SET 1) and elimination phase (predominantly starting Day 15 onwards; SET 2 & 3) adequately. In Set 1 of the Table 6 the partial AUCs - AUC(Day0-Day9); AUC(Day0-Day15); AUC(Day0-Day21) and AUC(Day0-Day36) represent predominantly the absorption phase while the partial AUCs- AUC(Day0-Day50); AUC(Day0-Day64); AUC(Day0-Day85) and AUC(Day0-Day113) represent both the absorption and the elimination phase.

In Set 2, the partial AUCs- AUC(Day15-Day113); AUC(Day21-Day113); AUC(Day36-Day113); AUC(Day50-Day113); AUC(Day64-Day113); AUC(Day71-Day113) and AUC(Day85-Day113) represent predominantly the elimination phase. Set 3 is the corresponding AUC values extrapolated to infinity.

Table 6. Summary of Partial AUCs

Partial AUC (day*ng/mL)	Bmab1200	US Stelara	EU Stelara
	Arithmetic mean (%CV)		
AUC0-Day9	26700 (33.5)	26700 (40.3)	27200 (34.3)
AUC0-Day15	51500 (28.4)	50400 (32.1)	51400 (29.7)
AUC0-Day21	73100 (25.7)	71100 (29.1)	72600 (27.8)
AUC0-Day36	116000 (23.8)	111000 (26.7)	112000 (27.2)
AUC0-Day50	144000 (23.9)	136000 (26.7)	138000 (28.0)
AUC0-Day64	164000 (23.8)	154000 (26.2)	157000 (29.1)
AUC0-Day85	183000 (24.9)	171000 (26.2)	173000 (30.5)
AUC0-Day113	194000 (25.7)	184000 (25.8)	186000 (31.6)
AUCDay15-113	143000 (28.2)	133000 (27.2)	133000 (36.5)
AUCDay21-113	120000 (30.5)	112000 (29.3)	113000 (39.1)
AUCDay36-113	77000 (36.5)	70900 (35.4)	71100 (46.7)
AUCDay50-113	49100 (42.4)	45100 (39.9)	44700 (52.4)
AUCDay64-113	29600 (47.9)	26700 (45.7)	26200 (61.0)
AUCDay71-113	21900 (51.9)	19800 (50.0)	19600 (63.8)
AUCDay85-113	11300 (54.4)	10300 (55.4)	10300 (70.0)
AUCDay15-inf	149000 (34.7)	135000 (36.5)	134000 (45.0)
AUCDay21-inf	127000 (37.9)	114000 (39.9)	114000 (48.9)
AUCDay36-inf	85300 (44.4)	75100 (46.9)	74400 (60.2)
AUCDay50-inf	58000 (53.3)	51000 (53.9)	50100 (68.7)
AUCDay64-inf	40000 (59.0)	33900 (61.5)	33900 (78.2)
AUCDay71-inf	32300 (64.3)	27700 (66.6)	27800 (82.0)
AUCDay85-inf	22300 (69.0)	18700 (75.6)	18800 (93.4)

CV: coefficient of variation

Table 7. Statistical Evaluation of Partial AUCs

Partial AUC	Treatment (T Vs. R)	Reference (R)		Test (T)		Point Estimate	90% C.I.		Between Subject %CV
		N	GLSM	N	GLSM		Lower	Upper	
Table 7**a: AUC(Day0-DayX) (SET 1)**									
AUC0-Day9	Bmab1200 Vs. US Stelara	85	21386	86	21305	0.9962	0.9097	1.0909	37.0
	Bmab1200 vs. EU Stelara	84	23286	86	22454	0.9643	0.8814	1.0550	36.4
	US Vs. EU Stelara	84	23907	85	22961	0.9604	0.8748	1.0544	37.9
AUC0-Day15	Bmab1200 Vs. US Stelara	85	43060	86	43542	1.0112	0.9410	1.0866	29.0
	Bmab1200 vs. EU Stelara	84	45444	86	44714	0.9839	0.9145	1.0587	29.3
	US Vs. EU Stelara	84	46610	85	45151	0.9687	0.8998	1.0429	29.6
AUC0-Day21	Bmab1200 Vs. US Stelara	84	62221	85	63505	1.0206	0.9574	1.0881	25.5
	Bmab1200 vs. EU Stelara	82	64524	85	64250	0.9958	0.9319	1.0640	26.2
	US Vs. EU Stelara	82	66340	84	64565	0.9733	0.9097	1.0412	26.7
AUC0-Day36	Bmab1200 Vs. US Stelara	81	99581	83	103689	1.0413	0.9799	1.1065	23.8
	Bmab1200 vs. EU Stelara	81	101401	83	103565	1.0213	0.9600	1.0866	24.2
	US Vs. EU Stelara	81	103859	81	101859	0.9807	0.9188	1.0469	25.5
AUC0-Day50	Bmab1200 Vs. US Stelara	82	122165	84	128577	1.0525	0.9901	1.1188	24.1
	Bmab1200 vs. EU Stelara	81	122951	84	126451	1.0285	0.9676	1.0932	23.9

	US Vs. EU Stelara	81	125795	82	123012	0.9779	0.9154	1.0447	25.9
AUC0-Day64	Bmab1200 Vs. US Stelara	83	138072	82	146298	1.0596	0.9975	1.1255	23.7
	Bmab1200 vs. EU Stelara	76	137332	82	143132	1.0422	0.9786	1.1100	24.2
	US Vs. EU Stelara	76	140494	83	138125	0.9831	0.9192	1.0515	26.0
AUC0-Day85	Bmab1200 Vs. US Stelara	81	151522	81	160813	1.0613	0.9996	1.1268	23.3
	Bmab1200 vs. EU Stelara	79	151243	81	160030	1.0581	0.9920	1.1286	25.0
	US Vs. EU Stelara	79	153128	81	152725	0.9974	0.9327	1.0665	26.0
AUC0-Day113	Bmab1200 Vs. US Stelara	77	162720	81	171194	1.0521	0.9884	1.1198	24.0
	Bmab1200 vs. EU Stelara	73	161613	81	169182	1.0468	0.9795	1.1188	25.2
	US Vs. EU Stelara	73	164376	77	163828	0.9967	0.9286	1.0697	26.5
Table 7**b: AUC(DayX-Day113) (SET 2)**									
AUCDay15-113	Bmab1200 Vs. US Stelara	77	117636	81	124945	1.0621	0.9903	1.1392	27.0
	Bmab1200 vs. EU Stelara	73	113218	81	122157	1.0790	0.9999	1.1643	29.0
	US Vs. EU Stelara	73	114745	77	116841	1.0183	0.9386	1.1047	30.7
AUCDay21-113	Bmab1200 Vs. US Stelara	76	98117	80	104397	1.0640	0.9846	1.1498	29.8
	Bmab1200 vs. EU stelara	71	94108	80	101720	1.0809	0.9940	1.1753	31.7
	US Vs. EU Stelara	71	95359	76	97024	1.0175	0.9292	1.1141	34.0
AUCDay36-113	Bmab1200 Vs. US Stelara	74	58883	79	64205	1.0904	0.9905	1.2004	37.0
	Bmab1200 vs. EU Stelara	71	55987	79	61998	1.1074	0.9996	1.2267	39.1
	US Vs. EU Stelara	71	56651	74	57725	1.0190	0.9112	1.1395	42.2
AUCDay50-113	Bmab1200 Vs. US Stelara	75	36239	80	38897	1.0733	0.9592	1.2011	44.0
	Bmab1200 vs. EU Stelara	72	33408	80	37486	1.1221	0.9985	1.2608	45.4
	US Vs. EU Stelara	72	33427	75	35138	1.0512	0.9270	1.1919	48.3
AUCDay64-113	Bmab1200 Vs. US Stelara	77	20710	80	22910	1.1062	0.9725	1.2584	51.7
	Bmab1200 vs. EU Stelara	70	18372	80	21816	1.1875	1.0313	1.3673	55.6
	US Vs. EU Stelara	70	19106	77	20517	1.0739	0.9234	1.2488	59.3
AUCDay71-113	Bmab1200 Vs. US Stelara	75	15170	81	16609	1.0948	0.9513	1.2600	56.7
	Bmab1200 vs. EU Stelara	73	13455	81	15721	1.1684	1.0048	1.3586	61.1
	US Vs. EU Stelara	73	13968	75	14952	1.0704	0.9108	1.2580	64.7
AUCDay85-113	Bmab1200 Vs. US Stelara	76	7538	80	8386	1.1126	0.9517	1.3006	64.2
	Bmab1200 vs. EU Stelara	73	6546	80	7788	1.1896	0.9992	1.4164	72.5
	US Vs. EU Stelara	73	7166	76	7672	1.0705	0.8872	1.2918	78.1
Table 7**c: AUC(DayX-Inf) (SET 3)**									
AUCDay15-inf	Bmab1200 Vs. US Stelara	85	119490	86	135110	1.1307	0.9990	1.2798	51.9
	Bmab1200 vs. EU Stelara	84	110812	86	123938	1.1185	1.0018	1.2486	45.3
	US Vs. EU Stelara	84	118532	85	118069	0.9961	0.8775	1.1308	53.1
AUCDay21-inf	Bmab1200 Vs. US Stelara	84	99618	85	114200	1.1464	0.9787	1.3428	68.5
	Bmab1200 vs. EU Stelara	82	92259	85	102868	1.1150	0.9707	1.2807	58.1
	US Vs. EU Stelara	82	99609	84	97923	0.9831	0.8430	1.1464	65.6
AUCDay36-inf	Bmab1200 Vs. US Stelara	81	61296	83	76650	1.2505	1.0445	1.4970	78.9
	Bmab1200 vs. EU Stelara	81	53319	83	66980	1.2562	1.0695	1.4756	68.5
	US Vs. EU Stelara	81	59753	81	61051	1.0217	0.8244	1.2662	98.5
AUCDay50-inf	Bmab1200 Vs. US Stelara	82	39601	84	48503	1.2248	0.9720	1.5433	111.0
	Bmab1200 vs. EU Stelara	81	30537	84	36867	1.2073	0.9958	1.4636	86.0
	US Vs. EU Stelara	81	34224	82	34920	1.0203	0.7987	1.3036	120.0

AUCDay64-inf	Bmab1200 Vs. US Stelara	83	24466	82	30768	1.2576	1.0261	1.5412	92.8
	Bmab1200 vs. EU Stelara	76	19492	82	25401	1.3031	1.0621	1.5988	90.4
	US Vs. EU Stelara	76	22298	83	23334	1.0464	0.8295	1.3201	108.0
AUCDay71-inf	Bmab1200 Vs. US Stelara	80	19156	83	22834	1.1920	0.9740	1.4588	91.1
	Bmab1200 vs. EU Stelara	79	16365	83	20467	1.2506	1.0179	1.5366	93.1
	US Vs. EU Stelara	79	18017	80	18982	1.0535	0.8516	1.3034	96.4
AUCDay85-inf	Bmab1200 Vs. US Stelara	81	11633	81	15402	1.3240	1.0650	1.6458	100.0
	Bmab1200 vs. EU Stelara	79	9581	81	13292	1.3872	1.1085	1.7361	104.0
	US Vs. EU Stelara	79	11364	81	11965	1.0529	0.8167	1.3574	125.0

Based on the above data presented in the Table 7 above, the applicant believes that the post-hoc analysis of partial AUCs for Bmab1200 and EU Stelara with various timepoints further supports the robustness of the demonstrated similarity in the primary PK endpoints of Study BM12H-NHV-01-G-01 between Bmab1200 and EU Stelara in normal healthy subjects, which is considered the most sensitive population to detect potential differences in PK between products. Further, therapeutic equivalence of Bmab1200 and Stelara was established in patient population and C_{trough} concentration from baseline to Week 52 were similar between the treatment groups, when multiple doses were given to patients.

Effect of ADA on PK Parameters

The number of subjects who were ADA negative was very few. The analysis supported that the overall absorption and exposure of all the 3 drug products were unaffected by the presence of ADA (including treatment emergent ADA) as GLSM and 90% CI were within the range of 0.800 to 1.2500. Also, mean $t_{1/2}$ values were comparable among the 3 treatment groups (~22 days). Few subjects were observed with comparatively lower $t_{1/2}$ (<11 days) values and have below limit of quantification (BLQ) concentrations in the terminal phase of PK concentration vs time profile. This was observed across the three treatment groups (n= 4, 4 and 5 in Bmab 1200, the US-Stelara and the EU-Stelara group, respectively).

Study BM12H-PSO-03-G-02

This is a randomised, double-blind, parallel group, multicentre, phase 3 study to compare the efficacy and safety of Bmab 1200 and Stelara in patients with moderate to severe chronic plaque psoriasis. Currently, the phase 3 study has been completed up to Week 28. . Updated analyses of data up to Week 52 was submitted during the procedure.

The PK evaluation was a secondary endpoint in the phase 3 study wherein the trough concentration (C_{trough}) was compared for Bmab 1200 with Stelara at pre-dose during TP1 (from baseline through Week 16) and during TP2 (from post-dose on Week 16 through Week 28 prior to dosing). The blood samples were collected for PK analysis to measure ustekinumab serum concentrations from all patients at baseline, Week 2, prior to dosing at Week 4, Week 8, Week 12, prior to dosing at Week 16, Week 20, and Week 28 (pre dose).

The results are summarised descriptively. PK results are presented by body weight category (<100 kg and ≥100 kg) which reflects administration of the higher dose (1 or 2 doses equivalent to 45 mg or 90 mg).

Treatment period 1 (TP1)

The PK Data Set (PKS) included all 191 patients (100%) dosed with Bmab 1200 and 192/193 patients (99.5%) dosed with EU-Stelara. The one patient excluded from the PKS did not have at least 1 post-treatment PK result.

Serum concentrations of ustekinumab were quantifiable at baseline in 6 patients, (1 in the Bmab 1200, 45 mg group, 3 in the Bmab 1200, 90 mg group and 2 in the Stelara group) with geometric mean values ranging from 12.000 to 347.667 ng/mL (see Table 8). All patients were naïve to ustekinumab per the eligibility criteria and there was no protocol deviation related to the sample collection. The reason for pre-dose concentration is currently unknown.

Patients with higher body weight and higher doses had higher C_{trough} levels compared to patients receiving the 45 mg dose. Serum concentrations of ustekinumab were similar in patients weighing >100 kg receiving 2 injections of either Bmab 1200 or Stelara. The 95% CI of the mean ustekinumab concentration at each study visit overlapped between the two treatments. In patients weighing ≤100 kg administered 1 injection of either Bmab 1200 or Stelara, the 95% CI of the mean ustekinumab concentrations were slightly higher in the Bmab 1200 treatment at each study visit compared to the Stelara treatment with the exception of Week 16 where the 95% CI of the mean overlapped. Variability (%CV) in ustekinumab serum concentrations in both treatments ranged from 26.2% to 68.1% throughout the treatment period. Considering the variability observed, ustekinumab serum concentrations were similar in patients administered 1 or 2 injections of Bmab 1200 compared to those administered 1 or 2 injections of Stelara, respectively.

Table 8. Summary of Ustekinumab Serum Concentrations at Baseline, and at Weeks 2, 4, 8, 12 and 16 (Treatment Period 1) (PK Analysis Set)

	Bmab 1200 1 injection N=151	**Bmab 1200 2 injections N=40**	**Stelara 1 injection N=149**	**Stelara 2 injections N=43**
Baseline				
n	1	3	2	0
Arithmetic Mean (SD)	12.000 (-)	347.667 (455.8688)	15.600 (10.1823)	
%CV	-	131.1	65.3	
95% CI	-	-784.774-1480.107	-75.885-107.085	
Week 2				
n	151	40	146	43
Arithmetic Mean (SD)	4015.033 (1232.1071)	5406.000 (1648.6868)	3610.982 (1200.1527)	5278.837 (1876.1323)
%CV	30.7	30.5	33.2	35.5
95% CI	3816.914-4213.152	4878.724-5933.276	3414.669-3807.294	4701.449-5856.226
Week 4				
n	150	40	148	43
Arithmetic Mean (SD)	2818.867 (921.0372)	3585.250 (1091.7429)	2438.757 (897.5035)	3418.767 (1383.0000)
%CV	32.7	30.5	36.8	40.5
95% CI	2670.266-2967.468	3236.094-3934.406	2292.961-2584.552	2993.143-3844.392
Week 8				
n	150	38	147	43
Arithmetic Mean (SD)	4077.073 (1469.7773)	5678.684 (1489.1212)	3555.265 (1419.9915)	4906.628 (2069.0816)
%CV	36.0	26.2	39.9	42.2

95% CI	3839.938-4314.208	5189.222-6168.146	3323.798-3786.733	4269.859-5543.397
Week 12				
n	148	39	140	42
Arithmetic Mean (SD)	1907.181 (905.0071)	2295.949 (834.8755)	1541.633 (852.1823)	2079.425 (1044.1050)
%CV	47.5	36.4	55.3	50.2
95% CI	1760.167-2054.195	2025.313-2566.584	1399.231-1684.034	1754.059-2404.791
Week 16				
n	145	39	132	40
Arithmetic Mean (SD)	891.526 (559.8582)	1039.128 (539.6758)	731.999 (498.1921)	952.865 (585.0087)
%CV	62.8	51.9	68.1	61.4
95% CI	799.627-983.424	864.186-1214.071	646.219-817.780	765.770-1139.960

Abbreviations: BLQ, below the limit of quantification; %CV, % coefficient of variation; N, number of patients in the treatment group; n, number of patients with available data; SD, standard deviation; 95% CI, 95% confidence interval of the mean.
Note: Patients weighing ≤ 100 kg at baseline received 1 injection (45 mg) study drug. Patients weighing >100 kg at baseline received 2 injections (90 mg) study drug. Patients with BLQ values were not included for descriptive summary. Lower limit of quantification = 8 ng/mL. Percentage (%) for number of BLQs was calculated using the number of patients with available data (including BLQ) at the visit.

Treatment period 2 (TP2)

PKS2 included all 371 patients eligible for re-randomisation, whereas 11 patients discontinued the study after TP1: 185 patients in the Bmab 1200 arm, 94 patients in the Stelara-Stelara arm and 92 patients in the Stelara-Bmab 1200 arm. Serum concentrations of ustekinumab at Week 20 and Week 28 are summarised in Table 9. Serum concentrations of ustekinumab were similar in patients weighing ≤100 kg receiving 1 injection and weighing >100 kg receiving 2 injections of either Bmab 1200 or Stelara, regardless of group. The 95% CI of the mean ustekinumab concentration after 1 injection or 2 injections at each study visit were comparable between the three study groups.

Table 9. Summary of Ustekinumab Serum Concentrations at Week 20 and Week 28 (Treatment Period 2) (PK Analysis Set 2)

	Bmab 1200 1 injection N=146	**Stelara-Stelara 1 injection N=73**	**Stelara-Bmab 1200 1 injection N=71**	**Bmab 1200 2 injections N=39**	**Stelara-Stelara 2 injections N=21**	**Stelara-Bmab 1200 2 injections N=21**
Week 20						
n	143	72	70	39	21	21
Arithmetic Mean (SD)	3282.385 (1201.3955)	2839.333 (1130.4270)	2914.857 (1120.4114)	4302.564 (1335.6128)	4241.619 (1860.7381)	4514.286 (1696.7721)
%CV	36.6	39.8	38.4	31.0	43.9	37.6
95% CI	3083.783-3480.986	2573.696-3104.971	2647.704-3182.010	3869.609-4735.520	3394.621-5088.617	3741.924-5286.647
Week 28						
n	142	68	67	39	18	21
Arithmetic Mean (SD)	677.753 (452.5273)	589.109 (419.7794)	624.394 (389.0534)	803.897 (405.1394)	952.183 (553.2285)	889.681 (550.6656)
%CV	66.8	71.3	62.3	50.4	58.1	61.9
95% CI	602.678-752.827	487.501-690.717	529.496-719.292	672.566-935.228	677.069-1227.297	639.021-1140.341

Abbreviations: BLQ, below the limit of quantification; %CV, % coefficient of variation; N, number of patients in the treatment group; n, number of patients with available data; SD, standard deviation; 95% CI, 95% confidence interval of the mean.
Note: Patients weighing ≤ 100 kg at baseline received 1 injection (45 mg) study drug. Patients weighing >100 kg at baseline received 2 injections (90 mg) study drug. Patients with BLQ values were not included for descriptive summary. Lower limit of quantification = 8 ng/mL. Percentage (%) for number of BLQs was calculated using the number of patients with available data (including BLQ) at the visit.

Treatment Period 2 + Treatment Period 3

During TP2+TP3, serum concentrations of ustekinumab were similar in patients weighing ≤100 kg administered 1 injection and weighing >100 kg administered 2 injections of either Bmab 1200 or Stelara, regardless of group. The 95% CI of the mean ustekinumab concentration after 1 injection or 2 injections at each study visit were comparable among the 3 study groups.

Table 10. Summary of Ustekinumab Serum Concentrations at Weeks 20, 28, 40, and 52 (Treatment Period 2 + Treatment Period 3) (Pharmacokinetic Analysis Set 3)

	Bmab 1200 1 injection N=146	**Stelara-Stelara 1 injection N=73**	**Stelara-Bmab 1200 1 injection N=71**	**Bmab 1200 2 injections N=39**	**Stelara-Stelara 2 injections N=21**	**Stelara-Bmab 1200 2 injections N=21**
Week 20						
n	130	61	61	36	15	20
Arithmetic Mean (SD)	3330.823 (1199.9401)	2882.063 (1092.2896)	2854.219 (1117.0924)	4361.944 (1367.3558)	4616.235 (1766.5371)	4464.500 (1725.0430)
%CV	36.0	37. 9	39.1	31.3	38.3	38.6
95% CI	3122.600-3539.046	2606.974-3157.153	2575.177-3133.260	3899.298-4824.591	3707.966-5524.505	3657.155-5271.845
Week 28						
n	130	61	61	36	15	20
Arithmetic Mean (SD)	678.308 (444.7791)	589.780 (418.9308)	620.793 (398.1352)	796.833 (392.6448)	1070.600 (522.0039)	861.665 (549.4014)
%CV	65.6	71.0	64.1	49.3	48.8	63.8
95% CI	601.127-755.490	482.487-697.073	518.826-722.761	663.981-929.685	781.524-1359.676	604.537-1118.793
Week 40						
n	128	61	61	36	16	20
Arithmetic Mean (SD)	749.909 (471.7678)	633.469 (426.3308)	637.943 (403.3880)	883.444 (561.4845)	898.238 (588.4221)	839.935 (593.6305)
%CV	62.9	67.3	63.2	63.6	65.5	70.7
95% CI	667.394-832.423	524.280-742.657	534.630-741.255	693.465-1073.423	584.689-1211.786	562.107-1117.763
Week 52						
n	127	60	61	35	17	20
Arithmetic Mean (SD)	728.029 (477.1775)	665.403 (379.9506)	653.908 (415.8309)	881.343 (510.0086)	1008.382 (671.8667)	898.450 (551.4494)
%CV	65.5	57.1	63.6	57.9	66.6	61.4
95% CI	644.234-811.824	567.252-763.555	547.409-760.407	706.149-1056.537	662.940-1353.824	640.364-1156.536

Note: Patients weighing ≤ 100 kg at baseline received 1 injection (45 mg) study treatment. Patients weighing >100 kg at baseline received 2 injections (90 mg) study treatment. Patients with BLQ values were not included for descriptive summary. Lower limit of quantification = 8 ng/mL. Percentage (%) for number of BLQs was calculated using the number of patients with available data (including BLQ) at the visit.

Effect of ADA on Ustekinumab Concentration

The impact of ADA status- positive/negative and NAb status- reactive/negative on C_{trough} concentrations has been conducted. The results from the exploratory analysis performed to assess the effects of ADA and NAbs on the concentration data showed no apparent treatment-related differences (Table 22).

Further, to assess the impact of ADA titres, the C_{trough} values for patients by ADA titre (high, low, and moderate) and NAb status was also provided by the applicant. The ADA titres have been classified into low, moderate and high based on quartile distribution of titre values [low (<=Q1, for first 25%), medium (Q1-Q3, between 25 – 75%), high (>Q3, for last 25%).

At each visit, for both Bmab1200 and Stelara treatment arm, the mean C_{trough} concentration in ADA titre- high/NAb-reactive stratum are nominally lower in comparison to ADA titre low/ moderate stratums. However, the 95% confidence interval for mean C_{trough} concentration for both Bmab1200 and Stelara overlap between ADA titres (high, low, and moderate) Nab status (reactive/negative) stratum.

The slight difference observed in mean C_{trough} concentrations in various strata by ADA titre (high/moderate/low) and NAb status (reactive/negative) are not deemed clinically significant as evident from the percentage change from baseline in PASI score at week 12 by ADA status-Positive (low/medium and high titre)/-negative and NAb (Reactive/Negative) shows no difference. This difference observed in ADA-high titre/NAb-reactive stratum is in accordance to that reported for Stelara.

Special populations

Not applicable.

6.1.3.2. Pharmacodynamics

Mechanism of action

Ustekinumab is a human IgG1 kappa monoclonal antibody that specifically binds to the shared p40 subunit of the human cytokines IL-12 and IL-23. Ustekinumab prevents human IL-12 and IL-23 from binding to the IL-12Rβ1 receptor chain of IL-12 (IL-12Rβ1/β2) and IL-23 (IL-12Rβ1/23R) receptor complexes on the surface of Natural Killer (NK) and T lymphocytes (T cells).

Primary and Secondary pharmacology

Since this is a biosimilar application, the primary and secondary pharmacology does not have to be characterised.

6.1.4. Discussion on clinical pharmacology

PK equivalence data for Bmab 1200 were generated in a single PK study in healthy volunteers (BM12H-NHV-01-G-01) following a single SC injection compared to US-approved and EU-approved Stelara. In addition, a Phase 3 confirmatory study in adult patients with moderate to severe chronic plaque psoriasis (BM12H-PSO-03-G-02) evaluated steady-state PK characteristics following multiple SC administrations of Bmab 1200 and EU-approved Stelara.

Bioanalytical methods

The analytical method for the determination of ustekinumab concentrations in normal and diseased human plasma was validated for precision and accuracy, bioanalytical similarity, selectivity, specificity, sample stability and dilution linearity according to the current ICH M10 guideline on bioanalytical method validation (EMA/CHMP/ICH/172948/2019). Analysis of study samples from healthy volunteers and patients with psoriasis supported the performance and precision of the PK assay and demonstrated acceptable incurred sample analysis and parallelism results. Overall, the analytical method is acceptable and meets the EMA acceptance criteria.

A standard three-step approach was used to detect and characterise ADA in accordance with the Guideline on Immunogenicity assessment of biotechnology-derived therapeutic proteins (EMEA/CHMP/BMWP/14327/2006 Rev.1) and on Immunogenicity assessment of monoclonal antibodies intended for in vivo clinical use (EMA/CHMP/BMWP/86289/2010): Screening of ADA-positive samples, confirmation of ADA-positivity and assessment of ADA titre in confirmed ADA-positive samples. ADA assay validation parameters included sensitivity, screening and inhibition cut points, selectivity, intra- and inter-run precision, hook effect and stability. The statistical method used to determine the cut points is generally consistent with the procedures recommended by Devanarayan et al, 2017 and Shankar et al, 2008. The immunogenicity assay used in the study had a highly drug tolerant ADA method with a high sensitivity. Hence, high ADA positive rate was observed in PsO patients in both groups and were over 95% at any time point during the study.

Nevertheless, given the comparable levels of ADA and NAbs observed between treatment arms and the extensive clinical data collected from patients, it has been decided not to investigate this issue further. The overall body of evidence appears to outweigh concerns about the performance of the assay in this context.

The NAb assay platform was sufficiently validated for sensitivity, cut points, selectivity, intra- and inter-run precision, hook effect and stability and is considered suitable for its intended use.

Pharmacokinetics in healthy volunteers (BM12H-NHV-01-G-01)

Design and conduct of clinical study

The pivotal PK study BM12H-NHV-01-G-01 was a Phase 1, multi-centre, randomised, double-blind, single-dose, 3-arm, parallel group study to establish PK equivalence between Bmab 1200, US-Stelara, and EU-Stelara in healthy subjects. Subjects were randomised in a 1:1:1 ratio to receive a single SC dose of 45 mg on Day 1 and followed up until Day 113.

According to the EMA "Guideline on similar biological medicinal products containing monoclonal antibodies - non-clinical and clinical issues" (EMA/CHMP/BMWP/403543/2010), a single-dose study in healthy volunteers at the lowest therapeutic dose used in patients is the preferred bioequivalence study design, which was used in this study. The selected 45 mg SC dose is considered to be a sufficiently sensitive dose to demonstrate biosimilarity between Bmab 1200 and Stelara. In addition, as the reference product is approved for both IV and SC administration, the SC route was selected, which is preferred for PK comparability studies as it covers both absorption and elimination. A parallel group design is acceptable given the expected long half-life of the monoclonal antibody (approximately 3 weeks). Overall, the study design, dose and route of administration were acceptable and in line with relevant EMA guidance (EMA/CHMP/BMWP/403543/2010) and previous EMA scientific advice (EMA/CHMP/SAWP/134492/2020). Blinding measures were acceptable.

Study objectives and endpoints were appropriate for a pivotal biosimilar PK study. The primary objective was to establish PK equivalence between Bmab 1200 and US-Stelara, Bmab 1200 and EU-Stelara, and EU Stelara and US Stelara after a single 45 mg subcutaneous injection in healthy subjects. As only the subcutaneous route of administration was evaluated, the co-primary endpoints of

$AUC_{0\text{-}inf}$ and C_{max} were selected following EMA guidance. A conservative bioequivalence approach was used based on the geometric least squares mean (GLSM) ratios of the primary PK parameters. In accordance with EMA guidance, bioequivalence was concluded if the ratio of GLSM and corresponding 90% CI are contained within the predefined bioequivalence range of 0.8000 to 1.2500. Secondary PK parameters included $AUC_{0\text{-}t}$, t_{max}, $t_{1/2}$, k_{el}, V_d/F, CL/F, and $\%AUC_{extrap}$. The selected PK sampling days allowed adequate coverage of the expected time of C_{max} and the elimination phase.

Healthy subjects between 18 and 55 years and with a BMI between 18.0 and 30.0 kg/m^2 were eligible. Stratification by ethnic origin (Japanese or non-Japanese), weight range (60.0 to 79.9 kg or 80.0 to 100.0 kg, inclusive), sex (male or female) and study site (Fortrea Clinical Research Unit or Medicines Evaluation Unit) was supported by the CHMP in the EMA Scientific Advice (EMA/CHMP/SAWP/134492/2020). Baseline characteristics were overall balanced between the groups. The overall mean age of subjects was 36.1 years and the overall mean BMI was 24.85 kg/m^2. The majority of subjects were male (72.5%) and white (66.7%).

A total of 258 participants were randomised and dosed (Bmab 1200 n=86, US-Stelara n= 87, EU-Stelara n= 85) of which 257 subjects (99.6%) completed the study. One subject in the US-Stelara group withdrew consent due to work commitments and discontinued the study prematurely on day 5 and was therefore excluded from the PK analysis set. Additionally, one participant in the US-Stelara group and one participant in the EU-Stelara group had a mix-up of samples on three consecutive days due to an error in the sample identification badge and were excluded from the PK analysis set as well. Although samples for these subjects were analysed and results are listed, it can be derived from the minutes of the blinded data review meeting that the decision to exclude these subjects from the PK analysis was taken before sample analysis and unblinding. Exclusion of these data is therefore agreed. No issues arise from the subject disposition.

Pharmacokinetic results

PK assessments demonstrated that the geometric mean of the co-primary endpoint C_{max} was comparable between treatment arms and the primary statistical analysis demonstrated that the 90% CIs of GLSM ratios for C_{max} were well contained within the acceptable bioequivalence range (0.80 – 1.25) for each of the three pairwise comparisons. The point estimate for the GLSM (Bmab 1200 vs. EU-Stelara) for C_{max} was 0.9736 (90% CI 0.9136, 1.0376). The geometric means for the co-primary endpoint $AUC_{0\text{-}inf}$ and $AUC_{0\text{-}t}$ (secondary endpoint) were slightly higher following administration of Bmab 1200 compared to either EU-Stelara or US-Stelara, indicating a trend towards higher exposure to Bmab 1200 compared to the originator drug. Although unity was only marginally contained in these analyses, the point estimates and 90% CIs of the GLSM ratios were within acceptable ranges for all three pairwise comparisons: For $AUC_{0\text{-}inf}$, the point estimate for the GLSM between Bmab 1200 and EU-Stelara was 1.0787 (90% CI 0.9959, 1.1685), for $AUC_{0\text{-}t}$ 1.0721 (90% CI 0.9941, 1.1563). Overall, bioequivalence acceptance criteria for the co-primary endpoints C_{max} and $AUC_{0\text{-}inf}$ were met.

Additional secondary PK parameters indicated a slightly longer elimination phase for Bmab 1200 compared to Stelara: Apparent total clearance and k_{el} were slightly decreased and half-life ($t_{1/2}$) was slightly longer for Bmab 1200 compared to US- and EU-Stelara. However, the mean $t_{1/2}$ of 22.1, 21.3, and 20.5 days for Bmab 1200, US-Stelara and EU-Stelara, respectively, was overall comparable to the $t_{1/2}$ stated in the Stelara SmPC (approximately 3 weeks).

Ustekinumab levels remained quantifiable until the last sample collected (median T_{last} = day 112). Nevertheless, AUC_{extrap} was < 3.45% for all treatments with no subject having an $AUC_{extrap} \geq 20\%$. This is considered to be in line with the EMA guidance 'Clinical pharmacology and pharmacokinetics: questions and answers, 7. Biosimilars'. Therefore, $AUC_{0\text{-}inf}$ can be considered a reliable parameter and the PK sampling time period is considered of sufficient length. The median T_{max} for all treatment groups was 9 days, which is consistent with the mean T_{max} reported in the SmPC for Stelara (8.5 days). However, a wide range of variability in T_{max} was noted.

According to guidance EMA/CHMP/BMWP/403543/2010, in the absence of intravenous PK data, partial AUCs should be assessed to ensure comparability of absorption and elimination and to support extrapolation of SC data to IV administration. This was also advised in the EMA SA (EMA/CHMP/SAWP/134492/2020). Partial AUC analyses showed comparability of Bmab 1200 and EU-Stelara during the absorption phase, as all GLSM ratios and corresponding 90% CIs for partial AUCs from 0 were all well within predefined bioequivalence range of 80-125%. In contrast, some differences in the elimination phase from day 15 onwards were noted. As the starting time point for AUC analysis increased, GLSM ratios between Bmab 1200 and EU-Stelara also increased, with 90% CIs widening and falling outside the predefined bioequivalence range. These findings align with the observed lower apparent total clearance and terminal elimination rate for Bmab 1200 compared to EU-Stelara. Nevertheless, the overall clinical data support the biosimilarity of Bmab1200 and EU-Stelara. The PK differences in clearance do not appear to have translated into clinically meaningful differences in efficacy or safety. Therefore, these data outweigh the uncertainties associated with the partial AUC analyses and extrapolation from the SC data to the IV route of administration can be granted.

A sensitivity analysis with correction for protein content protein of the primary parameters was also presented by the applicant by considering the protein concentration of the respective batch. Analysis of the protein-adjusted primary PK parameters $AUC_{0\text{-}inf}$/P and C_{max}/P supported the PK similarity of Bmab 1200 and Stelara, as 90% CIs of GLSMs ratios fell within the bioequivalence range of 0.8000 and 1.2500 for all pairwise comparisons.

Subgroup analysis indicated PK similarity irrespective of ethnicity (Japanese/non-Japanese). With regard to the ADA status, only the Bmab 1200 vs EU-Stelara comparison had all point estimates and 90% CIs of the GLSM ratio within the acceptable bioequivalence range of 0.8000 and 1.2500 for the ADA-negative and ADA-positive subgroups. In contrast, some of the 90% CIs for the comparisons between Bmab 1200 vs. US Stelara and US vs. EU Stelara in the ADA-negative subgroups were outside the acceptable range. Given that the comparison between Bmab 1200 and EU-Stelara is considered the most important and relevant for this MAA, no concern was raised for comparing US-Stelara to Bmab 1200/EU-Stelara. These results were further supported by the stratification of all PK parameters by ADA/Nab status, which showed no significant differences between subgroups. Although no effect of ADA on PK is indicated for either Bmab 1200 or EU-Stelara, some uncertainty remains due to the small sample size of ADA-negative subjects in both treatment groups.

Overall, the PK results in healthy volunteers support biosimilarity of Bmab1200 and EU-or US-Stelara.

PK in target population (Study BM12H-PSO-03-G-02)

Pharmacokinetic results

Trough concentrations were compared for Bmab 1200 with Stelara from baseline through Week 52. PK results are summarised descriptively and considered supportive only given the variability inherent to this population.

In treatment period 1, all subjects randomised and dosed with Bmab 1200 (191/191 (100%)) were included in the PK Data Set, whereas one patient in the Stelara group (192/93 (99.5%)) was excluded from the PKS due to missing at least 1 post-treatment PK result. 6 patients had measurable baseline serum concentrations of which one subject had a high non-zero baseline result (>5% of C_{max}). The applicant argued it was due to the samples mistakenly taken post-dose without documentation of the protocol deviation. Issue is no further pursued.

As expected, patients with higher body weight and receiving the 90 mg dose had higher C_{trough} levels compared to patients receiving the 45 mg dose. Similar to what is observed in healthy volunteers, exposure seems to be slightly higher with Bmab 1200 compared to Stelara. Comparative C_{trough} values are presented for patients stratified by body weight category (<100 kg and >100 kg) and these do not suggest important differences in PK between treatments for each BW group separately.

In a pooled summary of treatment period 2 and 3, the C_{trough} levels were overall comparable between Bmab 1200 and EU-Stelara, even after switching from EU-Stelara to Bmab 1200.

Although subjects with high ADA levels consistently displayed lower C_{trough} concentrations compared to those with low or moderate ADA levels, observed for both Bmab 1200 and Stelara, the ability to draw definitive conclusions is limited by the small sample sizes. Overall, the observed differences in C_{trough} levels do not appear to have translated into clinically relevant differences in efficacy or safety outcomes by ADA/NAb status.

6.1.5. Conclusions on clinical pharmacology

In summary, the available PK data support pharmacokinetic biosimilarity of Bmab 1200 with EU-Stelara and US-Stelara.

6.1.6. Clinical efficacy

6.1.6.1. Dose-response studies

Not applicable.

6.1.6.2. Main study

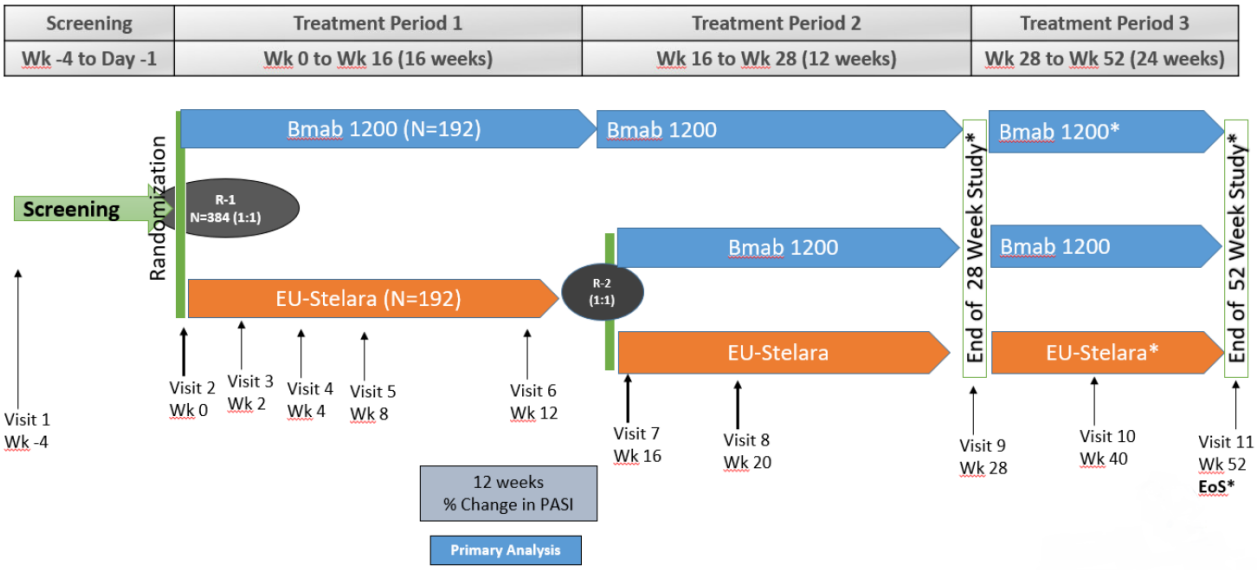
The clinical development programme for Bmab 1200 comprised a single randomised, double-blind, active-controlled phase 3 study BM12H-PSO-03-G-02 to compare the efficacy and safety of Bmab 1200 and EU-Stelara. The study also included PK assessments and evaluation of immunogenicity.

BM12H-PSO-03-G-02

Methods

The study consisted of a screening period (up to 4 weeks/28 days) and a double-blind, active-controlled treatment period, further subdivided into 3 treatment periods; treatment period 1 (**TP1**), **TP2** and **TP3** with a re-randomisation step for switching therapy after timepoint of primary efficacy analysis (Week 12) and before Week 16 dosing. The study lasted for 52 weeks, excluding the screening period.

Figure 2. Study schema



Study Participants

Study BM12H-PSO-03-G-02 was conducted in Estonia, Georgia, Latvia, Poland and the United States.

Main inclusion criteria:

- Patient was aged 18 to 80 years, both inclusive, and weighed <130 kg at the time of the screening visit.
- Patient had a diagnosis of chronic plaque psoriasis for at least 6 months and was a candidate for systemic therapy or phototherapy at the time of the screening visit.
- Patient had moderate to severe chronic plaque psoriasis as defined by BSA involvement ≥10%, PASI score ≥12, and sPGA ≥3 at the screening and baseline visits.
- Patient had stable disease for at least 2 months before the baseline visit (i.e., without CS changes in the Investigator's opinion).
- Patient had a previous failure, inadequate response, intolerance, or contraindication to at least 1 antipsoriatic systemic therapy.

Main exclusion criteria:

- Patient had nonplaque psoriasis, such as erythrodermic psoriasis, pustular psoriasis, guttate psoriasis, medication-induced psoriasis, other skin conditions (e.g., eczema), or other current or chronic systemic autoimmune or inflammatory disease at the time of screening visit that would have interfered with the evaluation of the effect of the study treatment of psoriasis. Patients with concurrent psoriatic arthritis were allowed to participate.
- Patient had a current or past history of infections.
- Patient had prior exposure to more than 1 biologic agent for the treatment of psoriasis or psoriatic arthritis.
- Patient had received or planned to receive prohibited medications or treatment that could have affected psoriasis (see prohibited medication below).

- Patient had a history of hypersensitivity to any biologic systemic therapy or any of the excipients of Stelara.

Treatments

Depending on the treatment arm, patients received either Bmab1200 or Stelara based on the patient's baseline body weight:

- Patients ≤100 kg: Bmab1200 or Stelara 45 mg (1 injection of 45 mg PFS)
- Patients >100 kg: Bmab1200 or Stelara 90 mg (2 injections of 45 mg PFS)

In TP1 and TP2 of the study, study treatment was administered at baseline, Week 4, and Week 16, and patients were followed until prior to dosing of Week 28.

TP3 included dosing at Week 40 and patients were followed up until Week 52.

Permitted medications

Low potency topical corticosteroids, specifically those classified as least potent and mild (Class VI to VII of USA 7 Group Topical Drug Classification System), were permitted for use on the scalp, face, axillae, groin, or genitalia as rescue medication. However, they were not to be applied within 24 hours prior to screening and other study visits that involved PASI or sPGA measurements.

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

Prohibited medications

All the following therapies were prohibited during the study period. For enrolment, patients who had received these prohibited therapies or plan to receive these prohibited therapies could not be included in the study.

- Ustekinumab, either approved or investigational (other than study treatment).
- Any drug that directly targets IL-12, IL-17, IL-23.

Patients receiving prohibited medications listed below could be enrolled treatment had been stopped before baseline as defined below:

- Any biologic systemic therapy for the treatment of psoriasis/psoriatic arthritis or one that could affect its course within 5 half-lives or 90 days, whichever is longer, before the baseline visit.
- Any nonbiologic systemic therapy that could affect psoriasis (including, but not limited to, methotrexate, cyclosporine, or systemic steroids) within 4 weeks before baseline visit.
- Any mAb within 5 half-lives or 90 days, whichever is longer, before the baseline visit.
- Topical therapies for the treatment of psoriasis (including, but not limited to, corticosteroids, vitamin D analogues, calcineurin inhibitors, or retinoids) within 2 weeks before the baseline visit. Restricted use of rescue topical treatment was allowed.
- Ultraviolet A phototherapy (with or without oral psoralen) or ultraviolet B phototherapy for the treatment of psoriasis within 4 weeks before the baseline visit.

- Any investigational drug other than study treatment Initiation of any other drug that may impact psoriasis (e.g., beta-blockers, lithium, antimalarials) 4 weeks or 5 half-lives (whichever is longer) before the baseline visit.
- Herbal or any nonpharmaceutical treatment that could affect psoriasis within 2 weeks before the baseline visit.
- Live or live-attenuated vaccination within 4 weeks before the baseline visit and until at least 15 weeks after last dose of study treatment.
- BCG vaccination within 1 year before the baseline visit and up to 1 year after last dose of study treatment.

Objectives

Primary Objective

To assess the efficacy in patients with moderate to severe chronic plaque psoriasis (measured as the percentage change from baseline in the PASI score at Week 12).

Equivalence margin

Bmab1200 was considered to be equivalent to Stelara for the primary endpoint based on the pre-defined margin of ±13% for the 95% CI.

Margin construction was in accordance with the EMA CHMP guideline CPMP/EWP/2158/998 on the choice of the non-inferiority margin. The equivalence margin was derived from the meta-analysis of the originator registration studies (PHOENIX 1 and 2), which showed a treatment difference of 70.66 and 95% CI [67.42, 73.89] at Week 12.

Secondary objectives

- To assess the efficacy of Bmab 1200 based on other efficacy parameters and time points 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.

Outcomes/endpoints

Primary Endpoint

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

Secondary Endpoints

- Percentage change from baseline in the Psoriasis Area and Severity Index (PASI) score at Weeks 4, 8, 16, 20, 28, 40, and 52 (time frame: baseline [Day 1] through Weeks 28 and 52).
- PASI 50, PASI 75, and PASI 90 at Weeks 4, 8, 12, 16, 20, 28, 40, and 52 (time frame: baseline [Day 1] through Weeks 28 and 52). PASI 50, PASI 75, and PASI 90 were defined as an improvement from baseline in PASI score of 50% or greater, 75% or greater, or 90% or greater, respectively.

- 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).
- AUECs of PASI score from baseline through 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 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 as measured by DLQI scores at Weeks 4, 8, 12, 16, 20, 28, 40, and 52 (time frame: baseline [Day 1] through Weeks 28 and 52).

Sample size

The sample size calculation was based on the primary endpoint, percentage change from baseline in the PASI score at Week 12, and based on the assumption that equivalence would be established if the 90% CI of the difference between the treatments (Bmab 1200, Stelara®) in the percentage change in the PASI score from baseline to Week 12 is within the equivalence margin of ±10%. Assuming that the treatments are equally effective and that the common SD of the percentage change from baseline in the PASI score at Week 12 is 30%, a total sample size of 384 patients including a dropout rate of 10% patients ensures a power of 85% with a two one-sided 5% level of significance. According to the EMA, the PMDA and other agencies, equivalence was considered established, if the 95% CI of the difference between the treatments (Bmab1200 and Stelara) in the percentage change in the PASI score from baseline to Week 12 fell within the equivalence margin of ±13%. For these requirements, a total sample size of 384 patients was considered with a power of 96% with a two one-sided 2.5% level of significance.

Randomisation and blinding (masking)

Patients were planned to be assigned to receive Bmab1200 or Stelara in a 1:1 allocation ratio using a permuted block design, stratified by the factors:

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

This study was planned to be double-blind. It was planned, that a separate unblinded Biostatistical team generates the randomisation schedule using SAS software Version 9.4 or later (SAS Institute Inc, Cary, North Carolina) for RAVE EDC, which would link sequential patient randomisation numbers to treatment codes.

All continuing patients who receive study treatment at Weeks 0 and 4 and achieve at least PASI 50 response by Week 12 were planned to be re-randomised before receiving study treatment at Week 16. Before dosing at Week 16, patients in the Stelara arm were planned to 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 were planned to also go through the re-randomisation procedure; however, they were planned to be assigned and continue to receive Bmab 1200. The re-randomisation was planned to take place using the original strata as recorded at baseline (under which the original

randomisation occurred). For patients continuing into TP3, the patients were planned to continue with the same treatment as randomised during TP2 in a blinded manner.

Statistical methods

Analysis Sets

The Full Analysis Set (FAS) was planned to be used for the primary analyses of efficacy. The Per-Protocol Set (PPS) was planned to consist of all patients in the FAS, who received at least 2 study treatment administrations (Baseline and Week 4), and didn't experience any important protocol deviations affecting primary efficacy at Week 12. The PPS was planned to be used for supportive analyses of efficacy.

Estimand

The estimand frameworks were applied for the primary efficacy endpoint, per ICH E9 Addendum. Three estimands were defined for the primary efficacy objective "to demonstrate equivalent efficacy between Bmab1200 and Stelara in patients with moderate to severe chronic plaque psoriasis". Death, discontinuation of study treatment due to any reason other than death, prohibited therapy used for treatment of psoriasis, deviations in dosing, obtaining data remotely were described as the intercurrent events (ICEs). The primary estimand, as defined, is mostly aligned with a treatment policy approach for all ICEs except death and data obtained through remote assessment. 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, patients were not 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. With this estimand, a comparative assessment closer to that of a PPS analysis is gained.

Analysis methods

The primary, secondary, and tertiary estimands were planned to be analysed 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 was planned to include the stratification factors (region, body weight at baseline category, baseline psoriatic arthritis status, and previous biologic use) used for the randomisation at baseline as fixed factors. The mean difference between treatment groups was planned to 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 were planned to be combined using the Rubin's rule as a single estimate of treatment difference presented with a 95% CI. Equivalence was planned to be concluded if the 95% CI at Week 12 falls within the predefined equivalence margin of ±13%.

Handling of missing data

For determination of the primary efficacy endpoint analyses of percentage change in PASI score from baseline to Week 12, and other PASI related endpoints during TP1, an MI approach for missing data was planned to be employed where appropriate.

Sensitivity and supplementary analyses

Additional to the analyses planned for the primary, secondary and tertiary estimand, a tipping point analyses assessing different levels of delta shift for the imputation in each treatment group was planned. Furthermore, it was planned to conduct a mixed model for repeated measurements analysis as well as an analysis of the primary, secondary and tertiary estimand on the per protocol set.

Subgroup analyses

Additional subgroup analyses based on baseline characteristics were planned to be presented with forest plots, as well as analyses of primary efficacy based on ADA and nAbs positive/negative status up to Week 12. Subgroup analyses of secondary efficacy based on ADA status (positive versus negative up to Week 16 and Week 28) and selected baseline characteristics were also planned to may also be explored. Additionally, to the planned subgroup analyses in the study protocol, the sponsor conducted an analysis in the subset of patients in the FAS who received treatment with 45mg Bmnab1200 or Stelara.

Interim analyses and multiplicity adjustment

There was no interim analysis planned as well as no adjustment for multiplicity.

Results

Participant flow

Patient Disposition (TP1 & TP2 & TP3)

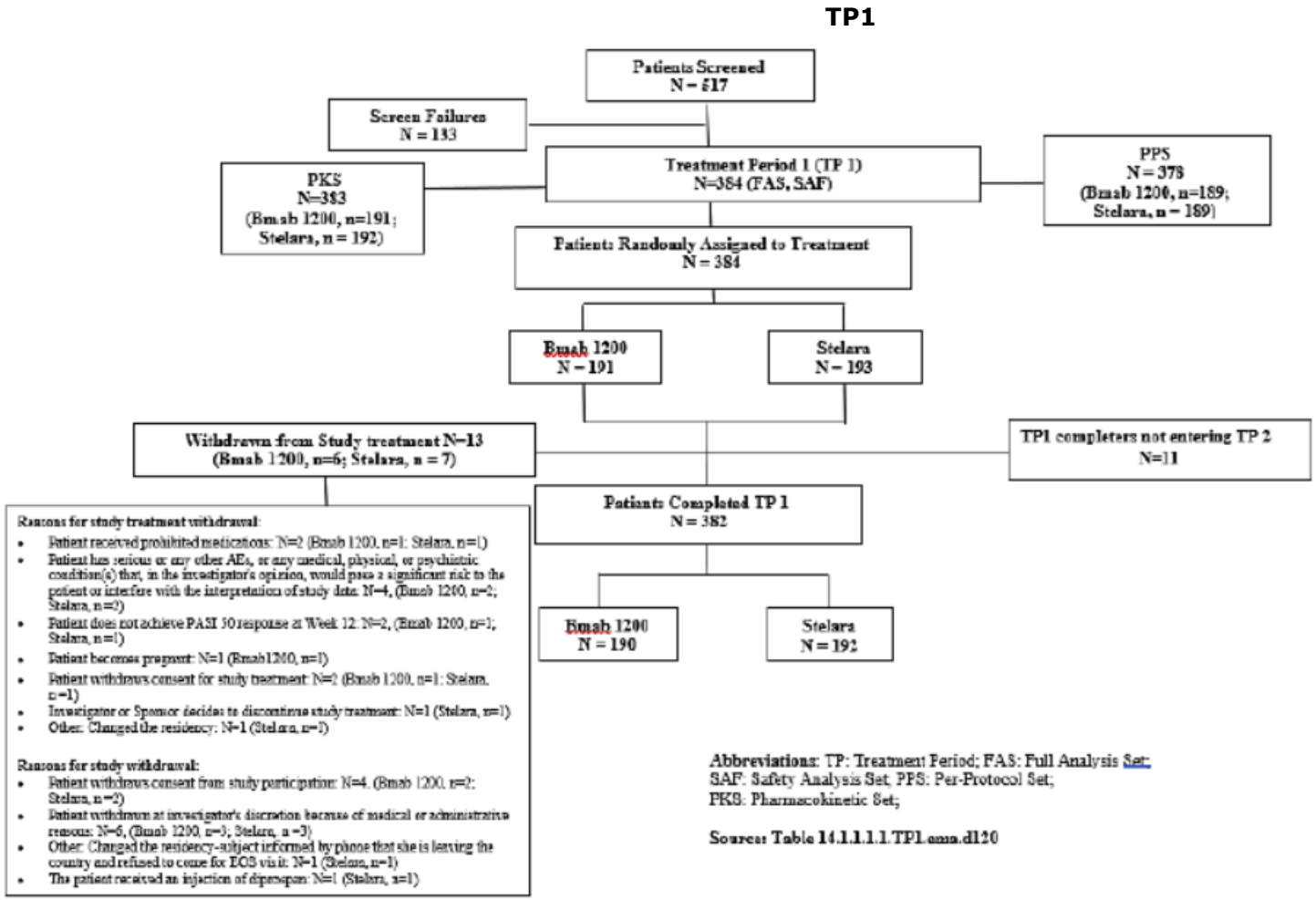
A total of 517 patients were screened. Of these, 133 patients were considered screen failures and 384 patients were enrolled in the FAS (i.e., who were randomised into TP1) and in the SAF (i.e., who received any treatment of Bmab 1200 or Stelara). 301 patients were randomised based on weight to receive 45 mg Bmab 1200 (151 patients) or 45 mg Stelara (150 patients). Almost all patients from the FAS and SAF were included in the PPS.

Of the total 384 patients enrolled, 191 were enrolled to receive Bmab 1200 and 193 patients were enrolled to receive Stelara in TP1. Overall, 382 patients (99.5%) completed treatment in TP1; 11 patients (2.9%) who completed TP1 did not enter TP2. A total of 371 patients completed the Week 28 visit. A total of 333 patients entered and were dosed in TP3. A total of 324 patients (84.4%) completed the study (52-week visit).

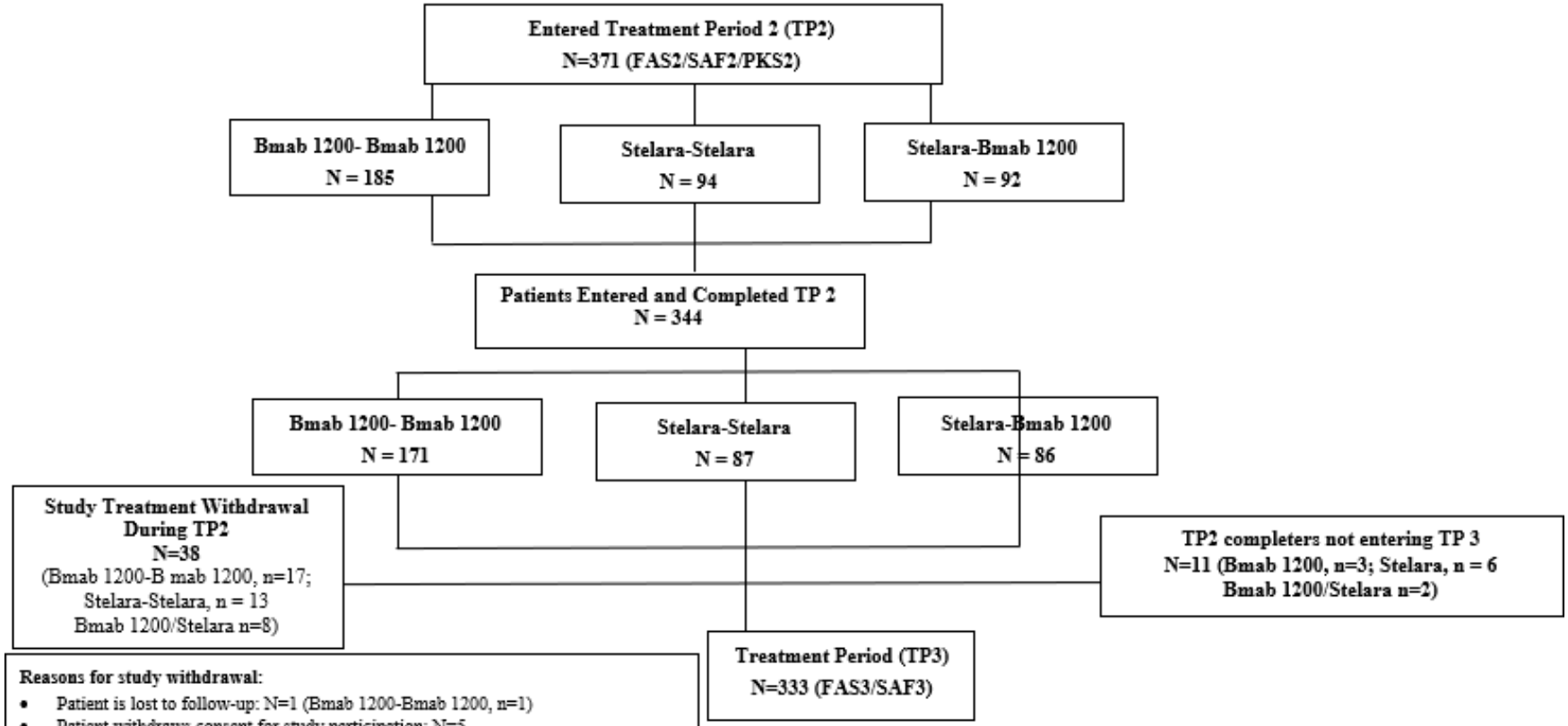
60 patients (15.6%) withdrew from the study. The most common reason for patients being withdrawn from the study was accidental partial unblinding of a few CRO and site personnel due to the RTSM configuration issue during re-randomisation (patient remained blinded) (23 patients; 6.0%). All 23 patients were withdrawn at the end of TP2 (28 week visit). Additionally, patients were withdrawn at the Investigator's discretion because of medical or administrative reasons (8 patients; 2.1%), and certain patients withdrew consent from study participation (5 patients; 1.3%).

Patient compliance throughout the study (TP1, TP2, and TP3) was 100%.

Figure 3. Flowchart showing summary of patient disposition during TP1, TP2 and TP3



TP2



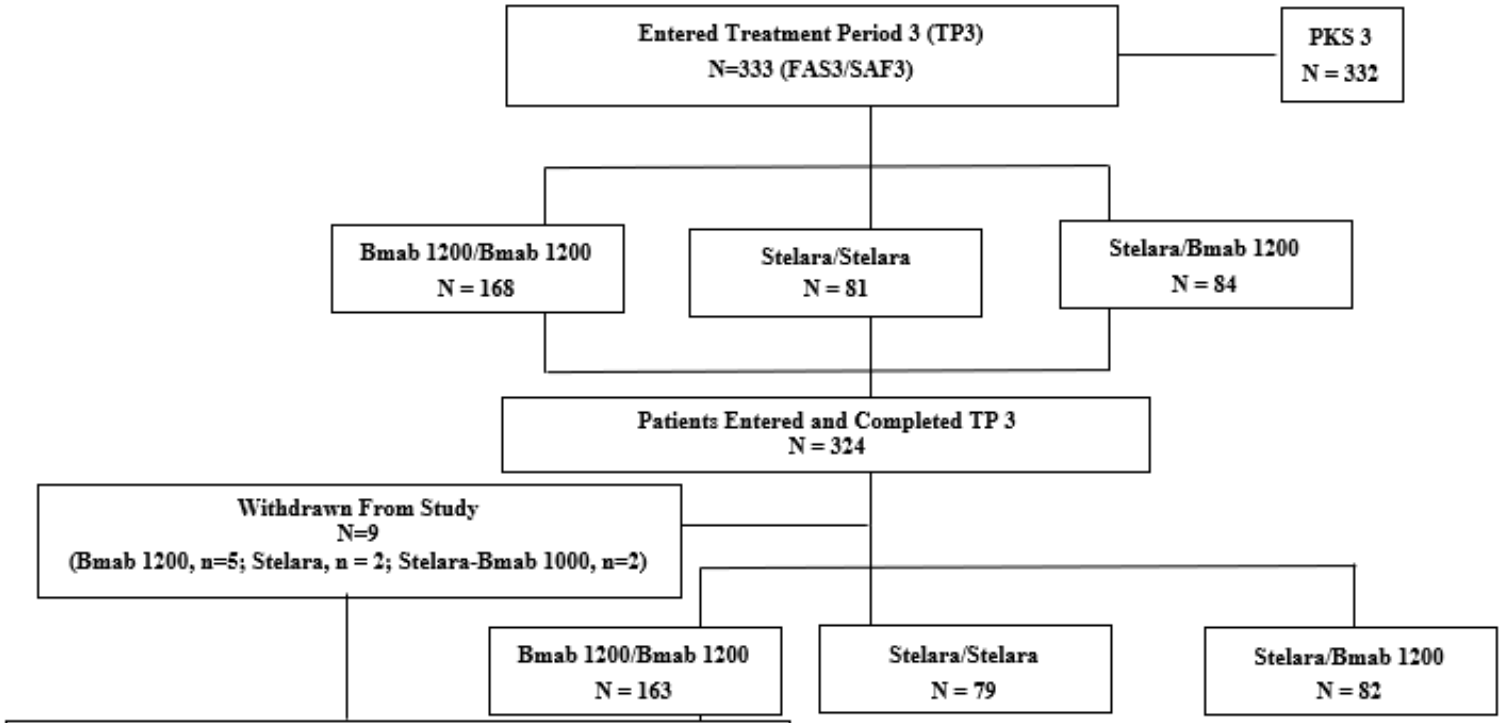
Reasons for study withdrawal:

- Patient is lost to follow-up: N=1 (Bmab 1200-Bmab 1200, n=1)
- Patient withdraws consent for study participation: N=5 (Bmab 1200- Bmab 1200, n=2; Stelara-Stelara, n =3)
- Patient withdrawn at investigator's discretion because of medical or administrative reasons: N=5 (Bmab 1200- Bmab 1200, n=1; Stelara-Stelara, n =2, Stelara-Bmab 1200, n=2).
- Patient does not achieve at least PASI 75 response at Week 28: N=3, (Bmab 1200-Bmab 1200, n=1; Stelara-Stelara, n =1; Stelara-Bmab 1200, n=1)
- Other: Accidental partial unblinding few CRO and site personnel due to RTSM configuration. Issue during rerandomization patient remains blinded: N=23 (Bmab 1200, n=11; Stelara, n =7; Stelara-Bmab 1200, n=5)
- Sponsor decided to discontinue the patient due to potential treatment unblinding which occurred in TP2: N=1 (Bmab 1200-Bmab 1200, n=1; Stelara-Stelara, n =0; Stelara-Bmab 1200, n=0)

Abbreviations: TP: Treatment Period; FAS: Full Analysis Set; SAF: Safety Analysis Set; PKS: Pharmacokinetic Set;

Source: Table 14.1.1.1.1.TP2.ema.d120

TP3



Abbreviations: TP: Treatment Period; FAS: Full Analysis Set; SAF: Safety Analysis Set; PKS: Pharmacokinetic Set;

Source: Table 14.1.1.1.1.TP3.ema.d120

Recruitment

First Patient First Visit:	28 June 2022
Last Patient Last Visit: (52 Week Analysis)	15 Nov 2023

Conduct of the study

Protocol amendments

There were 3 versions of the protocol: Version 1.0 (07 January 2022), Version 2.0 dated (16 May 2022), and Version 3.0 (12 January 2023). The first patient was enrolled under Protocol Version 2.0 (16 May 2022).

Version 2.0 included measures to evaluate early immunogenicity, changes the statistical analysis strategy to minimise the occurrence of ICEs, handling of COVID-19 patients in the study, and included PMDA requirements. Version 3.0 included TP3, which extended the study duration to 52 weeks.

Protocol deviations

In TP1, 58 patients (15.1%) had at least 1 major deviation (Bmab: 27 patients; 14.1% / Stelara: 31 patients; 16.1%). The majority of protocol deviations were reported under the category of study procedure (42 patients; 10.9%). Within this group, for 23 patients CRO personnel and site personnel were accidentally partially unblinded because of a RTSM configuration issue during re-randomisation at Week 16 (the 23 patients remained blinded). This occurred after the timing of the primary endpoint assessment (Week 12); hence, these patients were not excluded from PPS. 18 additional patients who had a major protocol deviation due to a study procedure; the majority of patients had their vital signs measured in the sitting position instead of the semisupine position. A total of 4 patients had 1 protocol deviation leading to the exclusion of patients from the PPS.

In TP2 and TP3 overall low numbers of patients with at least one major protocol deviations were observed (TP2: 4 patients (1.1%); TP3: 4 patients (1.2%).

Baseline data

Baseline demographics

The age of patients ranged from 18 to 79 years with a median age of 42.0 years. The majority of patients were White (382 patients; 99.5%), were male (257 patients; 66.9%) had an ethnicity of "not Hispanic or Latino" origin (372 patients; 96.9%) and were located in Europe (378 patients; 98.4%). The majority of patients (301 patients; 78.4%) weighed ≤100 kg at baseline, consistent of a psoriasis patient population. The mean (SD) BMI was 28.45 (5.3) kg/m2 (median: 27.88 kg/m2). Slightly more smokers were observed in the Bmab 1200 group (61 patients; 31.9%) vs the Stelara group (52 patients; 26.9%).

For patients who received treatment of 45 mg Bmab 1200 or Stelara, comparable patient demographics were observed.

Table 11. Patient Demographic and Baseline Characteristics (Full Analysis Set)

	Bmab 1200 (N=191) n (%)	Stelara (N=193) n (%)	Total (N=384) n (%)
Age (years)			
n	191	193	384
Mean (SD)	42.5 (13.09)	43.9 (13.58)	43.2 (13.34)
Median	41.0	42.0	42.0
Q1, Q3	31.0, 51.0	34.0, 54.0	33.0, 53.0
Min, Max	18, 74	20, 79	18, 79
Sex, n (%)			
Male	121 (63.4)	136 (70.5)	257 (66.9)
Female	70 (36.6)	57 (29.5)	127 (33.1)
Childbearing potential[a]			
Yes	48 (68.6)	35 (61.4)	83 (65.4)
Region, n (%)			
Europe	189 (99.0)	189 (97.9)	378 (98.4)
Estonia	10 (5.2)	9 (4.7)	19 (4.9)
Georgia	45 (23.6)	35 (18.1)	80 (20.8)
Latvia	11 (5.8)	18 (9.3)	29 (7.6)
Poland	123 (64.4)	127 (65.8)	250 (65.1)
US	2 (1.0)	4 (2.1)	6 (1.6)
Ethnicity, n (%)			
Hispanic or Latino	6 (3.1)	6 (3.1)	12 (3.1)
Not Hispanic or Latino	185 (96.9)	187 (96.9)	372 (96.9)
Race, n (%)			
American Indian or Alaska Native	0	0	0
Asian	0	0	0
Black or African American	1 (0.5)	1 (0.5)	2 (0.5)
Native Hawaiian or Other Pacific Islander	0	0	0
White	190 (99.5)	192 (99.5)	382 (99.5)
Other	0	0	0
Height (cm) at baseline			
n	191	193	384
Mean (SD)	172.84 (8.79)	174.17 (8.65)	173.51 (8.74)
Median	172.50	175.00	174.75
Q1, Q3	166.00, 179.00	168.00, 180.00	167.00, 180.00
Min, Max	143.0, 192.0	149.7, 198.0	143.0, 198.0
Weight (kg) at baseline			
n	191	193	384
Mean (SD)	84.70 (17.88)	86.99 (17.37)	85.85 (17.64)
Median	84.20	86.70	85.00
Q1, Q3	73.00, 97.00	73.00, 98.00	73.00, 97.55
Min, Max	48.00, 128.70	46.00, 128.40	46.00, 128.70
Weight at baseline ≤100 kg	151 (79.1)	150 (77.7)	301 (78.4)
Weight at baseline >100 kg	40 (20.9)	43 (22.3)	83 (21.6)
BMI (kg/ m^2)			
n	191	193	384
Mean (SD)	28.23 (5.06)	28.67 (5.44)	28.45 (5.25)
Median	27.32	28.40	27.88
Q1, Q3	24.70, 31.35	24.28, 32.20	24.40, 31.75
Min, Max	18.73, 41.55	17.71, 50.16	17.71, 50.16
Smoker Status			
Never Smoked	108 (56.5)	122 (63.2)	230 (59.9)
Ex-smoker	22 (11.5)	19 (9.8)	41 (10.7)
Smoker	61 (31.9)	52 (26.9)	113 (29.4)
Unknown	0	0	0
Alcohol Status			
Non-drinker	116 (60.7)	119 (61.7)	235 (61.2)
Ex-drinker	1 (0.5)	0	1 (0.3)
Current drinker	74 (38.7)	73 (37.8)	147 (38.3)

Abbreviations: FAS, full analysis set; N, number of patients in the treatment group; n, number of patients with available data; Q1, 1st quartile; Q2, 2nd quartile; Q3, 3rd quartile.

Note: Percentages are based on the number of patients in the treatment group (N).

Note: Baseline is defined as the last non-missing value before the first dose of study treatment.

a. Percentages (%) are based on the number of female patients in each treatment group.

b. Percentages (%) are based on the number of current drinkers in each treatment group.

Baseline Disease Characteristics

The mean (SD) PASI score, sPGA, BSA, and DLQI was 23.2 (9.2), 3.6 (0.7), 29.9 (16.3), and 14.4 (6.7), respectively. The majority of patients had an sPGA score of 3 (205 patients; 53.4%) or 4 (125 patients; 32.6%). sPGA scores of 4 or 5 were observed in slightly more patients in the Bmab 1200 group than the Stelara group. The majority of patients did not have previous exposure to biologic-based therapies (331 patients; 86.2%) and did not have concomitant psoriatic arthritis (322 patients; 83.9%).

Table 12. Summary of Baseline Characteristics of Psoriatic Condition (Full Analysis Set)

	Bmab 1200 (N=191) n (%)	Stelara (N=193) n (%)	Total (N=384) n (%)
PASI			
n	191	193	384
Mean (SD)	23.39 (9.127)	22.98 (9.292)	23.19 (9.201)
Median	20.10	20.20	20.10
Q1, Q3	16.80, 28.20	16.20, 27.90	16.20, 28.10
Min, Max	12.2, 59.5	12.2, 68.4	12.2, 68.4
sPGA			
n	191	193	384
Mean (SD)	3.7 (0.73)	3.5 (0.71)	3.6 (0.72)
Median	4.0	3.0	3.0
Q1, Q3	3.0, 4.0	3.0, 4.0	3.0, 4.0
Min, Max	3, 5	2, 5	2, 5
sPGA score			
0	0	0	0
1	0	0	0
2	0 (0.0)	1 (0.5)	1 (0.3)
3	93 (48.7)	112 (58.0)	205 (53.4)
4	69 (36.1)	56 (29.0)	125 (32.6)
5	29 (15.2)	24 (12.4)	53 (13.8)
BSA			
n	191	193	384
Mean (SD)	29.9 (16.29)	29.9 (16.31)	29.9 (16.28)
Median	26.0	25.0	25.0
Q1, Q3	18.0, 38.0	18.0, 37.0	18.0, 38.0
Min, Max	10, 90	10, 93	10, 93
DLQI			
n	191	193	384
Mean (SD)	15.0 (6.67)	13.9 (6.60)	14.4 (6.65)
Median	15.0	13.0	14.0
Q1, Q3	10.0, 20.0	9.0, 18.0	10.0, 19.0
Min, Max	0, 30	0, 30	0, 30
Previous exposure to biologic-based therapies			
Yes	26 (13.6)	27 (14.0)	53 (13.8)
No	165 (86.4)	166 (86.0)	331 (86.2)
Concomitant psoriatic arthritis			
Yes	30 (15.7)	32 (16.6)	62 (16.1)
No	161 (84.3)	161 (83.4)	322 (83.9)

Abbreviations: BSA, body surface area; DLQI, Dermatology Life Quality Index; N, number of patients in the treatment group; n, number of patients with available data; PASI, Psoriasis Area and Severity Index; sPGA, Static Physician's Global Assessment; Q1, 1st quartile; Q3, 3rd quartile.

Note: Baseline is defined as the last non-missing value before the first dose of study treatment.

Numbers analysed

Of the 384 patients in the Full Analysis Set (FAS). 378 patients (98.4%) were included in the Per-Protocol-Set (PPS). The primary analysis performed was based on the FAS.

Table 13. Summary of Analysis Set (Full Analysis Set)

Analysis set	Bmab 1200 (N=191) n (%)	Stelara (N=193) n (%)	Stelara-Stelara (N=94) n (%)	Stelara-Bmab 1200 (N=92) n (%)	Total (N=384) n (%)
Full Analysis Set (FAS)	191 (100)	193 (100)	-	-	384 (100)
Not randomized	0	0	-	-	133 (25.7)[a]
FAS for TP2 (FAS2)	185 (96.9)	0	94 (100)	92 (100)	371 (96.6)
Not eligible for rerandomization	6 (3.1)	7 (3.6)	0	0	13 (3.4)
FAS for TP3 (FAS3)	168 (88.0)	-	81 (86.2)	84 (91.3)	333 (86.7)
Consent withdrawn	1 (0.5)	-	0	0	1 (0.3)
Noncompliance and starting commercial drug	0	-	1 (1.1)	0	1 (0.3)
Not eligible for TP3	15 (7.9)	-	8 (8.5)	6 (6.5)	29 (7.6)
Patient did not want to participate in the study until Week 52	0	-	1 (1.1)	0	1 (0.3)
Patient's decision to withdraw informed consent	0	-	1 (1.1)	0	1 (0.3)
Study team decision	1 (0.5)	-	0	0	1 (0.3)
Patient meets the exclusion criterion for the study (patient has surgery scheduled during the study)	0	-	0	1 (1.1)	1 (0.3)
Patient was not able to fulfil the protocol requirements in relation to visits schedule	0	-	1 (1.1)	0	1 (0.3)
Patient withdrew consent for participation in the study	0	-	1 (1.1)	0	1 (0.3)
Withdrew consent	0	-	0	1 (1.1)	1 (0.3)
Safety Set (SAF)	191 (100)	193 (100)	-	-	384 (100)
Patients randomized but not treated	0	0	-	-	0
Safety Set for TP2 (SAF2)	185 (96.9)	-	94 (100)	92 (100)	371 (96.6)
Patients rerandomized but not treated	0	-	0	0	0
Safety Set for TP3 (SAF 3)	168 (88.0)	-	81 (86.2)	84 (91.3)	333 (86.7)
Reason for exclusion from SAF3	0	-	0	0	0
Per-Protocol Set (PPS)	189 (99.0)	189 (97.9)	-	-	378 (98.4)
Did not receive 2 study treatment doses (baseline and Week 4)	1 (0.5)	1 (0.5)	-	-	2 (0.5)
Major PD leading to exclusion	1 (0.5)	3 (1.6)	-	-	4 (1.0)
Pharmacokinetic Set (PKS)	191 (100)	192 (99.5)	-	-	383 (99.7)
Did not have at least 1 post-treatment PK result	0	1 (0.5)	-	-	1 (0.3)
Pharmacokinetic Set for TP2 (PKS2)	185 (96.9)	-	94 (100)	92 (100)	371 (96.6)
Reason for exclusion from PKS2	0	-	0	0	0
Pharmacokinetic Set for TP3 (PKS3)	167 (87.4)	-	81 (86.2)	84 (91.3)	332 (86.5)
Did not have at least 1 PK result at Week 40 or Week 52	1 (0.5)	-	0	0	1 (0.3)

Abbreviations: AE, adverse event; PD, protocol deviation; PK, pharmacokinetic; TP2, Treatment Period 2; TP3, Treatment Period 3.
Note: Percentages (%) are based on the number of patients in each treatment group (N).
[a] Percentages (%) are based on the number of patients screened.

Outcomes and estimation

Primary Endpoint

Percentage change from baseline in the PASI score at Week 12

For the primary estimand involving the FAS of 384 patients, the LS mean (SE) percentage change from baseline in PASI score at Week 12 was −79.87% (2.818) in the Bmab 1200 group and −80.55% (2.783) in the Stelara group. The LS mean difference between treatments was 0.6800% (90% CI, −1.27 to 2.63; 95% CI, −1.64 to 3.00).

Table 14. Percentage Change from Baseline in PASI Score at Week 12 (Full Analysis Set)

	Bmab1200 (N=191)	Difference Between Treatments	Stelara (N=193)
Primary estimand[a]			
n	191	-	193
LS mean (SE)	-79.87 (2.818)	-	-80.55 (2.783)
95% CI	-85.40, -74.35	-	-86.01, -75.10
LS mean difference	-	0.6800	-
90% CI	-	-1.27, 2.63	-
95% CI	-	-1.64, 3.00	-
Secondary estimand[b]			
n	191	-	193
LS mean (SE)	-80.15 (2.841)	-	-80.76 (2.801)
95% CI	-85.72, -74.58	-	-86.25, -75.27
LS mean difference	-	0.6067	-
90% CI	-	-1.36, 2.57	-
95% CI	-	-1.73, 2.95	-
Tertiary estimand[c]			
n	191	-	193
LS mean (SE)	-79.91 (2.788)	-	-80.58 (2.755)
95% CI	-85.38, -74.44	-	-85.98, -75.17
LS mean difference	-	0.6636	-
90% CI	-	-1.31, 2.64	-
95% CI	-	-1.69, 3.02	-

- Abbreviations: ANCOVA, analysis of covariance; CI, confidence interval; ICE, intercurrent event; LS mean, least squares mean; MAR, missing at random; N, number of patients in the treatment group; n, number of patients with available data; SE, standard error.
- Note: Percentages (%) are based on the number of patients in each treatment group (N).
- Note: ANCOVA model is used for percentage change from baseline as the dependent variable, including treatment group and randomization stratification variables (region, body weight at baseline category, baseline psoriatic arthritis status, and previous biologic use) as fixed factors.
- [a] → A composite strategy is applied for ICE1. A treatment policy strategy is applied for ICE2, ICE3, and ICE4 and a hypothetical strategy is applied for ICE5.
- [b] → A composite strategy is applied for ICE1, a treatment policy strategy is applied for ICE2, and a hypothetical strategy is applied for ICE3, ICE4 and ICE5.
- [c] → The tertiary estimand for the primary efficacy endpoint is based on a principal stratum strategy for all ICEs. For this estimand, no patients will have PASI data affected by an ICE, and no imputation will occur other than MAR imputation for missing data not due to an ICE.

Secondary Endpoints

Percentage Change from Baseline in the PASI Score at Weeks 4, 8, and 16 (TP1)

Results from the analysis of the percentage change from baseline in the PASI score at Weeks 4, 8, and 16 are shown in the Table 15 below.

Table 15. Percentage Change From Baseline in Psoriasis Area and Severity Index Score at Weeks 4, 8, and 16 – Primary Estimand (Full Analysis Set)

Primary estimand[a]	Bmab 1200 (N=191)	Difference Between Treatments	Stelara (N=193)
Week 4			
N	191		193
LS mean (SE)	-41.29 (5.201)		-41.48 (5.111)
95% CI	-51.48, -31.09		-51.50, -31.46
LS mean difference	-	0.1899	-
90% CI	-	-3.57, 3.95	-
95% CI	-	-4.30, 4.68	-
Week 8			
n	191		193
LS mean (SE)	-68.48 (4.171)		-72.51 (4.099)
95% CI	-76.65, -60.30		-80.54, -64.47
LS mean difference	-	4.0296	-
90% CI	-	1.01, 7.05	-
95% CI	-	0.43, 7.63	-
Week 16			
n	191		193
LS mean (SE)	-89.20 (2.513)		-88.94 (2.471)
95% CI	-94.13, -84.28		-93.79, -84.10
LS mean difference	-	-0.2601	-
90% CI	-	-2.09, 1.57	-
95% CI	-	-2.44, 1.92	-

Abbreviations: ANCOVA, analysis of covariance; CI, confidence interval; ICE, intercurrent event; LS mean, least squares mean; N, number of patients in the treatment group; n, number of patients with available data; SE, standard error.

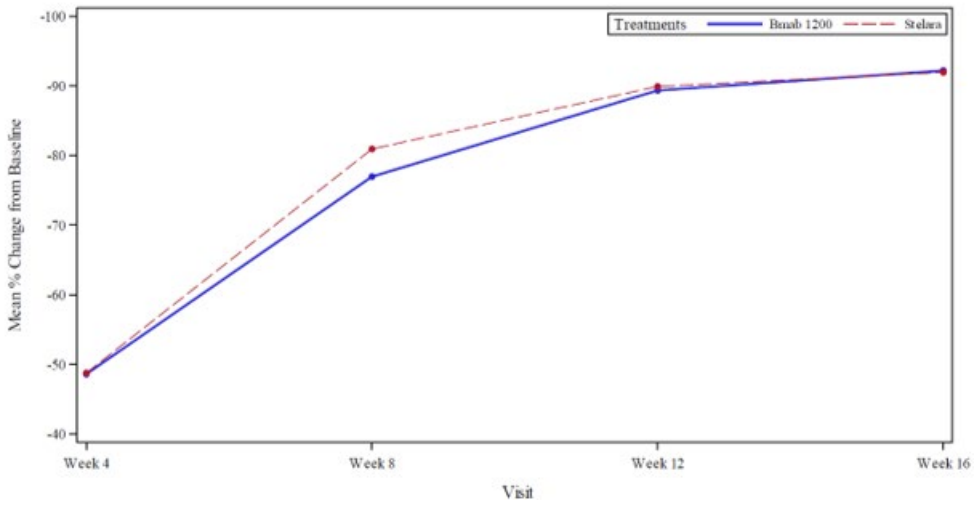
Note: Percentages (%) are based on the number of patients in each treatment group (N).

Note: ANCOVA model is used for percentage change from baseline as the dependent variable, including treatment group and randomization stratification variables (region, body weight at baseline category, baseline psoriatic arthritis status, and previous biologic use) as fixed factors.

a. A composite strategy is applied for ICE1. A treatment policy strategy is applied for ICE2, ICE3, and ICE4 and a hypothetical strategy is applied for ICE5.

There was comparable improvement (reduction) in PASI score in both treatment groups at each time point of Week 4, 8 and 16, with a greater improvement over time as expected showing the comparability of treatments (Figure 4).

Figure 4. Plot of Mean Percentage Improvement From Baseline in Psoriasis Area and Severity Index Score up to Week 16 (Full Analysis Set)



Percentage Change from Baseline in the PASI Score at Weeks 20, 28, 40, and 52 (TP2 & TP3)

There was a further improvement (reduction) in the PASI score at Week 20 with a mean (SD) percentage reduction from baseline of -94.17% (8.499), -94.27% (8.131), and -94.26% (8.537) in the Bmab 1200, Stelara-Stelara, and Stelara-Bmab 1200 treatment groups, respectively. There was minimal further improvement at Week 28 with a mean (SD) percentage reduction from baseline of -95.07% (7.066), -94.79% (10.764), and -93.69% (11.806) in the Bmab 1200, Stelara-Stelara, and Stelara-Bmab 1200 treatment groups, respectively, indicating that a plateau may have been reached at Week 20. Improvements in PASI were maintained at week 40 and 52. At Week 52, the mean (SD) percentage reduction from baseline was −95.50% (7.507), −96.60% (5.671), and −94.71% (7.950) in the Bmab 1200, Stelara-Stelara, and Stelara-Bmab 1200 treatment groups, respectively.

PASI 50, PASI 75, and PASI 90 Relative to Baseline at Weeks 4, 8, 12, and 16 (TP1)

Results from the analyses of the proportion of patients achieving PASI 50, PASI 75, and PASI 90 criteria at Weeks 4, 8, 12, and 16 for the FAS are summarised for the primary estimand in Table 16. The proportions of patients achieving PASI 50, PASI 75, and PASI 90 criteria increased in both treatment groups at each time point up to Week 16.

Table 16. Patients Achieving PASI 50, PASI 75, and PASI 90 Criteria at Weeks 4, 8, 12, and 16 – Primary Estimand (Full Analysis Set)

Primary Estimand[a]	PASI 50	PASI 75	PASI 90
Week 4			
Estimate (Bmab 1200; Stelara) (%)	46.07; 46.36	16.23; 11.49	1.57; 3.67
Estimated proportion difference (Bmab 1200-Stelara) (%)	-0.53	4.65	-2.13
Estimated 95% CI	-10.40, 9.33	-2.31, 11.60	-5.35, 1.10
Week 8			
Estimate (Bmab 1200; Stelara) (%)	91.62; 94.23	62.48; 72.17	33.75; 33.41
Estimated proportion difference (Bmab 1200-Stelara) (%)	-2.67	-9.87	-0.02
Estimated 95% CI	-7.88, 2.53	-19.30, -0.44	-9.55, 9.51
Week 12			
Estimate (Bmab 1200; Stelara) (%)	99.48; 98.96	89.93; 90.19	57.05; 62.80
Estimated proportion difference (Bmab 1200-Stelara) (%)	0.53	-0.67	-5.61
Estimated 95% CI	-1.25, 2.31	-6.60, 5.27	-15.37, 4.16
Week 16			
Estimate (Bmab 1200; Stelara) (%)	99.34; 99.58	89.97; 91.34	70.36; 68.88
Estimated proportion difference (Bmab 1200-Stelara) (%)	-0.23	-1.75	1.40
Estimated 95% CI	-1.83, 1.37	-7.64, 4.14	-7.96, 10.76

Abbreviations: CI, confidence interval; ICE, intercurrent event; N, number of patients in the population; n, number of patients with available data; PASI, Psoriasis Area and Severity Index.

Note: Estimated difference and CIs are from Cochran-Mantel-Haenszel test adjusted by the stratification variables (region, body weight at baseline category, baseline psoriatic arthritis status, and previous biologic use).

Note: PASI 50/75/90 is defined as ≥50/75/90% improvement in PASI from baseline.

Note: For Bmab 1200, N = 191 and n = 191 at Weeks 4, 8, 12, and 16 for PASI 50/75/90. For Stelara, N = 193 and n = 193 at Weeks 4, 8, 12, and 16 for PASI 50/75/90.

[a] A composite strategy is applied for ICE1, a treatment policy strategy for ICE2, ICE3 and ICE4 and a hypothetical strategy for ICE5.

Area Under the Effect Curves (AUECs) of PASI Score from baseline through Week 12 (TP1)

For the primary estimand, the LS mean (SE) AUECs of PASI score from baseline through Week 12 were 1148.99 (96.317) in the Bmab 1200 group and 1107.72 (94.679) in the Stelara group. The LS mean difference between treatments was 41.2766 (95% CI, −41.68, 124.23). Results for the secondary and tertiary estimands were similar to those for the primary estimand.

Change from baseline in affected Body Surface Area at Weeks 4, 8, 12, and 16 (TP1)

The change from baseline in the percentage affected BSA at Weeks 4, 8, 12, and 16 for the FAS is summarised.

Table 17. Change from Baseline in Percentage Affected Body Surface Area at Weeks 4, 8, 12, and 16 (Treatment Period 1) (Full Analysis Set))

	Bmab 1200 (N=191)	Difference Between Treatments	Stelara (N=193)
Week 4			
n	190		192
LS mean (SE)	-8.70 (1.501)		-8.19 (1.480)
95% CI	-11.65, -5.75		-11.10, -5.28
LS mean difference	-	-0.5114	-
95% CI	-	-2.88, 1.85	-
Week 8			
n	188		191
LS mean (SE)	-18.13 (1.434)		-19.16 (1.413)
95% CI	-20.95, -15.31		-21.94, -16.39
LS mean difference	-	1.0323	-
95% CI	-	-0.99, 3.05	-
Week 12			
n	187		188
LS mean (SE)	-23.55 (1.340)		-24.17 (1.320)
95% CI	-26.19, -20.92		-26.76, -21.57
LS mean difference	-	0.6135	-
95% CI	-	-0.83, 2.06	-
Week 16			
n	186		186
LS mean (SE)	-25.39 (1.320)		-25.30 (1.300)
95% CI	-27.99, -22.80		-27.86, -22.75
LS mean difference	-	-0.0879	-
95% CI	-	-1.38, 1.21	-

Abbreviations: CI, confidence interval; LS mean, least squares mean; N, number of patients in the treatment group; n, number of patients with available data; SE, standard error.

Note: Mixed-effect model for repeated measures approach includes change from baseline as the dependent variable including treatment group, visit and randomization stratification variables (region, body weight at baseline category, baseline psoriatic arthritis status, and previous biologic use) as fixed factors and Treatment-Visit as interaction effect.

Change from baseline in affected Body Surface Area at Weeks 20, 28, 40, and 52 (TP2 & TP3)

The baseline percentage affected BSA and the change from baseline in the percentage affected BSA at Weeks 20, 28, 40, and 52 for the FAS2 or FAS3 is presented below.

Table 18. Change from Baseline in Affected BSA at Weeks 20 and 28 (TP2) (FAS2)

Analysis Visit	Value	Statistics	Bmab 1200 (N=168)	Stelara - Stelara (N=81)	Stelara-Bmab 1200 (N=84)
Baseline	Observed Value	n	168	81	84
		Mean (SD)	28.88 (15.416)	27.64 (13.016)	31.06 (18.386)
		Median	23.50	23.00	25.50
		Q1, Q3	18.00, 38.00	18.00, 36.00	17.50, 38.50
		Min, Max	10.0, 90.0	12.0, 69.0	10.0, 93.0
Week 20	Observed Value	n	168	80	84
		Mean (SD)	2.96 (5.052)	2.34 (3.911)	3.36 (6.723)
		Median	1.00	1.00	0.50
		Q1, Q3	0, 4.00	0, 3.00	0, 3.00
		Min, Max	0, 29.0	0, 19.0	0, 38.0
	Change from Baseline	n	168	80	84
		Mean (SD)	-25.92 (15.210)	-25.29 (13.207)	-27.70 (17.021)
		Median	-21.00	-21.00	-23.50
		Q1, Q3	-32.00, -15.00	-32.00, -14.50	-35.00, -15.00
		Min, Max	-89.0, -5.0	-64.0, -7.0	-90.0, -1.0
Week 28	Observed Value	n	168	81	84
		Mean (SD)	2.36 (3.750)	1.73 (3.089)	2.73 (5.896)
		Median	1.00	1.00	0
		Q1, Q3	0, 3.00	0, 2.00	0, 2.50
		Min, Max	0, 17.0	0, 15.0	0, 33.0
	Change from Baseline	n	168	81	84
		Mean (SD)	-26.52 (15.152)	-25.91 (13.323)	-28.33 (17.251)
		Median	-21.00	-22.00	-23.50
		Q1, Q3	-33.00, -15.50	-32.00, -16.00	-35.50, -15.50
		Min, Max	-88.0, -7.0	-68.0, -10.0	-89.0, -1.0
Week 40	Observed Value	n	167	80	83
		Mean (SD)	2.39 (3.931)	1.53 (3.010)	2.02 (3.969)
		Median	1.00	0	0
		Q1, Q3	0, 3.00	0, 2.00	0, 2.00
		Min, Max	0, 20.0	0, 17.0	0, 20.0
	Change from Baseline	n	167	80	83
		Mean (SD)	-26.58 (15.237)	-26.21 (13.297)	-29.22 (17.455)
		Median	-21.00	-22.50	-25.00
		Q1, Q3	-33.00, -16.00	-33.50, -16.00	-37.00, -16.00
		Min, Max	-89.0, -4.0	-66.0, -7.0	-87.0, -9.0
Week 52	Observed Value	n	163	80	83
		Mean (SD)	1.83 (3.151)	1.13 (1.898)	2.02 (3.619)
		Median	0	0	0
		Q1, Q3	0, 2.00	0, 1.55	0, 2.00
		Min, Max	0, 20.0	0, 10.0	0, 17.0
	Change from Baseline	n	163	80	83
		Mean (SD)	-27.42 (15.119)	-26.50 (13.160)	-28.90 (17.560)
		Median	-22.00	-23.00	-25.00
		Q1, Q3	-36.00, -17.00	-34.50, -17.00	-36.00, -15.00
		Min, Max	-89.0, -6.0	-67.0, -10.0	-88.0, -10.0

Change From Baseline in Quality of Life as Measured by DLQI Scores (TP1 & TP2 & TP3)

The mean (SD) baseline DLQI score for the FAS was 15.0 (6.67) in the Bmab 1200 group and 13.9 (6.60) in the Stelara group. The DLQI score was comparable between treatment groups based on the MMRM analysis and decreased from baseline (improved) in both treatment groups at each time point up to Week 12. At Week 12, the mean (SE) change from baseline in DLQI score was -10.23 (0.912) in the Bmab 1200 group and -10.22 (0.896) in the Stelara group. The LS mean difference between treatments was −0.0067 (95% CI, −0.87 to 0.86). At Week 16, the mean (SE) change from baseline in the DLQI score decreased further from Week 12 in the Bmab 1200 group and increased slightly from Week 12 in the Stelara group (-10.38 [0.912] and -9.99 [0.895], respectively; estimated difference between treatments −0.3840 [95% CI, −1.24 to 0.47]). The reduction from baseline was maintained until Week 52. The mean (SE) change from baseline in the DLQI score was -12.8 [6.73] in the Bmab group, -12.7 [6.98] in the Stelara-Bmab 1200 group and -11.5 (6.35) in the Stelara-Stelara group respectively.

Ancillary analyses

Percentage change from baseline in the PASI score in patients ≤100 kg treated with 45 mg Bmab1200 or Stelara

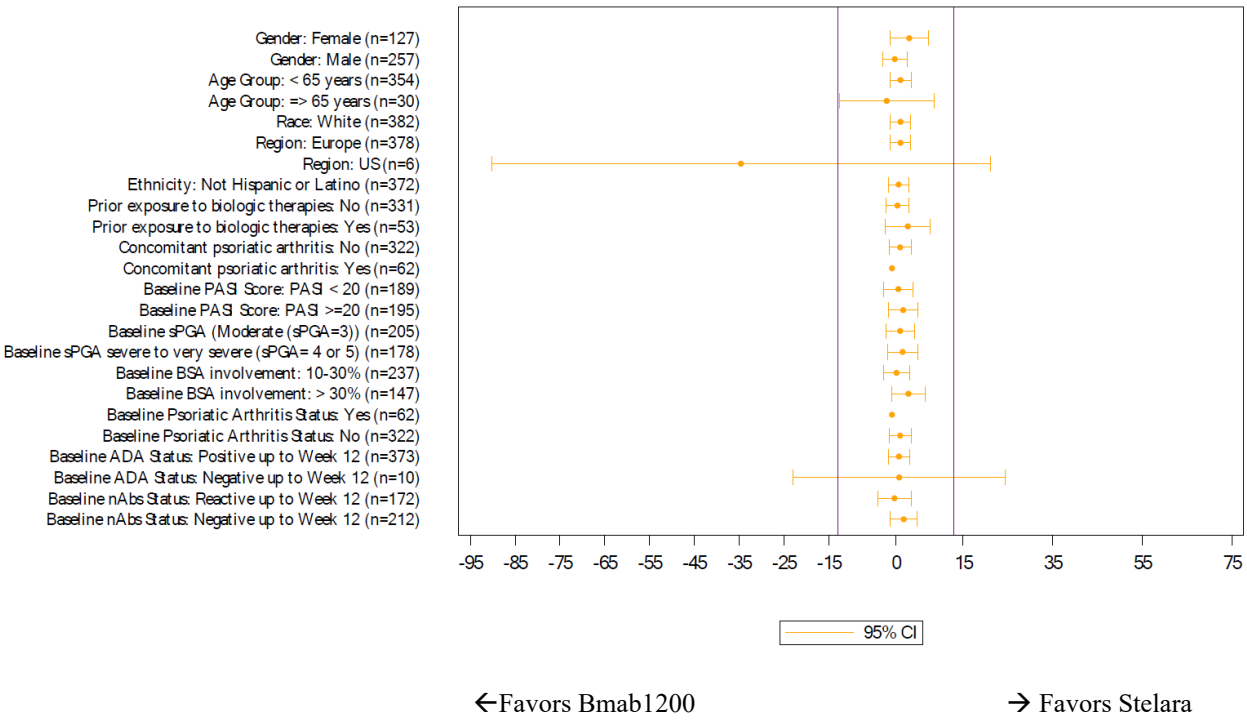
At week 12, the LS mean (SE) percentage change from baseline in PASI score at Week 12 was −77.44% (3.528) in the Bmab 1200 group and -78.55% (3.557) in the Stelara group, with a difference between treatments of 1.1061% (90% CI, -1.16 to 3.38; 95% CI, -1.60 to 3.81) for the primary estimand. Results from analysis of the secondary and tertiary estimands were similar to those of the primary estimand. The 95% CIs for all 3 estimands were contained entirely within the predefined margins specified for the total population.

The comparative efficacy for 45 mg subgroup (n=301) at weeks 4, 8, 12, and 16 was similar to the overall population (n=384).

Exploratory Subgroup Analysis of Primary Efficacy Endpoint

The exploratory subgroup analyses for the primary efficacy endpoint were conducted for gender, age group, race, ethnicity, prior exposure to biologic therapies for psoriasis or psoriatic arthritis, concomitant psoriatic arthritis, baseline PASI score, baseline sPGA, baseline BSA involvement, baseline psoriatic arthritis status, ADA status, and NAbs status.

Figure 5. Plot of Percentage Change from Baseline in PASI Score at Week 12 by Overall and Subgroup – Primary Estimand (Full Analysis Set)



Abbreviations: BSA, body surface area; CI, confidence interval; PASI, Psoriasis Area and Severity Index; sPGA, static Physician's Global Assessment; US, United States.
Note: Equivalence margin applied to primary efficacy analysis is ±13% for the 95% CI. Equivalence margins are used as a guide for subgroup analyses.

Percentage Change from Baseline in PASI at Week 12 by ADA/nAb Status

The overall incidence rate of ADA post baseline during TP1 (i.e., positive ADA anytime post baseline), irrespective of the baseline status, was observed to be 97.4% in the Bmab1200 group and 99.0% in

the Stelara group. A summary of the analysis of the percentage change from baseline in the PASI score at Week 12 by ADA status (positive/negative) up to Week 12, implementing the 3 defined estimand handling strategies for the FAS is presented in the Table 19 below.

Table 19. Percentage Change from Baseline In Psoriasis Area and Severity Index Score at Week 12 by ADA Status (Positive/Negative) Postbaseline up to Week 12 (Full Analysis Set)

ADA Status: Positive up to Week 12	Bmab 1200 (N=182)	Difference Between Treatments	Stelara (N=191)
Primary estimand[a]			
n	182	-	191
LS mean (SE)	-79.80 (2.841)	-	-80.48 (2.807)
95% CI	-85.37, -74.24	-	-85.98, -74.97
LS mean difference	-	0.6714	-
90% CI	-	-1.32, 2.66	-
95% CI	-	-1.70, 3.04	-
Secondary estimand[b]			
n	182	-	191
LS mean (SE)	-80.07 (2.862)	-	-80.68 (2.822)
95% CI	-85.67, -74.46	-	-86.22, -75.15
LS mean difference		0.6187	
90% CI		-1.38, 2.62	
95% CI		-1.77, 3.00	
Tertiary estimand[c]			
n	182	-	191
LS mean (SE)	-79.88 (2.810)	-	-80.53 (2.776)
95% CI	-85.39, -74.37	-	-85.97, -75.08
LS mean difference		0.6478	
90% CI		-1.36, 2.66	
95% CI	-	-1.75, 3.04	-
ADA Status: Negative up to Week 12	**Bmab 1200 (N=9)**	**Difference Between Treatments**	**Stelara (N=1)**
Primary estimand[a]			
n	9	-	1
LS mean (SE)	-93.07 (4.303)	-	-93.80 (12.784)
95% CI	NE	-	-118.94, -68.65
LS mean difference	-	0.7308	-
90% CI	-	-19.14, 20.60	-
95% CI	-	-22.97, 24.43	-
Secondary estimand[b]			
n	9		1
LS mean (SE)	-93.07 (4.203)		-93.83 (11.402)
95% CI	NE		-116.18, -71.48
LS mean difference		0.7620	
90% CI		-16.68, 18.20	
95% CI		-20.02, 21.54	
Tertiary estimand[c]			
n	9	-	1
LS mean (SE)	-93.07 (4.253)	-	-
95% CI	NE	-	-
LS mean difference	-	NE	-
90% CI	-	NE	-
95% CI	-	NE	-

Abbreviations: ANCOVA, analysis of covariance; CI, confidence interval; ICE, intercurrent event; LS mean, least squares mean; MAR, missing at random; N, number of patients in the treatment group; n, number of patients with available data; NE, non-estimable; SE, standard error.

Note: Percentages (%) are based on the number of patients in each treatment group (N).

Note: ANCOVA model is used for percentage change from baseline as the dependent variable, including treatment group and randomization stratification variables (region, body weight at baseline category, baseline psoriatic arthritis status, and previous biologic use) as fixed factors.

a. A composite strategy is applied for ICE1. A treatment policy strategy is applied for ICE2, ICE3, and ICE4 and a hypothetical strategy is applied for ICE5.

b. A composite strategy is applied for ICE1, a treatment policy strategy is applied for ICE2, and a hypothetical strategy is applied for ICE3, ICE4 and ICE5.

c. The tertiary estimand for the primary efficacy endpoint is based on a principal stratum strategy for all ICEs. For this estimand, no patients will have PASI data affected by an ICE, and no imputation will occur other than MAR imputation for missing data not due to an ICE.

The overall incidence rate of NAbs post baseline during TP1, irrespective of the baseline status, was observed to be 50.8% in the Bmab1200 group and 53.9% in the Stelara group. Results of the subgroup analysis by NAbs status (reactive/negative) are shown below.

Table 20. Percentage Change from Baseline in PASI at Week 12 by NAb Status (reactive/negative) up to Week 12 (Full analysis set)

NAbs Status: Reactive up to Week 12	Bmab1200 (N=83)	Difference Between Treatments	Stelara (N=89)
Primary estimand[a]			
n	83	-	89
LS mean (SE)	-77.61 (4.832)	-	-77.29 (4.814)
95% CI	-87.08, -68.14	-	-86.72, -67.85
LS mean difference	-	-0.3239	-
90% CI	-	-3.45, 2.80	-
95% CI	-	-4.05, 3.40	-
Secondary estimand[b]			
n	83	-	89
LS mean (SE)	-77.63 (4.833)	-	-77.28 (4.814)
95% CI	-87.10, -68.15	-	-86.71, -67.84
LS mean difference	-	-0.3509	-
90% CI	-	-3.48, 2.78	-
95% CI	-	-4.08, 3.38	-
Tertiary estimand[c]			
n	83	-	89
LS mean (SE)	-77.66 (4.843)	-	-77.28 (4.823)
95% CI	-87.15, -68.17	-	-86.73, -67.83
LS mean difference	-	-0.3839	-
90% CI	-	-3.53, 2.76	-
95% CI	-	-4.13, 3.36	-
NAbs Status: Negative up to Week 12	Bmab1200 (N=108)	Difference Between Treatments	Stelara (N=104)
Primary estimand[a]			
n	108	-	104
LS mean (SE)	-80.90 (3.443)	-	-82.66 (3.372)
95% CI	-87.65, -74.15	-	-89.27, -76.05
LS mean difference	-	1.7617	
90% CI	-	-0.75, 4.27	
95% CI	-	-1.23, 4.75	
Secondary estimand[b]			
n	108	-	104
LS mean (SE)	-81.25 (3.493)	-	-82.88 (3.417)
95% CI	-88.10, -74.40	-	-89.57, -76.18
LS mean difference	-	1.6280	-
90% CI	-	-0.92, 4.17	-
95% CI	-	-1.41, 4.66	-
Tertiary estimand[c]			
n	108	-	104
LS mean (SE)	-80.88 (3.386)	-	-82.66 (3.326)
95% CI	-87.52, -74.23	-	-89.19, -76.13
LS mean difference	-	1.7825	-
90% CI	-	-0.78, 4.34	-
95% CI	-	-1.27, 4.83	-

Abbreviations: ANCOVA, analysis of covariance; CI, confidence interval; ICE, intercurrent event; LS mean, least squares mean; MAR, missing at random; N, number of patients in the treatment group; n, number of patients with available data; NE, non-estimable; SE, standard error.
Note: Percentages (%) are based on the number of patients in each treatment group (N).

a. A composite strategy is applied for ICE1. A treatment policy strategy is applied for ICE2, ICE3, and ICE4 and a hypothetical strategy is applied for ICE5.

b. A composite strategy is applied for ICE1, a treatment policy strategy is applied for ICE2, and a hypothetical strategy is applied for ICE3, ICE4 and ICE5.

c. The tertiary estimand for the primary efficacy endpoint is based on a principal stratum strategy for all ICEs. For this estimand, no patients will have PASI data affected by an ICE, and no imputation will occur other than MAR imputation for missing data not due to an ICE.

An additional analysis based on ADA titres is provided below. For this analysis at week 12, the ADA titres have been classified into low, moderate and high based on quartile distribution of patient titre values [low (<=Q1, for first 25%), medium (Q1- Q3, between 25 – 75%), high (>Q3, for last 25%).

Table 21. Percentage Change from Baseline in PASI Score at Week 12 by ADA & nAb Status (FAS)

ADA/Nab Status	Bmab 1200	Stelara
Low/Reactive		
n	13	2
LS Mean (SE)	-93.54 (11.93)	-92.64 (16.92)
95% CI	-120.11, -66.97	-130.33, -54.95
LS Mean Difference	-0.9066	
90% CI	-28.98, 27.16	
95% CI	-35.42, 33.60	
Low/Negative		
n	47	21
LS Mean (SE)	-94.66 (2.17)	-93.65 (2.94)
95% CI	-99.00, -90.31	-99.52, -87.78
LS Mean Difference	-1.0056	
90% CI	-5.10, 3.09	
95% CI	-5.91, 3.90	
Moderate/Reactive		
n	27	16
LS Mean (SE)	-90.16(4.84)	-90.87(4.79)
95% CI	-99.96, -80.35	-100.57, -81.17
LS Mean Difference	0.7157	
90% CI	-5.85, 7.28	
95% CI	-7.17, 8.60	
Moderate/Negative		
n	54	69
LS Mean (SE)	-80.57(4.65)	-82.27(4.46)
95% CI	-89.79, -71.36	-91.11, -73.44
LS Mean Difference	1.7005	
90% CI	-2.44, 5.84	
95% CI	-3.25, 6.65	
High/Reactive		
n	8	44
LS Mean (SE)	-92.41(3.06)	-91.02(2.38)
95% CI	-98.58, -86.25	-95.81, -86.24
LS Mean Difference	-1.3923	
90% CI	-6.47, 3.69	
95% CI	-7.48, 4.70	
High/Negative		
n	8	21
LS Mean (SE)	-90.83(6.24)	-89.52(5.25)
95% CI	-103.71, -77.95	-100.36, -78.69
LS Mean Difference	-1.3071	
90% CI	-8.25, 5.64	
95% CI	-9.69, 7.07	

C_{trough} concentration and % change from baseline (%CHBL) in PASI scores are provided against ADA titre [low (<=Q1), medium (Q1-Q3), and high (>Q3)] and NAbs status (reactive/negative) are provided below.

Table 22. Summary of Ctrough concentration and % Change from Baseline in PASI Score at Week 12 based on ADA titre and nAb status

ADA	NAB	Statistics	Bmab 1200_Ctrough	Stelara_ Ctrough	Bmab 1200_PASI	Stelara_PASI
<=Q1	NEGATIVE	n	47	20	47	21
		Mean	1856.87234	2005.25	-92.46217372	-90.65289709
		SD	801.63579	797.6861852	8.155244088	10.61509991
		Median	1730	2070	-93.65070365	-94.30252336
	REACTIVE	n	13	2	13	2
		Mean	1852.615385	1755	-88.73724674	-82.85714286
		SD	992.6977637	813.1727984	14.46582507	24.24366107
		Median	1770	1755	-92.52873563	-82.85714286
Q1-Q3	NEGATIVE	n	54	69	54	69
		Mean	2141.033333	1844.101449	-86.6988347	-88.26018475
		SD	965.9824462	877.155549	13.15028529	14.21484299
		Median	1990	1710	-89.13640707	-92.8807589
	REACTIVE	n	27	16	27	16
		Mean	2268.777778	1952.1875	-90.21050546	-89.64610403
		SD	810.2422398	984.0337541	12.1038806	11.58378565
		Median	2160	1670	-93.10344828	-92.91162791
>Q3	NEGATIVE	n	8	21	8	21
		Mean	1656.125	1369.52381	-90.55311718	-90.7745757
		SD	778.467806	906.4012698	12.48370745	10.14792365
		Median	1745	1170	-93.72957516	-91.93548387
	REACTIVE	n	8	44	8	44
		Mean	1442.125	1205.213636	-93.75965079	-92.32552591
		SD	1063.442448	1010.745414	7.872811827	7.077907716
		Median	1290	1190	-98.35361731	-91.48206474

6.1.6.3. Summary of main efficacy results

The following Table 23 summarises the efficacy results from the main studies supporting the present application. These summaries should be read in conjunction with the discussion on clinical efficacy as well as the biosimilarity assessment (see later sections).

Table 23. Summary of efficacy for trial BM12H-PSO-03-G-02

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**		
Study identifier	BM12H-PSO-03-G-02 EudraCT Number: 2021-006668-25	
Design	Randomised, double-blind, active-controlled, parallel group, multicenter	
	Duration of main phase: Duration of Run-in phase: Duration of Extension phase:	52 weeks 28-Jun-2022 (First Patient First Visit) – 15-Nov-2023 (Last Patient Last Visit for Week 52) not applicable not applicable
Hypothesis	Equivalence	

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

Study identifier	BM12H-PSO-03-G-02 EudraCT Number: 2021-006668-25		
Treatments groups	Bmab 1200		Treatment: Bmab 1200 - SC 45 mg (≤100kg) / 90 mg (>100kg) Duration: 52 weeks Regimen: W0, W4, W16, W28, W40 Randomised: 191
	EU-Stelara		Treatment: EU-Stelara - SC 45 mg (≤100kg) / 90 mg (>100kg) Duration: 52 weeks Regimen: W0, W4, W16, W28, W40 Randomised: 193
Endpoints and definitions	Primary: Percentage change from baseline in the PASI score at Week 12	PE	PASI, a quantitative rating score for measuring the severity of psoriatic lesions based on area coverage and plaque appearance and their response to therapy
	Secondary: Percentage change from baseline in PASI score at Week 8	SE1	
	Secondary: PASI 75at Weeks 8 and 12	SE2	PASI 50, PASI 75, and PASI 90 were defined as an improvement from baseline in PASI score of 50% or greater, 75% or greater, or 90% or greater, respectively.
	Secondary: sPGA response of cleared or almost clear/minimal (PGA score of 0 or 1) at Weeks 8 and 12	SE3	sPGA. a quantitative rating score of the patient's psoriasis based on physician's assessment of induration, erythema, and scaling
Database lock	08-Dec-2023 (final CSR)		

Results and Analysis

Analysis description	**Analysis of primary and (key) secondary endpoints (Primary Estimand on the FAS)**		
Analysis population and time point description	Full Analysis Set (FAS): all patients who signed the ICF and were randomised into TP1 (the treatment as randomised). The primary analysis was conducted at Week 12 and as secondary analyses results at Week 8 are presented below		
Descriptive statistics and estimate variability	Treatment group	Bmab1200	Stelara
	Number of subjects	191	193

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

Study identifier	BM12H-PSO-03-G-02 EudraCT Number: 2021-006668-25		
	PE LS mean (SE) (95% CI)	 -79.87 (2.818) (-85.40, -74.35)	 -80.55 (2.783) (-86.01, -75.10)
	SE1 (Week 8) (LS mean) (SE) (95% CI)	-68.48 (4.171) (-76.65, -60.30)	-72.51 (4.099) (-80.54, -64.47)
	SE2 (PASI 75/Week 12) LS mean (SE) (95% CI)	 89.93 (--) (--)	 90.19 (--) (--)
	SE2 (PASI 75/Week 8) LS mean (SE) (95% CI)	 62.48 (--) (--)	 72.17 (--) (--)
	SE3 (Week 12) LS mean (SE) (95% CI)	 83.93 (--) (--)	 86.31 (--) (--)
	SE3 (Week 8) LS mean (SE) (95% CI)	 59.34 (--) (--)	 65.97 (--) (--)
Effect estimate per comparison	Primary: Mean difference of percentage change from baseline in the PASI score at Week 12	Comparison groups	Bmab1200 vs. Stelara
		LS mean difference	0.6800
		95% CI	(-1.64, 3.00)
	Secondary: Mean difference of percentage change from baseline in the PASI score at Week 8	Comparison groups	Bmab1200 vs. Stelara
		LS mean difference	4.0296
		95% CI	(0.43, 7.63)
	Secondary: Proportion difference patients achieving PASI 75 at Week 12	Comparison groups	Bmab1200 vs. Stelara
		LS mean difference	-0.67
		95% CI	(-6.60, 5.27)
	Secondary: Proportion difference patients achieving PASI 75 at Week 8	Comparison groups	Bmab1200 vs. Stelara
		LS mean difference	-9.87
		95% CI	(-19.30, -0.44)

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**			
Study identifier	BM12H-PSO-03-G-02 EudraCT Number: 2021-006668-25		
	Secondary: Proportion difference of patients with sPGA response at Week 8	Comparison groups	Bmab1200 vs. Stelara
		LS mean difference	-6.93
		95% CI	(-16.61, 2.75)
	Secondary: Proportion difference of patients with sPGA response at Week 12	Comparison groups	Bmab1200 vs. Stelara
		LS mean difference	-2.84
		95% CI	(-10.00, 4.32)
Analysis description	**Sensitivity Analysis (Tertiary Estimand on the PPS)**		
Analysis population and time point description	PPS: The PPS consisted of all patients in the FAS who received at least 2 study treatment administrations (baseline and Week 4) and did not experience any important protocol deviations affecting primary efficacy at Week 12. At week 12		
Descriptive statistics and estimate variability	Treatment group	Bmab1200	Stelara
	Number of subject	189	189
	PE LS mean (SE) (95% CI)	-76.67 (3.062) (-82.67, -70.67)	-77.59 (2.998) (-83.47, -71.72)
Effect estimate per comparison	Mean difference of percentage change from baseline in the PASI score at Week 12	Comparison groups	Bmab1200 vs. Stelara
		LS mean difference	0.9250
		95% CI	(-1.40, 3.25)

6.1.6.4. Clinical studies in special populations

6.1.7. Clinical studies in special populations

6.1.7.1. In vitro biomarker test for patient selection for efficacy

Not applicable

6.1.7.2. Analysis performed across trials (pooled analyses and meta-analysis)

Not applicable

6.1.7.3. Supportive studies

Not applicable

6.1.8. Discussion on clinical efficacy

Design and conduct of clinical studies

The clinical development programme for Bmab 1200 comprised a single randomised, double-blind, active-controlled phase 3 study BM12H-PSO-03-G-02 to compare the efficacy and safety of Bmab 1200 and EU-Stelara. The study also included PK assessments and evaluation of immunogenicity.

Study Design

Study BM12H-PSO-03-G-02 was conducted in patients with moderate-to-severe plaque psoriasis with dosing at baseline, at week 4 and every 12 weeks thereafter according to the Stelara labelling. The study population represents the most sensitive population to demonstrate biosimilarity between the Bmab1200 and Stelara-EU reference product. The study included active-controlled treatment for 52 weeks.

The treatment period was subdivided into 3 treatment periods (i.e.. TP1, TP2, TP3). In TP1 (Week 0 to Week 16), patients were either assigned to EU-Stelara or Bmab 1200 and received treatment at baseline and Week 4. Patients achieving at least PASI 50 at the time of the primary analysis were eligible to proceed to TP2 (Week 16 to Week 28). In TP2, patients initially assigned to Stelara were re-randomised to either Stelara or Bmab 1200 before study treatment at Week 16. In TP3 (Week 28 to Week 52), all continuing patients who completed TP2 and achieved at least PASI 75 response at Week 28 were offered to enter TP3 receiving the same treatment as assigned in TP2.

The primary efficacy endpoint was the percentage change in PASI score between baseline and 12 weeks. The use of the PASI to evaluate changes in efficacy is appropriate. However, as also pointed out in the Scientific Advice (EMA/CHMP/SAWP/134492/2020), the sensitivity to detect differences is higher at earlier time points (e.g. Week 8), as the response curve in the originator registrational trials was already starting to reach a plateau at Week 12. As such, evaluation of differences in response before Week 12 are also relevant for the comparative efficacy analysis.

Changes in PASI at various time points until week 52 were evaluated as secondary endpoints. Other secondary endpoints include the proportion of patients achieving PASI 50, 75 or 90, disease severity evaluation by sPGA scoring, as well as change in affected BSA at different time points through week 52. AUECs of PASI from baseline through week 12 were also evaluated. Change from baseline in DLQI scores at different time points up to Week 52 was also included. The choice of secondary endpoints is considered appropriate for comparability evaluation.

The predefined equivalence margin for EMA was ±13% for the 95% CI, which is considered overall appropriate and was previously agreed by CHMP (EMEA/H/SA/4410/1/2020/III).

Study population

The study enrolled patients with moderate-to-severe chronic plaque psoriasis as defined by BSA involvement ≥10%, PASI score ≥12, and sPGA ≥3 that were candidates for systemic therapy or

phototherapy with previous failure, inadequate response, intolerance, or contraindication to at least 1 antipsoriatic systemic therapy. Patients with psoriasis arthritis were included and patient enrolment was stratified accordingly.

Patients with a body weight up to 130 kg were included. As per Stelara labelling patients ≤100 kg received a 45 mg dose, while patients above this threshold received a 90 mg dose (2x 45 mg). Enrolment was stratified for body weight (≤100 kg versus >100 kg) and efficacy analysis include subgroup data for patients (≤100 kg) receiving the 45mg dose only.

During the study, patients were not allowed to receive any biologic treatment for the treatment of psoriasis or psoriasis arthritis. Non-biologic systemic therapies (such as immunosuppressants) were also prohibited as well as topical therapies (except for rescue treatment) were not allowed.

Patients with prior exposure to a maximum of 1 biologic agent for the treatment of psoriasis or psoriatic arthritis with a washout of at least 5 half-lives or 90 days (whichever was longer) were allowed to be enrolled. This creates some level of heterogeneity in the results but can be understood considering the feasibility of patient enrolment. Of note, patients with use of ustekinumab or other biologic therapies targeting IL-17, or IL-23 or IL-12 at any time prior to the study were not allowed for enrolment. Patient enrolment was stratified for previous exposure to biologic-based therapies accordingly and subgroup data were provided.

Study Conduct

There was a high number of major protocol deviations reported during TP1 (n=58; 15.1%). Still, the majority of the events appear to have not affected efficacy evaluation. 4 patients had major protocol deviation leading to exclusion from the PPS.

A substantial number of major protocol deviations (n=23) was attributed to an accidental unblinding due to a RTSM configuration issue during the re-randomisation at Week 16 as part of the transition of patients from TP1 to TP2. CRO and site personnel could have potentially viewed the TP1 treatment assignment. As the event occurred after the timing for the primary endpoint, these patients were not excluded from the primary analysis. This is agreed. Despite the unblinding events, the 23 patients remained in TP2; 16 patients were assigned to Bmab1200 and 7 patients were assigned to Stelara. All 23 patients were withdrawn at the Week 28 visit. This is acceptable and potential effects on the efficacy evaluation (if any) can be considered neglectable.

Disposition

A total of 384 patients were randomised into TP1 and received either Bmab 1200 (n=191) or Stelara (N=193). According to the EMA requirements (95% CI, equivalence margin of ±13%), a total sample size of 384 patients was considered with a power of 96% with a two one-sided 2.5% level of significance. These patients were included in the FAS which was used as base for the primary analysis (for further discussion on this point see discussion on efficacy data below). The per-protocol set mainly included the same patients as for the FAS, except for 6 patients that were excluded. Nearly all of the patients completed TP1 (99.5%). Only 2 patients did not achieve a PASI 50 response at Week 12. A total of 371 patients entered TP2 and subsequently completed the 28 Week visit. 301 patients (Bmab 1200: 151; Stelara: 150 patients) had a body weight below 100 kg and were randomised to receive the 45 mg dosing. The patient disposition for this subgroup was similar to all patients. A total of 333 patients entered and were dosed in TP3 and 324 patients (84.4%) finally completed the study (52-week visit).

Baseline data

The recruited study population was considered representative of the targeted population of plaque psoriasis. Baseline disease characteristics were overall balanced between the groups and overall reflect the anticipated study population of patients with moderate-to-severe plaque psoriasis.

The mean age was 43.2 years; 66.9 % of patients were males. Patients were mainly recruited in Poland (65.1%) and Georgia (20.8%). Only 2 participants were Black or African American, while the others were White. A total of 301 patients (78.4%) had a body weight below 100 kg and thus received the 45 mg dosing. Demographics and disease characteristics for this subgroup were similar to all patients. A total of 62 patients (16.1%) reported concomitant psoriatic arthritis. While prior use of one biologic for the treatment of psoriasis or psoriatic arthritis was allowed as per inclusion criteria, the majority of patients (86.2%) did not report any previous exposure to biologics. Prior use of biologics in the other 13.8% of patients was mainly attributed to the use of adalimumab.

Efficacy data and additional analyses

The predefined equivalence margin for EMA was ±13% for the 95% CI. The Full Analysis Set (FAS) was used for the primary analyses of efficacy. This analysis set consisted of all patients who signed the ICF and were randomised into TP1 (n=384). Three different estimands were defined and analysed on the FAS and additionally also on the per-protocol set (PPS) that included all patients in the FAS who received at least 2 study treatment administrations (baseline and Week 4) and who did not experience any important protocol deviations affecting primary efficacy at Week 12. Accordingly, 6 patients were excluded and the PPS included 378 patients. The primary estimand was mostly aligned with an IIT analysis. Which estimand, in this (bioequivalence) setting here, is the most sensitive estimand to detect differences between the test product and the originator is discussable. However, all three estimands on the ITT set as well as on the per-protocol set lead to very similar results and all respective 95% confidence intervals were included the predefined +-13% margin.

Percentage Change from Baseline in PASI Score (Primary Endpoint)

Regarding the primary endpoint, the *percentage change from baseline in the PASI Score at Week 12* was comparable between Bmab 1200 and Stelara (LS mean change: -79.87 vs. -80.55) in the FAS. The LS mean difference for the primary estimand was 0.6800 (95% CI: 1.64, 3.00). Very similar results are also observed for the secondary and tertiary estimands. For all estimands, the 95% CI was within a very narrow range, thus clinical comparability can be concluded. The Week 12 analysis based on the PPS (which differs from the FAS analysis set by only 6 patients) yielded overall similar changes in PASI in both groups and do support the results seen for the FAS, which is overall reassuring. Regarding earlier timepoints, there is notable difference in the response at Week 8 between the Bmab 1200 and Stelara 4.0296 (95% CI: 0.43; 7.63). Still, the size of the difference is not considered to principally question the comparability of efficacy. The difference was contained within the pre-specified equivalence margin.

Secondary Endpoints

The *proportion of patients achieving PASI 50, PASI 75, PASI 90* was similar between the groups and does reflect the overall reductions in PASI seen for the primary analysis. The improvements were maintained until week 52. Of note, similar to what is observed for the percentage PASI change, a markedly lower proportion of PASI75 responders was observed at Week 8 in the Bmab 1200 group (difference: -9.87), which was, however, not seen to this extent at later time points (i.e. Week 16, 20 and 28). Symptom improvements as per percentage PASI change were maintained until week 52 and were similar between the Bmab 1200 and the comparator. A similar pattern was observed for the

Change from baseline in affected Body Surface Area. The *Area Under the Effect Curves of PASI from Baseline trough Week 12* were only slightly different between the groups with similar results obtained for the other estimands and when based on the PPS. Similar results were also seen for the *Change From Baseline in Quality of Life as Measured by DLQI Scores*.

Subgroup analysis

Efficacy data from the 45 mg dosing subgroup (n=301) at Week 12 support the clinical comparability as concluded for the total patient population. The LS mean *percentage change from baseline in PASI Score at Week 12* was similar between Bmab 1200 and Stelara (-77.44 vs. 78.55) with a slightly LS mean difference (1.1061) as compared to all patients. Still, the 95% CI was again very narrow. Changes in PASI at weeks 4, 8, 12, and 16 were also similar to the overall population that included all patients irrespective of baseline weight.

Subgroup analyses for the primary efficacy endpoint were conducted for gender, age group, race, ethnicity, prior exposure to biologic therapies for psoriasis or psoriatic arthritis, concomitant psoriatic arthritis, baseline PASI score, baseline sPGA, baseline BSA involvement, and baseline psoriatic arthritis status do not reveal any major differences within certain subgroups.

The provided subgroup analysis for ADA and nAbs based on the overall occurrence of ADAs did not allow to conclude on immunogenicity between Bmab 1200 and the comparator as the number of ADA positive patients was remarkably high (nearly all positive at Week 12). This observation might be explained by the high sensitivity of the ADA assay used although issues with the ADA assay have been noted (see discussion on clinical pharmacology). An additional analysis was provided based on ADA titres (low, moderate, high) that do not indicate major differences in the induction of ADA and nAbs and effects on mAb exposure as well as reductions in PASI between Bmab 1200 and Stelara. Based on the data provided, similar immunogenicity is assumed.

6.1.9. Conclusions on clinical efficacy

The overall consistent results of the efficacy analysis conducted in study BM12H-PSO-03-G-02 based on the Full Analysis Set as well as on the Per Protocol Set with 3 different estimand strategies used support the clinical comparability between Bmab 1200 and Stelara up to 52 weeks.

6.1.10. Clinical safety

Please refer to the table of studies in section 6.3.2

For the purpose of this document, the following definitions apply:

'Adverse event – AE' means any untoward medical occurrence in a subject to whom a medicinal product is administered and which does not necessarily have a causal relationship with this treatment.

'Serious adverse event – SAE' means any untoward medical occurrence that at any dose requires inpatient hospitalisation or prolongation of existing hospitalisation, results in persistent or significant disability or incapacity, results in a congenital anomaly or birth defect, is life-threatening, or results in death. The definition (in line with ICH E2A) includes important medical events that may not be immediately life-threatening or result in death or hospitalisation but may jeopardise the patient or may require intervention to prevent one of the other outcomes listed in the definition above.

'Adverse drug reaction – ADR' means any untoward and unintended response to a medicinal product related to any dose administered, for which, after a thorough assessment, a causal relationship between the medicinal product and the adverse event is at least a reasonable possibility, based for

example, on their comparative incidence in clinical trials, or findings from epidemiological studies and/or on an evaluation of causality from individual case reports

The overall safety profile of Bmab1200 and Stelara has been assessed in two clinical studies, a clinical Phase 1 pharmacokinetic (PK) study in healthy subjects (BM12H-NHV-01-G-01) and a clinical Phase 3 study in patients with moderate to severe chronic plaque psoriasis (BM12H-PSO-03-G-02). Due to differences between the two studies [BM12H-NHV-01-G-01 (phase 1) and Study BM12H-PSO-03-G-02 (phase 3)] in terms of the design, dose, patient population, treatment duration, and data collection, a pooled safety analysis of both studies was not considered meaningful and safety results are discussed per individual study. Overall, the Bmap1200 Phase 1 study design is considered adequate to evaluate the comparability of Bmab1200 and its reference product EU-Stelara in terms of pharmacokinetic and safety.

In Study BM12H-PSO-03-G-02, patients initially randomised to EU-Stelara were re-randomised in a 1:1 ratio at Week 16, to enter Treatment Period 2 (TP2) and either continue treatment with EU-Stelara or to switch to Bmab1200. Patients were treated through 52-weeks. Data analyses sets were defined for each treatment period - TP1, TP2 and TP3; full analysis set (FAS) for TP1, FAS2 for TP2, and FAS3 for TP3.

For the development of Bmab1200, EMA Scientific Advice was received in March 2020 and Dec 2023. With regard to the BM12H-PSO-03-G-02 study design it was noted that the switch from Stelara to Bmab1200 to assess safety and immunogenicity should be done in such a way that allows follow up of sufficient numbers of patients for one year to compare the safety and immunogenicity of the proposed biosimilar to ustekinumab.

The safety evaluations were planned according to the known safety profile of ustekinumab, considering the adverse reactions presented in the SmPC and other available clinical information. The safety analyses were performed on the safety analysis sets, consisting of all subjects receiving at least 1 dose of either Bmab1200 or ustekinumab.

6.1.10.1. Patient exposure

In Study BM12H-NHV-01-G-01, 258 (100.0%) subjects received the study drug per planned dose. Overall, 86 subjects received a single dose of 45 mg Bmab 1200, 87 subjects received a single dose of 45 mg US Stelara, and 85 subjects received a single dose of 45 mg EU Stelara (Table 24). The demographic and baseline characteristics were well balanced between the 3 treatment groups.

Table 24. Overall Extent of Exposure to Study Treatment

Study No	**No of subjects/patients administered ≥1 dose of Study Drug**			
	Bmab 1200	**US-Stelara**	**EU-Stelara**	**Total**
BM12H-NHV-01-G-01	86	87	85	258
BM12H-PSO-03-G-02	191	-	193	384
Total	277*	87	278	**642**

* A total of 92 patients were re-randomised from Stelara to Bmab1200 in TP2 and thus 369 (277+92) patients received at least one dose of Bmab 1200 across the 2 studies.

For Study BM12H-PSO-03-G-02, a total of 384 patients were randomised in a 1:1 ratio to receive Bmab1200 or Stelara in Treatment Period 1 (Bmab1200=191 patients; EU-Stelara=193). Prior to week

16 dosing in Treatment Period 2 (TP2), patients receiving originator ustekinumab were re-randomised (1:1) to continue originator ustekinumab or switch to Bmab1200; patients initially randomised to Bmab1200 continued receiving Bmab1200. Overall, 382 patients (99.5%) completed treatment in TP1; 11 patients (2.9%, 5 patients in the Bmab1200 group and 6 patients in the Stelara) who completed TP1 did not enter TP2. Of the 371 patients who received study treatment in TP2, 94 patients continued to receive EU-Stelara in TP2, 185 patients who continued to receive Bmab1200 and 92 switching from EU-Stelara to Bmab 1200 in Treatment Period 2 (TP2). Twenty-three patients were discontinued from TP2 because of unblinding issues related to re-randomisation at Week 16 and an additional 4 patients were discontinued from TP2. Thus, 344 patients completed TP2. Of these, 11 patients (2.9%) who completed TP2 did not enter TP3. A total of 333 patients entered and were dosed in TP3 and a total of 324 patients (84.4%) completed the study (Bmab1200/Bmab1200=163; Stelara/Stelara=79; Stelara/Bmab1200=82).

Through Week 52, the overall mean (SD) duration of treatment was 327.7 days (94.82) and the mean (SD) total dose administered was 256.9 mg (99.68). Treatment compliance was 100% for all patients for each treatment period through the study. Table 25 summarises patient exposure to study drug and treatment compliance for the SAF through Week 52.

Table 25. Summary of Exposure to Study Drug and Treatment Compliance Through the Study (Baseline Through Week 52) (Safety Analysis Set)

Characteristic	Statistics	Bmab 1200 (N=191)	Stelara (N=101)	Stelara-Bmab 1200 (N=92)	Total (N=384)
Treatment duration (days)[1]	n	191	101	92	384
	Mean (SD)	330.9 (91.26)	308.2 (114.67)	342.5 (73.05)	327.7 (94.82)
	Median	365.0	365.0	365.0	365.0
	Q1, Q3	361.0, 366.0	358.0, 367.0	362.0, 368.0	360.0, 367.0
	Min, Max	1, 392	1, 385	106, 405	1, 405
Total dose administered (mg)[2]	n	191	101	92	384
	Mean (SD)	257.0 (98.87)	247.3 (100.95)	267.1 (100.03)	256.9 (99.68)
	Median	225.0	225.0	225.0	225.0
	Q1, Q3	225.0, 225.0	225.0, 225.0	225.0, 225.0	225.0, 225.0
	Min, Max	45, 450	45, 450	135, 450	45, 450
Dose received					
45 mg	n (%)	151 (79.1)	79 (78.2)	71 (77.2)	301 (78.4)
90 mg	n (%)	40 (20.9)	22 (21.8)	21 (22.8)	83 (21.6)
Total dose planned (mg)[3]	n	191	101	92	384
	Mean (SD)	257.0 (98.87)	247.3 (100.95)	267.1 (100.03)	256.9 (99.68)
	Median	225.0	225.0	225.0	225.0
	Q1, Q3	225.0, 225.0	225.0, 225.0	225.0, 225.0	225.0, 225.0
	Min, Max	45, 450	45, 450	135, 450	45, 450
Treatment compliance (%)[4]	n	191	101	92	384
	Mean (SD)	100.0 (0)	100.0 (0)	100.0 (0)	100.0 (0)
	Median	100.0	100.0	100.0	100.0
	Q1, Q3	100.0, 100.0	100.0, 100.0	100.0, 100.0	100.0, 100.0
	Min, Max	100, 100	100, 100	100, 100	100, 100
Compliance					
<80%	n (%)	0	0	0	0
80 - <90%	n (%)	0	0	0	0
90 - 100%	n (%)	191 (100)	101 (100)	92 (100)	384 (100)
Abbreviations: N = number of patients in the treatment group, n (%) = number (percentage) of patients with available data, Q1 = 1st quartile, Q3 = 3rd quartile, SAF = Safety Set for Treatment Period 1, SD = standard deviation, TP1 = Treatment Period 1.					

Characteristic	Statistics	Bmab 1200 (N=191)	Stelara (N=101)	Stelara-Bmab 1200 (N=92)	Total (N=384)
Note: Percentages (%) are based on the number of patients in each treatment group/overall on the SAF (N). [1]Treatment duration is calculated for patients completing to Week 52 as (date of Week 52 - date of first treatment) + 1 for through the study, and for patients completing to Week 16 as (date of 1 day prior to the Week 16 treatment - date of first treatment) + 1 for TP1. For patients discontinuing study treatment prior to the end of the study/treatment period, treatment duration is calculated as (date of last study treatment - date of first treatment) + 1. [2]Total dose administered is calculated as the sum of all doses of study drug administered for the treatment period/overall. [3]Total dose planned is calculated as the sum of all doses of study drug planned during the overall treatment period through the study (dispensed) according to the treatment schedule of the treatment group. [4]Treatment compliance is calculated as the ratio (%) between the total number of actual injections and the total number of expected injections × 100. The total number of actual injections is counted based on collected study drug administration data. The total number of expected injections is counted based on the dosage schedule and dispensed as per protocol.					

Demographics

BM12H-PSO-03-G-02

The demographic and baseline characteristics were generally balanced, with some small differences observed between the groups. Treatment arms (Bmab1200 and EU Stelara) were comparable with regard to age, weight (including percentage of patients in each BW category) and BMI. The majority of patients were male (66.9%); the percentage of male participants was slightly higher in the EU-Stelara group (70.5%) compared with the Bmab1200 (63.4%) group. Slightly more smokers were observed in the Bmab1200 group [61 patients (31.9%)] vs the Stelara group [52 patients (26.9%)].

Almost 100% of all patients in Study BM12H-PSO-03-G-02 had a history of prior medications. Differences observed in individual medications between cohorts are not considered to impact the safety evaluation. For both patients group, the most frequently-reported concomitant medications in patients by ATC Level 2 were: emollients and protectives, HMG-CoA reductase inhibitors, fixed combinations progestogens and oestrogens, biguanides, plain ACE inhibitors, anilides, beta blocking agents, other antihistamines for systemic use, and plain angiotensin II receptor blockers.

6.1.10.2. Adverse events

An overall summary of TEAEs across the controlled studies (Study BM12H-NHV-01-G-01 and Study BM12H-PSO-03-G-02) is presented in Table 26. Numerically higher incidences were observed in almost all TEAEs categories in the Bmab1200 group compared to the Stelara group in study BM12H-PSO-03-G-02 in TP1 and TP2 and in the Stelara-Bmab1200 group compared to the Stelara-Stelara group in TP2 and TP3 and throughout the study (Table 27).

Table 26. Overall Analysis of BM12H-NHV-01-G-01 and BM12H-PSO-03-G-02: Summary of Treatment-emergent Adverse Events

	Patients with Moderate to Severe Chronic Plaque Psoriasis Study BM12H-PSO-03-G-02							Healthy Subjects Study BM12H-NHV-01-G-01		
	Treatment Period 1		Treatment Period 2			Treatment Period 2 + Treatment Period 3				
	Bmab 1200 (N=191)	Stelara (N=193)	Bmab 1200 (N=185)	Stelara-Stelara (N=94)	Stelara-Bmab 1200 (N=92)	Stelara-Stelara (N=81)	Stelara-Bmab 1200 (N=84)	Bmab 1200 (N=86)	US-Stelara (N=87)	EU-Stelara (N=85)
Any TEAE, n (%)	82 (42.9)	66 (34.2)	47 (25.4)	21 (22.3)	25 (27.2)	27 (33.3)	36 (42.9)	61 (70.9)	52 (59.8)	67 (78.8)
Any treatment-related TEAE	16 (8.4)	12 (6.2)	12 (6.5)	2 (2.1)	8 (8.7)	6 (7.4)	9 (10.7)	28 (32.6)	25 (28.7)	30 (35.3)
Any serious TEAE, n (%)	3 (1.6)	1 (0.5)	1 (0.5)	0	0	0	0	2 (2.3)	0	0
Any serious treatment-related TEAE, n (%)	0	0	1 (0.5)	0	0	0	0	0	0	0
Any TEAE leading to study treatment interruption, n (%)	0	0	0	0	0	0	0	-	-	-
Any TEAE leading to study treatment withdrawal, n (%)	2 (1.0)	3 (1.6)	1 (0.5)	0	0	0	0	-	-	-
Any treatment-related TEAE leading to treatment discontinuation, n (%)	0	2 (1.0)	1 (0.5)	0	0	0	0	-	-	-
Any TEAE leading to study discontinuation, n (%)	2 (1.0)	3 (1.6)	1 (0.5)	0	0	0	0	0	0	0
Any TEAE of special interest by categories, n (%)*	41 (21.5)	34 (17.6)	19 (10.3)	8 (8.5)	18 (19.6)	10 (12.3)	22 (26.2)	-	-	-
Infections, n (%)	38 (19.9)	32 (16.6)	18 (9.7)	8 (8.5)	17 (18.5)	10 (12.3)	21 (25.0)	22 (25.6)	27 (31.0)	29 (34.1)
Malignancy, n (%)	2 (1.0)	0	0	0	0	0	0	1 (1.2)	-	-
Hypersensitivity reaction, n (%)	1 (0.5)	3 (1.6)	1 (0.5)	0	1 (1.1)	0	1 (1.2)	-	-	-
PRES	0	0	0	0	0	0	0	-	-	-

	Patients with Moderate to Severe Chronic Plaque Psoriasis Study BM12H-PSO-03-G-02							Healthy Subjects Study BM12H-NHV-01-G-01		
	Treatment Period 1		Treatment Period 2			Treatment Period 2 + Treatment Period 3				
	Bmab 1200 (N=191)	Stelara (N=193)	Bmab 1200 (N=185)	Stelara-Stelara (N=94)	Stelara-Bmab 1200 (N=92)	Stelara-Stelara (N=81)	Stelara-Bmab 1200 (N=84)	Bmab 1200 (N=86)	US-Stelara (N=87)	EU-Stelara (N=85)
Non-infectious pneumonia	0	0	0	0	0	0	0	-	-	-
Any TEAE leading to death, n (%)	0	0	0	0	0	0	0	0	0	0
Any AE leading to death, n (%)	0	0	0	0	0	0	0			

*AESIs were prespecified for the Phase 3 study only; however, the same type of AEs (infections and malignancies) did occur in the Phase 1 study and these details are also captured in the table.
Abbreviations: N = number of patients/subjects in the treatment group, n (%) = number (percentage) of patients/subjects with adverse events of interest, PRES = posterior reversible encephalopathy syndrome, TEAE = treatment-emergent adverse event.
Note: Study treatment-related TEAEs are those for which a "Possibly," "Probably," and "Definitely" relationship is reported, or with missing relationship.

Table 27. Overall Summary of Adverse Events of BM12H-PSO-03-G-02 Through the Study (Baseline Through Week 52) (Safety Analysis Set)

	Bmab 1200 (N=191) n (%) E	Stelara (N=101) n (%) E	Stelara-Bmab 1200 (N=92) n (%) E	Total (N=384) (%) E
Any TEAE	111 (58.1) 282	48 (47.5) 103	51 (55.4) 107	210 (54.7) 492
Any treatment-related TEAE	25 (13.1) 50	11 (10.9) 14	13 (14.1) 20	49 (12.8) 84
Any serious TEAE	6 (3.1) 8	0	1 (1.1) 1	7 (1.8) 9
Any serious treatment-related TEAE	1 (0.5) 2	0	0	1 (0.3) 2
Any TEAE leading to study treatment interruption	0	0	0	0
Any TEAE leading to study treatment withdrawal	3 (1.6) 4	3 (3.0) 3	0	6 (1.6) 7
Any treatment-related TEAE leading to treatment discontinuation	1 (0.5) 2	2 (2.0) 2	0	3 (0.8) 4
Any TEAE leading to study discontinuation	3 (1.6) 4	3 (3.0) 3	0	6 (1.6) 7
Any TEAE of special interest by categories	61 (31.9) 90	23 (22.8) 34	34 (37.0) 50	118 (30.7) 174
Infections	58 (30.4) 86	21 (20.8) 31	34 (37.0) 49	113 (29.4) 166
Malignancy	2 (1.0) 2	0	0	2 (0.5) 2
Hypersensitivity reaction	1 (0.5) 2	3 (3.0) 3	1 (1.1) 1	5 (1.3) 6
PRES	0	0	0	0
Non-infectious pneumonia	0	0	0	0
Any TEAE leading to death	0	0	0	0
Any AE leading to death	0	0	0	0

Abbreviations: AE = adverse event, E = number of events, N = number of patients in the treatment group, n (%) = number (percentage) of patients with adverse events of interest, PRES = posterior reversible encephalopathy syndrome, SAF = Safety Set for Treatment Period 1, TEAE = treatment-emergent adverse event, TP1 = Treatment Period 1.
Note: Percentages (%) are based on the number of patients in each treatment group/overall on the SAF (N).
Note: AEs are coded using MedDRA Version 26.1.
Note: Patients in the Stelara group were re-randomised at Week 16 to either Bmab 1200 or Stelara.
Note: Study treatment-related TEAEs are those for which a "Possibly," "Probably," and "Definitely" of relationship is reported, or with missing relationship.

Study BM12H-NHV-01-G-01 in healthy participants after single dose

The proportion of subjects who experienced TEAEs was similar among the Bmab 1200 and EU Stelara treatment groups, whereas around 10% less subjects reported TEAEs in the US-Stelara group ([61 (70.9%), 52 (59.8%), and 67 (78.8%) subjects in Bmab 1200, US-Stelara, and EU-Stelara, respectively] (Table 26). The same numerical differences were observed:

- for the proportion of subjects with treatment related TEAEs between the 3 treatment groups [Bmab1200: 28 (32.6%), US-Stelara: 25 (28.7%); EU-Stelara: 30 (35.3)],
- for the proportion of subjects with moderate TEAEs, which were higher in the subjects receiving EU-Stelara [32 (37.6%) subjects] compared to that of Bmab 1200 [24 (27.9%) subjects] and US-Stelara [16 (18.4%) subjects] as well as for subjects with treatment related moderate TEAEs (8.1%, 11.8%, and 5.7% of TEAEs deemed related to Bmab 1200, EU-Stelara, and US-Stelara, respectively.

A total of 5 severe AEs [Bmab 1200: 2 (2.3%); US-Stelara: 1 (1.1%); EU-Stelara: 2 (2.4%)] were reported during the study. These were tonsil cancer, transaminases increased, retinal migraine, muscle spasms, and hypocalcaemia. None of the severe TEAEs were considered treatment-related and all except tonsil cancer were recovered.

By SOC, the most frequently TEAEs were Infections and infestations followed by nervous system disorder and respiratory, thoracic and mediastinal disorders (Table 28).

Table 28. Overall Analysis of BM12H-NHV-01-G-01 and BM12H-PSO-03-G-02: Summary of Treatment Emergent Adverse Events

System Organ Class Preferred Term	45 mg Bmab 1200 (N = 86)	45 mg US-Stelara (N = 87)	45 mg EU-Stelara (N = 85)	Overall (N = 258)
Infections and infestations	22 (25.6%)	27 (31.0%)	29 (34.1%)	78 (30.2%)
COVID-19	7 (8.1%)	9 (10.3%)	11 (12.9%)	27 (10.5%)
Nasopharyngitis	5 (5.8%)	7 (8.0%)	9 (10.6%)	21 (8.1%)
Rhinitis	3 (3.5%)	7 (8.0%)	5 (5.9%)	15 (5.8%)
Nervous system disorders	17 (19.8%)	17 (19.5%)	20 (23.5%)	54 (20.9%)
Headache	12 (14.0%)	15 (17.2%)	16 (18.8%)	43 (16.7%)
Respiratory, thoracic and mediastinal disorders	13 (15.1%)	13 (14.9%)	9 (10.6%)	35 (13.6%)
Oropharyngeal pain	6 (7.0%)	6 (6.9%)	6 (7.1%)	18 (7.0%)
Musculoskeletal and connective tissue disorders	9 (10.5%)	10 (11.5%)	15 (17.6%)	34 (13.2%)
Back pain	3 (3.5%)	5 (5.7%)	6 (7.1%)	14 (5.4%)

MedDRA = Medical Dictionary for Regulatory Activities; nS = number of subjects with an adverse event; N = number of subjects; % = percentage of subjects with an adverse event (nS/N×100)
The nS (%) statistics presented.
Adverse events were coded using the MedDRA Version 25.1.

In general, the safety profile reported in Study BM12H-NHV-01-G-01 for Bmab 1200 is comparable to the EU and US Stelara treatment groups. Numerical differences were overserved; however, small sample size makes it difficult to interpret this data. Overall, the safety profile is consistent with the known safety profile of Stelara.

Study BM12H-PSO-03-G-02 in PsO patients

The safety results for study BM12H-PSO-03-G-02 are presented for 3 different time periods:

- TP1 (from Baseline Visit to Week 16 (predosing).
- TP2 (from Week 16 Dosing to Week 28 predosing). The safety section pertaining to TP2 comprises of 2 different comparisons:
    - The first comparison is between the patients who received the same treatment during TP1 and TP2 per initial randomisation (Bmab 1200 vs Stelara). This comparison is between unequal treatment groups because all patients who received Bmab 1200 in TP1 also received Bmab in TP2, whereas at week 16, due to re-randomisation (1:1), only 50% of patients who received Stelara in TP1 were to receive Stelara in TP2, while the remaining 50% of patients were to switch from Stelara to Bmab 1200.
    - The second comparison is between the patients who received Stelara in TP1 and continued on Stelara in TP2 (Stelara-Stelara) vs those patients who switched post randomisation (Stelara-Bmab 1200).
    - TP3 (i.e., on or after Week 28 dosing to Week 52/End of Study).

Analysis set:

Safety Set (SAF)

The SAF consists of all patients who receive at least one full or partial study treatment administration. The SAF was used for analysing safety and immunogenicity data during the treatment period. Patients in the SAF were analysed under the treatment as actually received.

Safety Set for Treatment Period 2

Safety Set for TP2 (SAF2): The SAF2 consists of all patients who received the re-randomised study treatments administration at Week 16 or later. Patients from the SAF2 were analysed under the treatment as actually received during TP2. The SAF2 was used for the analyses of safety and immunogenicity during TP2.

Safety Set for Treatment Period 3

The SAF for TP3 (SAF3) consisted of all patients who continued to receive the study treatment administration at Week 28 or later. Patients from the SAF3 were analysed under the treatment as actually received during TP3. The SAF3 was used for the analyses of safety and immunogenicity during TP3.

Overall Safety Profile (Baseline Through Week 52) of Patients Who Remained on the Same Treatment Throughout the Study (Bmab 1200 vs Stelara)

An overall summary of treatment-emergent adverse events (TEAEs) for study BM12H-PSO-03-G-02 is presented in Table 29. The proportion of patients who experienced at least one **TEAEs** was higher in the Bmab1200 group (58.1%) compared to the Stelara group (47.5%). In addition, the number of **treatment-related TEAEs** was higher in the Bmab1200 compared to the Stelara group (13.1% and 10.9% patients in the Bmab1200 and Stelara, respectively), albeit to a lesser extent. **TEAEs of special interest** were reported in 31.9% of patients in the Bmab 1200 group and 22.8% of patients in the Stelara group, with the majority of TEAEs of special interest being in the category of infection (30.4% vs 20.8%, respectively).

Table 29. Overall Summary of Adverse Events of BM12H-PSO-03-G-02 Through the Study (Baseline Through Week 52) (Safety Analysis Set)

	Bmab 1200 (N=191) n (%) E	Stelara (N=101) n (%) E	Stelara-Bmab 1200 (N=92) n (%) E	Total (N=384) (%) E
Any TEAE	111 (58.1) 282	48 (47.5) 103	51 (55.4) 107	210 (54.7) 492
Any treatment-related TEAE	25 (13.1) 50	11 (10.9) 14	13 (14.1) 20	49 (12.8) 84
Any serious TEAE	6 (3.1) 8	0	1 (1.1) 1	7 (1.8) 9
Any serious treatment-related TEAE	1 (0.5) 2	0	0	1 (0.3) 2
Any TEAE leading to study treatment interruption	0	0	0	0
Any TEAE leading to study treatment withdrawal	3 (1.6) 4	3 (3.0) 3	0	6 (1.6) 7
Any treatment-related TEAE leading to treatment discontinuation	1 (0.5) 2	2 (2.0) 2	0	3 (0.8) 4
Any TEAE leading to study discontinuation	3 (1.6) 4	3 (3.0) 3	0	6 (1.6) 7
Any TEAE of special interest by categories	61 (31.9) 90	23 (22.8) 34	34 (37.0) 50	118 (30.7) 174
Infections	58 (30.4) 86	21 (20.8) 31	34 (37.0) 49	113 (29.4) 166
Malignancy	2 (1.0) 2	0	0	2 (0.5) 2
Hypersensitivity reaction	1 (0.5) 2	3 (3.0) 3	1 (1.1) 1	5 (1.3) 6
PRES	0	0	0	0
Non-infectious pneumonia	0	0	0	0
Any TEAE leading to death	0	0	0	0
Any AE leading to death	0	0	0	0

At **SOC** level, the most frequently occurring TEAEs belonged to "infections and infestations" in 58 patients (30.4%) in the Bmab 1200 group vs 21 patients (20.8%) in the Stelara group, followed by investigations in 36 patients (18.8%) versus 17 patients (16.8%) in the Bmab1200 and Stelara group, respectively ()**.** 4.7% of the TEAEs in the SOC infections and infestations were considered as treatment-related in the Bmab1200 group compared to 2.0% in the Stelara group. A summary of TEAEs by **PT** occurring in ≥2% of patients in either treatment group who took the same treatment throughout the study is provided in Table 30. The most frequently reported TEAEs in both groups were nasopharyngitis (9.4% in the Bmab 1200 group vs 5.9% in the Stelara group), followed by alanine aminotransferase increased (6.3% in the Bmab 1200 group vs 5.9% in the Stelara group) and blood triglycerides increased (5.8% in the Bmab1200 group vs 3 in the Stelara group). Alanine aminotransferase increased was also the most commonly reported treatment-related TEAE (3.1% in the Bmab 1200 group vs 1.0% in the Stelara group), followed by aspartate aminotransferase increased (2.1% vs 1.0%), gamma-glutamyltransferase increased (1.0% vs 2.0%), influenza (none vs 2.0%), and nasopharyngitis (1.6% vs none).

Table 30. Treatment-emergent Adverse Events by Preferred Term Occurring in ≥2% of Patients in Either Treatment Group Who Took the Same Treatment Through the Study (Baseline Through Week 52) (Safety Analysis Set)

Preferred Term	Bmab 1200 – Bmab 1200 (N=191) n (%) E	Stelara-Stelara (N=101) n (%) E
Any TEAE	111 (58.1) 282	48 (47.5) 103
Nasopharyngitis	18 (9.4) 23	6 (5.9) 6
Upper respiratory tract infection	6 (3.1) 7	1 (1.0) 1
Urinary tract infection	6 (3.1) 6	2 (2.0) 2
COVID-19	4 (2.1) 4	0
Influenza	4 (2.1) 4	5 (5.0) 8
Pharyngitis	4 (2.1) 5	1 (1.0) 1
Rhinitis	2 (1.0) 2	2 (2.0) 2
Oral herpes	1 (0.5) 1	2 (2.0) 2
Pneumonia	0	2 (2.0) 2
Alanine aminotransferase increased	12 (6.3) 14	6 (5.9) 9
Blood triglycerides increased	11 (5.8) 13	3 (3.0) 4
Aspartate aminotransferase increased	7 (3.7) 7	2 (2.0) 2
Gamma-glutamyltransferase increased	6 (3.1) 7	2 (2.0) 2
Blood cholesterol increased	4 (2.1) 6	2 (2.0) 3
Blood pressure increased	3 (1.6) 3	2 (2.0) 2
Blood glucose increased	2 (1.0) 3	3 (3.0) 3
C-reactive protein increased	0	2 (2.0) 2
Hypertriglyceridemia	6 (3.1) 8	1 (1.0) 1
Hyperlipidaemia	5 (2.6) 5	0
Hyperglycaemia	4 (2.1) 4	0
Obesity	0	2 (2.0) 2
Anaemia	4 (2.1) 4	0
Neutropenia	4 (2.1) 4	0
Arthralgia	2 (1.0) 2	3 (3.0) 4
Proteinuria	4 (2.1) 4	1 (1.0) 1
Pruritus	2 (1.0) 2	2 (2.0) 2

Abbreviations: AE = adverse event, E = number of events, MedDRA = Medical Dictionary for Regulatory Activities, N = number of patients in the treatment group, n (%) = number (percentage) of patients who experienced events, SAF = Safety Set for Treatment Period 1, TEAE = treatment-emergent adverse event.
Note: Percentages (%) are based on the number of patients in each treatment group/overall on the SAF (N).
Note: AEs are coded using MedDRA Version 26.1

The incidence of AEs per treatment period is presented below.

From Baseline to Week 16, *Trial Period 1 (TP1, SAF)*

An overview of TEAEs up to Week 16 for all patients is presented in Table 31

During TP1, 148 patients (38.5%) patients experienced at least 1 **TEAE** (42.9% and 34.2% of patients in the Bmab 1200 and Stelara treatment groups, respectively, Table 31). The proportion of patients who reported at least one **treatment-related TEAE** was comparable between the treatment groups (8.4% and 6.2% of patients in the Bmab 1200 and Stelara treatment groups, respectively, Table 31. The majority of the TEAEs were Grade 1 to Grade 2 in severity. The incidence of Grade 2 (20.9 % in Bmab1200 arm % vs 15.5% in Stelara arm) was slightly higher in the Bmab1200 compared to the Stelara group. Twelve patients (3.1%) had 13 Grade ≥3 TEAEs; of these 8 patients (4.2%) had 9 TEAEs in the Bmab 1200 group and 4 patients (2.1%) had 4 TEAEs in the Stelara group. None of these events was treatment-related. Blood triglycerides increased was the most commonly reported Grade

≥3 TEAE, all were in the Bmab 1200 group, and all events were assessed as not related or unlikely related.

A summary of TEAEs by PT occurring in ≥1% of total patients during TP1 is provided in Table 31.

Table 31. Treatment-Emergent Adverse Events Occurring in ≥1% of Total Patients During Treatment Period 1 (Safety Analysis Set)

Preferred Term	Bmab 1200 (N=191) n (%) E	Stelara (N=193) n (%) E	Total (N=384) n (%) E
Any TEAE	82 (42.9) 162	66 (34.2) 106	148 (38.5) 268
Nasopharyngitis	13 (6.8) 16	6 (3.1) 6	19 (4.9) 22
Alanine aminotransferase increased	7 (3.7) 8	7 (3.6) 7	14 (3.6) 15
Blood triglycerides increased	9 (4.7) 9	2 (1.0) 3	11 (2.9) 12
Influenza	4 (2.1) 4	6 (3.1) 6	10 (2.6) 10
Upper respiratory tract infection	4 (2.1) 4	5 (2.6) 5	9 (2.3) 9
Blood cholesterol increased	4 (2.1) 4	3 (1.6) 3	7 (1.8) 7
Rhinitis	2 (1.0) 2	3 (1.6) 3	5 (1.3) 5
Urinary tract infection	4 (2.1) 4	1 (0.5) 1	5 (1.3) 5
Blood pressure increased	3 (1.6) 3	2 (1.0) 2	5 (1.3) 5
Hypertriglyceridemia	5 (2.6) 6	0	5 (1.3) 6
Pruritus	2 (1.0) 2	3 (1.6) 3	5 (1.3) 5
Proteinuria	3 (1.6) 3	2 (1.0) 2	5 (1.3) 5
Gamma-glutamyltransferase increased	3 (1.6) 3	1 (0.5) 1	4 (1.0) 4
Hyperlipidaemia	4 (2.1) 4	0	4 (1.0) 4
Aspartate aminotransferase increased	3 (1.6) 3	1 (0.5) 1	4 (1.0) 4
Arthralgia	2 (1.0) 2	2 (1.0) 2	4 (1.0) 4

Abbreviations: AE = adverse event, E = number of events, MedDRA = Medical Dictionary for Regulatory Activities, N = number of patients in the treatment group, n (%) = number (percentage) of patients who experienced events, SAF = Safety Set for Treatment Period 1, TEAE = treatment-emergent adverse event, TP1 = treatment period 1.
Note: Percentages (%) are based on the number of patients in each treatment group/overall on the SAF (N).
Note: AEs are coded using MedDRA Version 26.1.
Note: TEAEs during TP1 are defined as AEs with onset date on or after the first dose date before Week 16 dosing or early discontinuation date, whichever is earlier.

Abbreviations: AE, adverse event; E, number of events; N, number of patients in the treatment group; n (%), number (percentage) of patients who experienced events; TEAE, treatment-emergent adverse event; SAF, Safety Set for Treatment Period 1.

Note: Percentages (%) are based on the number of patients in each treatment group/overall on the SAF (N).

Note: AEs are coded using MedDRA Version 26.0.

Note: TEAEs during TP1 are defined as AEs with onset date on or after the first dose date before Week 16 dosing or early discontinuation date, whichever is earlier.

In general, the incidences and frequency of the majority of the TEAEs by **SOC** and **PT** were comparable across the treatment groups in TP1. All TEAEs with incidences >5% of patients were reported in the SOC "infections and infestations" (19.9% in the Bmab 1200 and 15.5% in the Stelara group, respectively) followed by "Investigations" (12.0% in the Bmab 1200 and 9.8% in the Stelara group, respectively) and "Metabolism and nutrition disorders" (6.8% in the Bmab and 1.0% in the Stelara group, respectively). At PT level, the most frequent treatment-related TEAEs was headache followed by "COVID-19" and nasopharyngitis.

***From Week 16 to Week 28**, Trial Period 2 (TP2, SAF2)*

Following TP1, patients who had received originator Stelara were re-randomised (1:1) to either continue originator Stelara or switch Bmab1200 in TP2 (weeks 16–28). Patients previously assigned to Bmab 1200 continued to receive Bmab. Eleven patients (2.9%) who completed TP1 did not enter TP2 (5 in the Bmab 1200 group and 6 in the Stelara group), thus a total of 371 patients were included in TP2. 185 patients continued to receive Bmab. 186 patients were re-randomised: 94 patients continued on Stelara (Stelara-Stelara group) and 92 patients switched to Bmab 1200 (Stelara-Bmab group) (Table 32). Of the 371 patients treated during TP2, 93 (25.1%) patients experienced at least 1 **TEAE** and the percentage of patients is comparable between the treatment groups [47 (25.4%), 21 (22.3%), and 25 (27.2%) patients in the Bmab 1200, Stelara-Stelara, and Stelara-Bmab 1200 groups, respectively]. The proportion of patients who experienced at least one **treatment related TEAE** was higher in the Bmab1200 group (6.5%) and Stelara-Stelara group (8.7%) compared to the Stelara-Stelara group (2.1%).

Table 32. Treatment-Emergent Adverse Events Occurring in ≥1% of Total Patients During Treatment Period 2 (Safety Analysis Set 2)

Preferred Term	Bmab 1200 (N=185) n (%) E	Stelara-Stelara (N=94) n (%) E	Stelara-Bmab 1200 (N=92) n (%) E	Total (N=371) n (%) E
Any TEAE	47 (25.4) 75	21 (22.3) 22	25 (27.2) 31	93 (25.1) 128
Nasopharyngitis	6 (3.2) 6	3 (3.2) 3	1 (1.1) 1	10 (2.7) 10
Alanine aminotransferase increased	4 (2.2) 4	2 (2.1) 2	1 (1.1) 1	7 (1.9) 7
COVID-19	1 (0.5) 1	0	3 (3.3) 3	4 (1.1) 4
Influenza	0	3 (3.2) 3	1 (1.1) 1	4 (1.1) 4
Urinary tract infection	1 (0.5) 1	1 (1.1) 1	2 (2.2) 2	4 (1.1) 4
Abbreviations: AE = adverse event, E = number of events, MedDRA = Medical Dictionary for Regulatory Activities, N = number of patients in the treatment group, n (%) = number (percentage) of patients who experienced events, SAF2 = Safety Set for Treatment Period 2, TEAE = treatment-emergent adverse event, TP2 = treatment period 2. Note: Percentages (%) are based on the number of patients in each treatment group/overall on the SAF2 (N). Note: AEs are coded using MedDRA Version 26.1. Note: Patients in the Stelara group were re-randomised at Week 16 to either Bmab 1200 or Stelara. Note: TEAEs during TP2 are defined as adverse events with onset date on or after Week 16 treatment to before Week 28 dosing or early discontinuation date, whichever is earlier.				

Abbreviations: AE, adverse event; E, number of events; N, number of patients in the treatment group; n (%), number (percentage) of patients who experienced events; TEAE, treatment-emergent adverse event; SAF2, Safety Set for Treatment Period 2.

Note: Percentages (%) are based on the number of patients in each treatment group/overall on the SAF2 (N).

Note: AEs are coded using MedDRA Version 26.0.

Note: Patients in the Stelara group were re-randomised at Week 16 to either Bmab 1200 or Stelara.

Note: TEAEs during TP2 are defined as adverse events with onset date on or after Week 16 treatment to before Week 28 dosing or early discontinuation date, whichever is earlier.

The most frequently reported SOC in all patients was infections and infestations (43 patients; 11.6%) similarly to TP1. The overall incidence of individual AEs in general was low. Treatment related TEAEs were reported for 6.5% (12/185) patients in the Bmab 1200 group compared to 2.1% (2/94) of patients in the Stelara-Stelara group, and 8.7% (6/92) of patients in the Stelara-Bmab 1200 group. The overall incidence was low and, with the exception of nasopharyngitis, events were of single occurrence. The number of patients having Grade ≥3 TEAEs was low [3 (3.3%) patients in Stelara-Bmab 1200 group vs 1 (1.1%) patient in Stelara-Stelara group]. The incidence of Grade 2 TEAEs was comparable across the arms (8.5% in Stelara-Stelara arm vs 7.6% in Stelara-Bmab1200 arm). Most

treatment-related TEAEs were laboratory findings. Two of them (abdominal pain and jaundice cholestatic) in TP2 Bmab 1200 treatment group were Grade 4 severity; both TEAEs were assessed as serious.

- *Safety Profile of Patients in **Treatment Period 2** Who Received the Same Treatment During Treatment Period 1 and Treatment Period 2 as Per Initial Randomisation (Bmab 1200-Bmab 1200 [N=185] vs Stelara-Stelara [N=94])*

In patients who remained on Bmab 1200 or Stelara across both TP1 and TP2, a similar percentage of patients experienced TEAEs across the 2 groups [47/185 (25.4%) in the Bmab 1200 group vs 21/94 [22.3%] in the Stelara group). Incidence of Grade ≥3 TEAEs (1.6% of patients in the Bmab 1200 group vs 1.1% of patients in the Stelara group) and treatment-related TEAEs (6.5% of patients in the Bmab 1200 group vs 2.1% of patients in the Stelara group) was low. Most treatment-related TEAEs were reported in the SOC infections and infestations. However, a disbalance was also noted for individual TEAEs in the SOC Investigations. Treatment-emergent ALT and AST increases were reported in 2 patients each in the Bmab 1200 group and none in the Stelara group.

- *Safety Profile of Patients in **Treatment Period 2** Who were on Stelara in Treatment Period 1 and were Switched Post-randomisation to Stelara or Bmab 1200 at Week 16 (Stelara-Stelara [N=94] vs Stelara-Bmab 1200 [N=92])*

Overall, the percentage of patients with TEAEs in patients who switched treatment was lower during TP2 compared to the percentage observed during TP1 and comparable between the Stelara-Bmab 1200 group and the Stelara-Stelara group [25 (27.2%) vs 21 (22.3%) patients, respectively] (Table 32). The number of patients having Grade ≥3 TEAEs was low [3 (3.3%) patients in Stelara-Bmab 1200 group vs 1 (1.1%) patient in Stelara-Stelara group]. The incidence of the SOC of infections and infestations was higher in the Stelara-Bmab 1200 group (18.5% of patients) compared to the Stelara-Stelara group (8.5% of patients). However, the differences cannot be attributed to a single PT, as the overall incidence of individual TEAEs was low. Furthermore, the trend that individual TEAEs such as nasopharyngitis, influenza, blood triglycerides increased and hypertriglyceridaemia occurred more frequently in the Bmab 1200 group during TP1, could not be confirmed in TP2 despite continued treatment with Bmab 1200. The incidence of treatment-related TEAEs were numerically higher in the Stelara-Bmab 1200 compared to the Stelara-Stelara group [8 (8.7%) vs 1 (1.1%) patients, respectively]. Of the treatment-related TEAEs by SOC, infections and infestations had a higher frequency in the Stelara-Bmab 1200 group (6.5%) and the Bmab 1200 group (2.7%) compared to the Stelara group (0%).

Treatment Period 2 + Treatment Period 3

This includes the comparison of patients who received Stelara in TP1 and continued on Stelara in TP2 + TP3 (Stelara-Stelara) versus patients who received Stelara during TP1 switched post randomisation to Bmab 1200 (Stelara-Bmab 1200). There were 42.9% of patients in the Stelara-Bmab 1200 group and 33.3% of patients in the Stelara-Stelara group who experienced **TEAEs** in TP2 + TP3 (Table 26), with no significant difference observed in the number of events between each treatment group. Of these, 10.7% vs 7.4% patients experienced **treatment-related TEAEs**, respectively, in the Stelara-Bmab 1200 and Stelara-Stelara groups. The only treatment-related TEAE reported in more than 1 patient in either treatment group was influenza (2.5% in the Stelara-Stelara group and 1.2% in the Stelara Bmab 1200 group). The incidence of Grade ≥3 TEAEs in both groups was low in general (4.8% in the Stelara-Bmab 1200 group vs 3.7% in the Stelara-Stelara group). The differenced observed in TP2 with regard to treatment-related TEAEs in the SOC infections and infestations were confirmed in TP2+TP3 with 9.5% in the Stelara-Bmab group compared to 2.5% in the Stelara-Stelara treatment group. As for TP1 and TP2, the highest incidence of TEAEs occurred in the PT of nasopharyngitis (3.7% in the Stelara-Stelara group and 3.6% in the Stelara-Bmab 1200 group).

6.1.10.3. Serious adverse events of special interest, serious adverse events and deaths, and other significant events

Deaths and SAE

There were no deaths reported in either of the studies BM12H-NHV-01-G-01 and BM12H-PSO-03-G-02. In healthy subjects, 2 subjects each had 1 serious TEAEs during the study which were considered unlikely related to the study drug and did not result in the discontinuation of the subject from the study.

Study BM12H-PSO-03-G-02

Baseline Through Week 52

In patients with PsO, 7 patients (1.8%) experienced 9 serious TEAEs trough the study: 6 patients (3.1%) had 8 serious TEAEs in the Bmab1200 group compared to 1 patient (1.1%) that had 1 serious TEAE in the Stelara group. Of those, 2 serious TEAEs occurring in the same patient of the Bamb1200 group, both with Grade 4 intensity (abdominal pain and jaundice cholestatic) were assessed as possible related to study treatment. They occurred on D160 and resolved on D172 and were assessed as SUSAR. All other SAEs were considered as unlikely related or not related to study treatment. Details are provided below:

***Treatment Period 1**:*

Four patients reported 5 serious TEAEs in TP1. Of those, 3 patients (1.6%) with 4 events were in the Bmab 1200 group and 1 patient (0.5%) with 1 event was in the Stelara group. All serious TEAEs were Grade 3 in severity, except 1 Grade 2 event. All serious TEAEs in TP1 were assessed as unlikely related or not related to study treatment

- One patient (Bmab 1200) had Grade 3 cardiac failure (SOC: cardiac disorder) and acute myocardial infarction (SOC: cardiac disorder) on Day 7. Both TEAEs resolved on Day 15 and were assessed as not related to study treatment. The patient had a long-standing history of coronary artery disease.
- One patient (Bmab 1200) had Grade 3 endometrial adenocarcinoma [SOC: neoplasms benign, malignant, and unspecified (incl cysts and polyps)] on Day 22. The TEAE was assessed as not related to study treatment. The patient had a history of NCS abnormal bleeding from genital tract prior to dosing. This TEAE was also assessed as an adverse event of special interest (AESI; malignancy).
- One patient (Bmab 1200) had Grade 2 squamous cell carcinoma of the tongue [SOC: neoplasms benign, malignant, and unspecified (incl cysts and polyps)] on Day 30. The TEAE was assessed as unlikely related to study treatment because the patient had been using dentures for approximately 15 years prior to study participation leading to chronic irritation and probable aetiology leading to carcinoma. This TEAE was also assessed as an AESI (malignancy).
- One patient (Stelara) had Grade 3 cholecystitis acute (SOC: hepatobiliary disorders) on Day 16. The TEAE was assessed as not related to study treatment. The alternate causality was reported as gallstone disease due to inadequate fatty diet and no water ingestion.

***Treatment Period 2**:*

In TP2, 2 serious TEAEs, both of Grade 4 severity and possibly related to study treatment, were reported in 1 patient of the Bmab 1200 group.

- One patient (Bmab 1200-Bmab 1200) had Grade 4 abdominal pain (SOC: gastrointestinal disorders) and Grade 4 jaundice cholestatic (SOC: hepatobiliary disorders) on Day 160. Both TEAEs

resolved on Day 172 and were assessed as suspected unexpected serious adverse reaction (SUSARs; possibly related to study treatment). SUSAR reports were submitted.

Treatment Period 3:

In TP3, 2 patients (both in the Bmab 1200 group) reported 2 serious TEAEs. One of these was Grade 2 while the other was Grade 3 in severity. One of these was assessed as unlikely related while the other was assessed as not related to study treatment.

- One patient (Bmab 1200) had Grade 3 ischemic stroke (SOC: nervous system disorders) on Day 339. The TEAE resolved on Day 347 and was assessed as unlikely related to study treatment. The patient had a medical history of left-sided ischemic stroke, which was resolved by the time the patient was enrolled in the study.
- One patient (Bmab 1200) had Grade 2 uterovaginal prolapse (SOC: reproductive system and breast disorders) on Day 267. The TEAE resolved on Day 270 and was assessed as not related to study treatment. The patient reported previous history of ongoing urinary incontinence.

Treatment-Emergent Adverse Events with CTCAE Grade 3 or Higher

Study BM12H-NHV-01-G-01

While CTCAE criteria was not used for phase 1 study, severity was assessed based on criteria specified in Section 16.1.1, CSR, BM12H-NHV-01-G-01. A total of 5 severe AEs were reported during the study (Section 2.7.4.2.1.2). These were tonsil cancer, transaminases increased, retinal migraine, muscle spasms, and hypocalcaemia. None of the severe TEAEs were considered treatment-related and all except tonsil cancer were recovered.

Study BM12H-PSO-03-G-02

Baseline Through Week 52

A summary of Grade ≥3 TEAEs through the study by PT is presented in Table 33. Of the patients who remained on Bmab 1200 or Stelara through the study (baseline to Week 52), a comparable percentage of patients who experienced Grade ≥3 TEAEs was observed (6.8% in the Bmab 1200 group and 5.0% in the Stelara group).

Table 33. Summary of Grade ≥3 Treatment-emergent Adverse Events by Preferred Term in Either Treatment Group Who Remained on Bmab 1200 or Stelara Through the Study (Baseline Through Week 52) (Safety Analysis Set)

Preferred Term	Bmab 1200 (N=191) n (%) E	Stelara (N=101) n (%) E
Any TEAE with CTCAE severity Grade 3 or higher	13 (6.8) 19	5 (5.0) 5
Blood triglycerides increased	3 (1.6) 3	3 (3.0) 3
Lipids increased	0	1 (1.0) 1
Alanine aminotransferase increased	1 (0.5) 1	0
Aspartate aminotransferase increased	1 (0.5) 1	0
Gamma-glutamyltransferase increased	1 (0.5) 2	0
Hyperlipidaemia	2 (1.0) 2	0
Hypertriglyceridemia	2 (1.0) 2	0
Neutropenia	2 (1.0) 2	0
Jaundice cholestatic	1 (0.5) 1	0
Acute myocardial infarction	1 (0.5) 1	0
Cardiac failure	1 (0.5) 1	0
Abdominal pain	1 (0.5) 1	0
Arthralgia	0	1 (1.0) 1
Endometrial adenocarcinoma	1 (0.5) 1	0

Preferred Term	Bmab 1200 (N=191) n (%) E	Stelara (N=101) n (%) E
Ischemic stroke	1 (0.5) 1	0

Abbreviations: AE = adverse event, E = number of events, MedDRA = Medical Dictionary for Regulatory Activities, N = number of patients in the treatment group, n (%) = number (percentage) of patients who experienced events, SAF = safety set for treatment period 1, TEAE = treatment-emergent adverse event.
Note: Percentages (%) are based on the number of patients in each treatment group/overall on the SAF (N).
Note: AEs are coded using MedDRA Version 26.1.
Note: If patients experienced multiple same events, the patients are counted once at the event with the maximum grade.
Note: Patients in the Stelara group were re-randomised at Week 16 to either Bmab 1200 or Stelara.

Treatment Period 1 (TP1):

In TP1, 12 patients (3.1%) had 13 Grade ≥3 TEAEs out of a total of 266 TEAEs reported during this period; of these 8 patients (4.2%) had 9 TEAEs in the Bmab 1200 group and 4 patients (2.1%) had 4 TEAEs in the Stelara group (Table 34). Blood triglycerides increased was the most commonly reported Grade ≥3 TEAE which occurred in 3 patients (0.8%), all were in the Bmab 1200 group, and all events were assessed as not related or unlikely related.

Four Grade 3 (severe) TEAEs were assessed as serious: cardiac failure and acute myocardial infarction, endometrial adenocarcinoma, and cholecystitis acute. Details of TESAEs are provided in Section 6.1.10.3.

Table 34. Summary of Grade ≥3 Treatment-Emergent Adverse Events During Treatment Period 1 (Safety Analysis Set)

Preferred term	Bmab 1200 (N=191) n (%) E	Stelara (N=193) n (%) E	Total (N=384) n (%) E
Any TEAE with CTCAE severity Grade ≥3	8 (4.2) 9	4 (2.1) 4	12 (3.1) 13
Blood triglycerides increased	3 (1.6) 3	0	3 (0.8) 3
Lipids increased	0	1 (0.5) 1	1 (0.3) 1
Neutrophil count decreased	0	1 (0.5) 1	1 (0.3) 1
Hyperlipidaemia	1 (0.5) 1	0	1 (0.3) 1
Hypertriglyceridaemia	1 (0.5) 1	0	1 (0.3) 1
Neutropenia	1 (0.5) 1	0	1 (0.3) 1
Acute myocardial infarction	1 (0.5) 1	0	1 (0.3) 1
Cardiac failure	1 (0.5) 1	0	1 (0.3) 1
Cholecystitis acute	0	1 (0.5) 1	1 (0.3) 1
Arthralgia	0	1 (0.5) 1	1 (0.3) 1
Endometrial adenocarcinoma	1 (0.5) 1	0	1 (0.3) 1

Abbreviations: AE, adverse event; E, number of events; N, number of patients in the treatment group; n (%), number (percentage) of patients who experienced events; TEAE, treatment-emergent adverse event; SAF, Safety Set for Treatment Period 1.

Note: Percentages (%) are based on the number of patients in each treatment group/overall on the SAF (N).

Note: Aes are coded using MedDRA Version 26.0.

Note: If patients experienced multiple same events, then the patients are counted once at the event with the maximum grade.

Note: TEAEs during TP1 are defined as AEs with onset date on or after the first dose date before Week 16 dosing or early discontinuation date, whichever is earlier.

Treatment Period 2:

A summary of TEAEs with CTCAE Grade ≥3 severity during TP2 by SOC and PT for the SAF2 is presented in Table 35. Most of Grade ≥3 TEAEs observed in TP2 were laboratory findings. Of note, 2

TEAEs (abdominal pain and jaundice cholestatic) in TP2 were Grade 4 severity; both TEAEs were assessed as serious. Details of TESAEs are provided in Table 35.

Table 35. Summary of Grade ≥3 Treatment-Emergent Adverse Events During Treatment Period 2 (Safety Analysis Set 2)

Preferred term	Bmab 1200 (N=185) n (%) E	Stelara-Stelara (N=94) n (%) E	Stelara–Bmab 1200 (N=92) n (%) E	Total (N=371) n (%) E
Any TEAE with CTCAE severity Grade ≥3	3 (1.6) 8	1 (1.1) 1	3 (3.3) 3	7 (1.9) 12
Neutropenia	1 (0.5) 1	0	0	1 (0.3) 1
Proteinuria	0	0	2 (2.2) 2	2 (0.5) 2
Alanine aminotransferase increased	1 (0.5) 1	0	0	1 (0.3) 1
Aspartate aminotransferase increased	1 (0.5) 1	0	0	1 (0.3) 1
Blood triglycerides increased	0	1 (1.1) 1	0	1 (0.3) 1
Gamma-glutamyl transferase increased	1 (0.5) 2	0	0	1 (0.3) 2
Lipids increased	0	0	1 (1.1) 1	1 (0.3) 1
Abdominal pain	1 (0.5) 1	0	0	1 (0.3) 1
Jaundice cholestatic	1 (0.5) 1	0	0	1 (0.3) 1
Hyperlipidaemia	1 (0.5) 1	0	0	1 (0.3) 1

Abbreviations: AE, adverse event; E, number of events; N, number of patients in the treatment group; n (%), number (percentage) of patients who experienced events; TEAE, treatment-emergent adverse event; SAF2, Safety Set for Treatment Period 2.

Note: Percentages (%) are based on the number of patients in each treatment group/overall on the SAF2 (N).

Note: AEs are coded using MedDRA Version 26.0.

Note: If patients experienced multiple same events, then the patients are counted once at the event with the maximum grade.

Note: TEAEs during TP2 are defined as AEs with onset date on or after Week 16 treatment to before Week 28 dosing or early discontinuation date, whichever is earlier.

Treatment Period 2 + Treatment Period 3:

The proportion of patients who experienced Grade ≥3 TEAEs was comparable in the Stelara-Stelara (3/81 [3.7%]) and in the Stelara-Bmab (4/84 [4.8%]) treatment group.

Treatment-Related Treatment-Emergent Adverse Events with CTCAE Grade 3 or Higher

Study BM12H-NHV-01-G-01

Of the 5 severe TEAEs reported in this study, none were treatment related.

Study BM12H-PSO-03-G-02

Baseline Through Week 52

Through the study (baseline through Week 52), 3 patients (0.8%) overall reported 7 Grade ≥3 treatment-related TEAEs. Of the Grade ≥3 treatment-related TEAEs in the study, 2 patients (1.0%) had 6 TEAEs in the Bmab 1200 group and 1 patient (1.1%) had 1 TEAE in the Stelara Bmab 1200 group. No Grade ≥3 TEAEs were reported in the Stelara-Stelara group. All treatment-related Grade ≥3 TEAEs occurred in TP2. For further details, refer to TP2.

Treatment Period 1 (TP1):

No Grade ≥3 ADRs were reported in TP1.

Treatment Period 2 (TP2):

Three patients (0.8%) experienced 7 Grade ≥3 ADRs [2 (1.1%) patients in Bmab 1200 group and 1 patient in Stelara group] during TP2. Two patients (1.1%) in the Bmab 1200 group had 6 treatment-related Grade ≥3 TEAEs.

Further details on the 3 patients with Grade ≥3 treatment-related TEAEs in TP2 are described below:

In the Bmab 1200 group, of the 2 patients, 1 patient (48008021, for details refer to Section 4.4) experienced 5 events (Grade 3 severity: alanine aminotransferase increased, aspartate aminotransferase increased, and gamma-glutamyltransferase and Grade 4 severity: abdominal pain and jaundice cholestatic) and another patient experienced 1 event of Grade 3 neutropenia. All these 6 events were assessed as possibly related to the study treatment and were resolved or were resolving. In the Stelara group, one patient had Grade ≥3 treatment-related TEAE of lipids increased and was assessed as probably related to the study treatment and was resolved.

Treatment-emergent Adverse Events of Special Interest (AESI)

Study BM12H-PSO-03-G-02

Infections (including TB and sepsis), malignancies (including but not limited to cutaneous and noncutaneous malignancies), hypersensitivity reactions (including anaphylaxis identified according to Sampson criteria19 and angioedema), posterior reversible encephalopathy syndrome, and noninfectious pneumonia were defined as AESI in patients with PsO.

Baseline Through Week 52

Throughout the study, AESI were reported more frequently in patients from the Bmab 1200 group (31.9%) compared to patients from the Stelara group (22.8%, Table 29) mainly due to a higher incidence of patients experiencing Infections (30.4% vs 20.8%) in the Bmab 1200 group. None of these TEAEs of special interest were assessed as serious TEAEs. Nasopharyngitis was the most frequently reported TEAE in both groups (9.4% in the Bmab 1200 group vs 5.9% in the Stelara group), followed by influenza (2.1% vs 5.0%), urinary tract infection (3.1% vs 2.0%), and upper respiratory tract infection (3.1% vs 1.0%). Two TEAEs of special interest of malignancy (PT: endometrial adenocarcinoma and squamous cell carcinoma of the tongue) occurred in 2 patients (1.0%) in the Bmab 1200 group. Both TEAEs were considered as unrelated to the study treatment.

One patient (0.5%) in the Bmab 1200 group and 3 patients (3.0%) in the Stelara group had TEAEs of special interest of hypersensitivity reactions. All were considered to be treatment related.

Treatment Period 1

In TP1, the most common TEAEs in both the groups were in the category of infections and were similar in both groups (19.9 % of patients in the Bmab 1200 and 16.6% patients in the Stelara group).

Treatment Period 2 (TP2):

There were 45 patients (12.1%) who reported 49 TEAEs of special interest. The majority of TEAEs of special interest were infections (43 patients; 11.6%), followed by hypersensitivity reactions (2 patients; 0.5%). No TEAEs of special interest of malignancy, PRES, and non-infectious pneumonia were reported in TP2. TEAEs of special interest in TP2 were Grade 1 or Grade 2 in severity and all TEAEs were resolved except 1 TEAE (otitis media) that resolved with sequelae. None of the TEAEs of special interest in TP2 were assessed as serious

Of the patients who received the same treatment in TP1 and TP2, infections were the most common category of TEAE of special interest in both treatment groups, with similar incidences in both treatment groups. Also in the switching groups, infections were the most common category of TEAEs, however, a

higher incidence was observed in those patients who were switched from Stelara to Bmab1200 compared to the Stelara maintenance group (17 patients [18.5%] vs 8 patients [8.5%], respectively). All TEAEs of special interest were mild to moderate in severity. One hypersensitivity TEAE of special interest (PT: urticaria) was reported from a patient in the Stelara-Bmab 1200 group.

Treatment Period 2 + Treatment Period 3

Only TEAEs of special interest in the categories of infections and hypersensitivity reactions were reported in TP2 + TP3. The most common TEAEs of special interest were nasopharyngitis (3.7% in the Stelara-Stelara group vs 3.6% in the Stelara-Bmab 1200 group), urinary tract infection (1.2% vs 3.6%), influenza (2.5% vs 2.4%), upper respiratory tract infection (none vs 3.6%), COVID-19 (none vs 3.6%), bronchitis (none vs 2.4%), and cystitis (none vs 2.4%). The TEAE of special interest of hypersensitivity reaction was urticaria reported in 1 patient (1.2%) in the Stelara-Bmab 1200 group. The patient had Grade 1 urticaria on Day 114, which resolved on Day 118. The TEAE was assessed as probably related by the Investigator and no action was taken due to the nature of the TEAE. Most of the TEAEs of special interest were Grade 1 or Grade 2 in severity. None of the TEAEs of special interest in TP2 + TP3 were assessed as serious.

In study **BM12H-NHV-01-G-01** AESIs were not predefined, however, infections and malignancies were reported in this study occurred at a comparable incidence across the 3 groups.

6.1.10.4. Laboratory findings

Study BM12H-NHV-01-G-01

In healthy subjects, there were no clinical laboratory findings or vital signs findings considered to be of clinical importance or which indicated safety concerns for any treatment group.

Study BM12H-PSO-03-G-02

In PsO patients, all mean clinical laboratory (clinical chemistry, haematology, and urinalysis) changes from baseline were generally small and there were no notable differences among the treatment groups except for blood triglyceride increase/hypertriglyceridemia and alanine aminotransferase increase occurring more frequently in the Bmab1200 groups. Most changes in clinical laboratory parameters were deemed not clinically significant (NCS) by the Investigator. Those deemed clinically significant (CS) were reported as TEAEs. None of the TEAEs of abnormal clinical laboratory results were assessed as serious.

Numerical differences were observed in the incidence of the TEAEs related to abnormal clinical laboratory results. Although during TP1, a higher incidence of the TEAEs of blood triglycerides increased and hypertriglyceridemia in the Bmab 1200 group compared to the Stelara group was observed (blood triglycerides: 9 patients (4.7%) with 9 events in the Bmab 1200 group and 2 patients (1.0%) with 3 events in the Stelara group; hypertriglyceridemia: 5 patients (2.6%) with 6 events in the Bmab 1200 group and none in the Stelara group), the proportion of patients with these TEAEs decreased during TP2. The Applicant provided a summary of all events of blood triglyceride increase/ hypertriglyceridemia that occurred in Bmab1200 clinical development programme summarising their intensity, relatedness and any associated TEAEs. In the Phase 1 study, no subject reported adverse event of blood triglyceride increase/ hypertriglyceridemia. In PsO patients, 31/33 events were considered not related/unlikely related and were attributed to other underlying diseases like obesity, metabolic disorder, diabetes, improper diet, medical history, etc. The majority of the events (24/33) were Grade-1/ Grade-2 in severity. Most (25/33) events were resolved by the end of the study despite continuing treatment. A few subjects reported more than one episode with each episode having been resolved. None of these events were deemed serious or led to treatment/study withdrawal. In patients

in treatment groups who took the same treatment trough the study (Baseline through Week 52), the incidence of Blood Triglyceride increase/ Hypertriglyceridemia, was numerically higher in patients who remained on Bmab1200 throughout (8.9%) versus those who remained on Stelara throughout (4.0%). However, the incidence of Grade 3 AEs of Blood Triglyceride increase/ Hypertriglyceridemia, was comparable (2.6% vs 3.0%) between both treatment groups. Furthermore, the incidence in patients Who Received Stelara in Treatment Period 1 and Either Remained on Stelara (Stelara-Stelara) or Switched Post-Randomisation from Stelara to Bmab 1200 (Stelara-Bmab 1200) in Treatment Period 2 and Treatment Period 3 (Safety Analysis Set 3) was comparable between the 2 arms (4.9% vs 3.6%). During TP1, increased alanine aminotransferase was the second most frequently reported TEAE with no difference between treatment groups (8 events in 7 patients [3.7%] vs 7 events in 7 patients [3.6%]). In the Bmab 1200 group this TEAE was considered, however, as treatment-related in more patients compared to the Stelara group. During TP2, increased alanine aminotransferase occurred in 4 patients (2.2%) of the Bmab 1200 group vs 1 patient (1.1%) in the Stelara-Stelara group and in 1 patient (1.1%) in the Stelara-Bmab 1200 group. The Applicant provided a summary of all events of alanine aminotransferase increase in the Bmab clinical development programme. In the Phase 1 study, only 1 subject in the 45 mg EU Stelara group has a severe TEAE of ALT and AST increase. In the Phase 3 study, 26 events (19 mild, 6 moderate, and 1 severe) of alanine aminotransferase increase were reported in 20 patients. The majority (18/26) of the events had resolved by the end of the study despite continuing treatment. Most of these events (17/26) were deemed not related/unlikely related. In patients in treatment groups who took the same treatment trough the study (Baseline through Week 52), the incidence of Alanine Aminotransferase Increased was similar in patients who remained on Bmab1200 throughout (6.3%) versus those who remained on Stelara throughout (5.9%). The incidence was also comparable across the arms for TP1, TP2 and TP3.

Neutropenia was observed in 5 patients (4 in the Bmab1200 and 1 in the Stelara group). The Applicant provided further details of all events of neutropenia and neutrophil count decrease that occurred in the Bmab1200 clinical development. In healthy subjects, only 1 event of mild neutropenia (treatment-related) was reported in the Phase-1 study in the 45 mg US Stelara arm. It was not deemed serious and did not result in study withdrawal. In PsO patients, on event of neutropenia was reported in the Bmab1200 group (Grade 3, Not related and Resolved within 3 weeks) while 1 event of Neutrophil count decrease (Grade 3, Not related and Resolved within 3 weeks) was reported in Stelara group. During TP2, 3 events [1 Not related Grade-1 and 2 possibly related (1 Grade-2 and 1 Grade-3)] of neutropenia were reported in Bmab1200-Bmab1200 group. Notably, all of these had resolved by the end of the study, and there was no specific trend with repeat dosing. Only one subject (Sub 48019005) had a prolonged duration of neutropenia. This subject already had low neutrophil counts (2790/ µL) at screening. No new TEAE of neutropenia was reported in TP3. Furthermore, neutropenia did not result in any serious infection or any other clinically significant signs or symptoms that could be attributed to neutropenia.

No significant changes in vital signs and ECG parameters over time were observed across the treatment groups, and no meaningful differences between treatment groups were observed, neither in healthy subjects nor in patients with PsO. However, 1 patient in the Bmab1200 group had 1 event of tachycardia (this patient also experienced Grade 3 cardiac failure and acute myocardial infarction on the same day. In patients no infection site reactions have been reported.

6.1.10.5. In vitro biomarker test for patient selection for safety

Not applicable.

6.1.10.6. Safety in special populations

Not applicable

6.1.10.7. Immunological events

The bioanalytical methods are described

Study BM12H-NHV-01-G-01

At baseline, 10.5%, 2.3%, and 5.9% of subjects were ADA+ in the Bmab 1200, the US Stelara, and the EU Stelara groups, respectively.

The number of subjects who were ADA- at baseline and ADA+ post-dose at any given timepoint until the EOS visit was lower in the Bmab 1200 group (54.7%) compared to the EU-Stelara (75.3%) and the US-Stelara (83.9%) treatment groups. The median ADA titres were comparable between the 3 treatment groups. However, there was a higher mean ADA titre in the Bmab 1200 group compared to the EU and the US-Stelara groups, which was majorly attributed to high titres in 2 subjects. These high titres showed a declining trend over time and were not associated with any major safety concerns.

Overall, there were no safety concerns related to incidence or titres of ADA in any of the treatment groups.

Study BM12H-PSO-03-G-02

Treatment Period 1

At baseline, 92.1 % of patients in the Bmab 1200 group and 91.7% of patients in the Stelara group were negative for antibodies. According to the Applicant, the reason for predose ADA positivity is currently unknown. Following 2 weeks of study treatment, 67.0% of patients in the Bmab 1200 treatment group and 78.2% of patients in the Stelara treatment group tested positive for ADAs, regardless of the patients' ADA status at baseline (Table 36). The percentage of ADA testing positive increased consistently over time and was observed to be 80.1% and 87.9% of patients in the Bmab1200 and Stelara group at Week 16. The ADA titre was consistent over time, and it was observed that the median titre was lesser in the Bmab 1200 group compared to the Stelara group, similar to the ADA incidence.

Table 36. Summary of Overall Immunogenicity Results (Treatment Period 1) (Safety Analysis Set)

	Bmab 1200 N=191	Stelara N=193
Patients with no postbaseline ADA result	0	1
Overall (postbaseline TP1)[a]		
ADA positive at any point	186 (97.4)	191 (99.0)
ADA negative	5 (2.6)	1 (0.5)
NAb reactive	97 (50.8)	104 (53.9)
NAb negative	89 (46.6)	86 (44.6)
Within the first 12 weeks		
ADA positive at any point	182 (95.3)	191 (99.0)
NAb reactive	83 (43.5)	89 (46.1)
ADA negative	5 (2.6)	1 (0.5)
Baseline		
ADA positive	14 (7.3)	16 (8.3)
ADA negative	176 (92.1)	177 (91.7)
Week 2		
ADA positive	128 (67.0)	151 (78.2)
ADA negative	63 (33.0)	39 (20.2)
Week 4		
ADA positive	141 (73.8)	168 (87.0)
ADA negative	49 (25.7)	24 (12.4)
Week 8		
ADA positive	140 (73.3)	172 (89.1)
ADA negative	48 (25.1)	19 (9.8)
Week 12		
ADA positive	157 (82.2)	174 (90.2)
ADA negative	30 (15.7)	14 (7.3)
Week 16		
ADA positive	153 (80.1)	168 (87.0)
ADA negative	33 (17.3)	17 (8.8)

Abbreviations: ADA, antidrug antibody; N, number of patients in the treatment group; NAb, neutralizing antibody; TP1, Treatment Period 1.

Note: Percentages (%) are based on the number of patients in each treatment group (N). Postbaseline TP1 refers to patients with an ADA positive result at any point from Week 2 to Week 16.

a. Irrespective of baseline ADA.

Treatment Period 2

An overall summary of immunogenicity is presented in Table 37. In TP2, there was no further increase in the incidence of ADAs to ustekinumab at Week 20. Overall, the ADA+ rate was comparable between the 2 treatment groups throughout the study, with no apparent impact of switching from Stelara to Bmab 1200. The NAb reactive rate was higher in Stelara group vs the Bmab 1200 group in TP1 and also a higher rate was observed in Stelara-Stelara groups compared to the Stelara-Bmab 1200 group post switching in TP2.. The antibody titre was also similar to TP1 and the titre did not rise in the Stelara-Bmab 1200 group.

Table 37. Summary of Overall Immunogenicity Results (Treatment Period 2) (Safety Analysis Set 2)

	Bmab 1200 N=185	**Stelara-Stelara N=94**	**Stelara-Bmab 1200 N=92**
Patients with no postbaseline ADA result	2	0	1
Overall (postbaseline TP2)[a]			
ADA positive at any point	162 (87.6)	88 (93.6)	86 (93.5)
ADA negative	21 (11.4)	6 (6.4)	5 (5.4)
NAb reactive	54 (29.2)	42 (44.7)	31 (33.7)
NAb negative	108 (58.4)	46 (48.9)	55 (59.8)
Week 20			
ADA positive	142 (76.8)	83 (88.3)	80 (87.0)
ADA negative	41 (22.2)	10 (10.6)	11 (12.0)
Week 28			
ADA positive	129 (69.7)	78 (83.0)	70 (76.1)
ADA negative	53 (28.6)	15 (16.0)	21 (22.8)

Abbreviations: ADA, antidrug antibody; N, number of patients in the treatment group; NAb, neutralising antibody; TP2, Treatment Period 2.
Note: Percentages (%) are based on the number of patients in each treatment group (N).
[a.]Irrespective of baseline ADA.

Treatment Period 3

An overall summary of immunogenicity results is presented in Table 38. In the TP3, there was no further increase in the incidence of ADAs to ustekinumab at Week 40, where 66.1% of patients in the Bmab 1200 group, 77.8% of patients in the Stelara-Stelara group and 65.5% of patients in the Stelara-Bmab 1200 group tested positive. In the Stelara-Bmab 1200 group despite switching there was no increase in incidence of ADA by Week 40 or Week 52. Similarly, the incidence of NAbs was higher in the Stelara-Stelara group compared to the Stelara-Bmab 1200 group. There was no increase in NAb despite switching from Stelara to Bmab 1200. The antibody titre was also similar to TP2 and the titre was similar or lower in the Stelara-Bmab 1200 group. At Week 52, the mean ADA titre was 322.560, 2216.608, and 1108.774 for Bmab 1200, Stelara-Stelara and Stelara-Bmab 1200 groups, respectively

Table 38. Summary of Overall Immunogenicity Results (Treatment Period 3) (Safety Analysis Set 3)

	Bmab 1200 N=168	Stelara-Stelara N=81	Stelara-Bmab 1200 N=84
Patients with no postbaseline ADA result	1	0	0
Overall (during TP3)[a]			
ADA positive at any point	131 (78.0)	73 (90.1)	74 (88.1)
ADA negative	36 (21.4)	8 (9.9)	10 (11.9)
NAb reactive	27 (16.1)	19 (23.5)	12 (14.3)
NAb negative	104 (61.9)	54 (66.7)	62 (73.8)
Week 40			
ADA positive	111 (66.1)	63 (77.8)	55 (65.5)
ADA negative	56 (33.3)	17 (21.0)	28 (33.3)
Week 52			
ADA positive	107 (63.7)	65 (80.2)	61 (72.6)
ADA negative	56 (33.3)	15 (18.5)	22 (26.2)

Abbreviations: ADA, antidrug antibody; N, number of patients in the treatment group; NAb, neutralizing antibody; TP3, Treatment Period 3.

Note: Percentages (%) are based on the number of patients in each treatment group (N).

[a] Irrespective of baseline ADA.

Table 39. NAb reactive participants

System Organ Class Preferred Term	Bmab1200 N=116 n (%) E	Stelara N=66 n (%) E	Stelara - Bmab1200 N=54 n (%) E	Total N=236 n (%) E
Any TEAE	63 (54.3) 205	31 (47.0) 100	29 (53.7) 101	123 (52.1) 406

Table 40. NAb negative participants (throughout)

System Organ Class Preferred Term	Bmab1200 N=75 n (%) E	Stelara N=34 n (%) E	Stelara - Bmab 1200 N=38 n (%) E	Total N=147 n (%) E
Any TEAE	48 (64.0) 133	16 (47.1) 40	22 (57.9) 54	86 (58.5) 227

Overall, the frequency of TEAEs was generally consistent between treatment groups in NAb reactive participants (Table 39), whereas numerically differences were noted in participants who were nAb negative (Table 40).

To evaluate the course of ADA status and hypersensitivity reaction in ADA-positive patient, visit-wise titres of these patients were provided by the Applicant.

6.1.10.8. Safety related to drug-drug interactions and other interactions

Not applicable for biosimilars.

6.1.10.9. Discontinuation due to adverse events

Study BM12H-NHV-01-G-01

No TEAEs led to treatment discontinuation during the study.

Study BM12H-PSO-03-G-02

Six patients (3 patients in the Bmab 1200 group and 3 patients in the Stelara group) had 7 TEAEs leading to study discontinuation (Table 41).

Table 41. Overall Summary of Treatment-emergent Adverse Events Leading to Study Treatment Withdrawal by Preferred Term Through the Study (Baseline to Week 52) (Safety Analysis Set)

	Bmab 1200 (N=191) n (%) E	Stelara (N=101) n (%) E	Stelara-Bmab 1200 (N=92) n (%) E	Total (N=384) n (%) E
Any TEAE leading to study treatment withdrawal	3 (1.6) 4	3 (3.0) 3	0	6 (1.6) 7
Endometrial adenocarcinoma	1 (0.5) 1	0	0	1 (0.3) 1
Squamous cell carcinoma of the tongue	1 (0.5) 1	0	0	1 (0.3) 1
Angioedema	0	1 (1.0) 1	0	1 (0.3) 1
Rash maculo-papular	0	1 (1.0) 1	0	1 (0.3) 1
Abdominal pain[1]	1 (0.5) 1	0	0	1 (0.3) 1
Jaundice cholestatic[1]	1 (0.5) 1	0	0	1 (0.3) 1
Alcohol poisoning	0	1 (1.0) 1	0	1 (0.3) 1

Abbreviations: AE = adverse event, E = number of events, MedDRA = Medical Dictionary for Regulatory Activities, N = number of patients in the treatment group, n (%) = number (percentage) of patients with adverse events of interest, SAF = safety set for treatment period 1, TEAE = treatment-emergent adverse event.
Note: Percentages (%) are based on the number of patients in each treatment group/overall on the SAF (N).
Note: AEs are coded using MedDRA Version 26.1.
Note: Patients in the Stelara group were re-randomised at Week 16 to either Bmab 1200 or Stelara.
[1]One patient experienced both TEAEs of Grade 4 abdominal pain and jaundice cholestatic. These TEAEs were also assessed as serious.

Bmab1200:

- One patient had endometrial adenocarcinoma which assessed as not related to study treatment. As this TEAE was also assessed as an AESI (malignancy) and serious, details have been provided in Section 6.1.10.3.
- One patient had squamous cell carcinoma of the tongue which was assessed as unlikely related to study treatment. As this TEAE was also assessed as an AESI (malignancy) and serious, details have been provided in Section 6.1.10.3.
- One patient had abdominal pain and jaundice cholestatic. The TEAEs resolved on Day 172 and were assessed as SUSARs (possibly related to study treatment). Both TEAEs were also assessed as serious, details have been provided in Section 6.1.10.3

Stelara

- One patient had Grade 2 rash maculo-papular (SOC: skin and subcutaneous tissue disorders) on Day 33. The TEAE resolved after the study treatment was withdrawn on Day 51; study treatment was not restarted. The TEAE was assessed as probably related to study treatment. This TEAE was also assessed as an AESI (hypersensitivity reaction).

- One patient had Grade 1 alcohol poisoning (SOC: injury, poisoning and procedural complications) on Day 106. The TEAE was ongoing at the time of the last report and was assessed as not related to study treatment.
- One patient had Grade 2 angioedema (SOC: skin and subcutaneous tissue disorders) on Day 2. The TEAE resolved on the same day and was assessed as definitely related to study treatment. This TEAE was also assessed as an AESI.

Six patients (3 patients in the Bmab 1200 group and 3 patients in the Stelara group) had 7 TEAEs leading to study discontinuation. Four of the TEAEs occurring in 3 patients were assessed as being treatment-related: One patient in the Bmab1200 group experienced 2 Grade 4 TEAEs (abdominal pain and jaundice cholestatic) on Day 160. Both TEAEs resolved on Day 172 and were assessed as suspected unexpected serious adverse reaction (SUSARs) (possibly related to study treatment). Two patients in the Stelara group experienced TEAEs that led to study treatment discontinuation. One patient had Grade 2 rash maculo-papular on Day 33. The TEAE resolved after the study treatment was withdrawn on Day 51; study treatment was not restarted. The TEAE was assessed as probably related to study treatment. This TEAE was also assessed as an AESI (hypersensitivity reaction). Another patient had Grade 2 angioedema on Day 2. The TEAE resolved on the same day and was assessed as definitely related to study treatment. This TEAE was also assessed as an AESI (hypersensitivity reaction). No patients in the Stelara-Bmab 1200 group had TEAEs leading to study treatment withdrawal.

TEAES leading to treatment withdrawal during TP1 and TP2 were equally distributed between Bmab1200 and Stelara. In TP2, 1 patient in the Bmab1200 group reported 2 TEAEs leading to treatment discontinuation. Both events (abdominal pain and jaundice cholestatic) were assessed as serious and as SUSARs and were already discussed above. Both TEAEs resolved on Day 172, and the patient discontinued the study on Day 199. No patients in the Stelara-Stelara group or the Stelara-Bmab 1200 group had TEAEs leading to study treatment withdrawal.

Treatment Period 2 + Treatment Period 3

No patients had TEAEs that led to study treatment discontinuation or discontinuation from the study during TP2 + TP3.

6.1.10.10. Post marketing experience

Not applicable.

6.1.11. Discussion on clinical safety

The overall safety profile of Bmab1200 and Stelara has been assessed in two clinical studies, a clinical Phase 1 pharmacokinetic (PK) study in healthy subjects (BM12H-NHV-01-G-01) and a clinical Phase 3 study in patients with moderate to severe chronic plaque psoriasis (BM12H-PSO-03-G-02). Due to differences between the two studies [BM12H-NHV-01-G-01 (phase 1) and Study BM12H-PSO-03-G-02 (phase 3)], a pooled safety analysis of both studies was not considered meaningful and safety results are discussed per individual study. Overall, the Bmap1200 Phase 1 study design is considered adequate to evaluate the comparability of Bmab1200 and its reference product EU-Stelara in terms of pharmacokinetic and safety.

Study BM12H-NHV-01-G-01 in healthy participants

In Study BM12H-NHV-01-G-01, the pooled SAF comprised 258 healthy participants: Bmab 1200 n=86, EU-Stelara n=85, and US-Stelara n=87. The percentage of subjects with an TEAE being slightly lower for US Stelara: 59,8% and slightly higher for EU Stelara (78.8%) compared to Bmab 1200 (70.9%). The proportion of subjects who experienced TEAEs considered to be related to the IP by the Investigator were comparable across the three treatment groups. Most were considered of mild intensity. TEAEs by SOC and PT were comparable between treatment groups. No drug related lab findings were considered of clinical importance for any treatment group. No study-related vital signs, ECG or physical examination findings occurred in any of the treatment groups. No TEAEs led to treatment withdrawal during the study. None of the subjects were discontinued from the study due to TEAEs. Overall, the safety profile is consistent with the known safety profile of Stelara.

Study BM12H-PSO-03-G-02 in PsO patients

Key safety data are derived from the clinical Phase III study (BM12H-PSO-03-G-02) in patients with moderate to severe plaque psoriasis. A total of 384 patients were randomised in a 1:1 ratio to receive Bmab1200 or Stelara in Treatment Period 1 (TP1). The Safety Set for TP1 (SAF) includes all randomised patients that have received any treatment with study drug: 191 patients treated with Bmab 1200 and 193 patients treated with EU-Stelara. Prior to week 16 dosing in Treatment Period 2 (TP2), patients receiving originator ustekinumab were re-randomised (1:1) to continue originator ustekinumab or switch to Bmab1200; patients initially randomised to Bmab1200 continued receiving Bmab1200. Overall, 382 patients (99.5%) completed treatment in TP1; 11 patients (2.9%, 5 patients in the Bmab1200 group and 6 patients in the Stelara) who completed TP1 did not enter TP2. The Safety Set for TP2 (SAF2) consists of all patients who received the re-randomised study treatment administration at Week 16 or later: n=371, (185 patients treated with Bmab 1200 and 94 patients treated with Stelara-Stelara and 92 patients with Stelara-Bmab 1200). Twenty-three patients were discontinued from TP2 because of unblinding issues related to re-randomisation at Week 16 and an additional 4 patients were discontinued from TP2. Thus, 344 patients completed TP2. Of these, 11 patients (2.9%) who completed TP2 did not enter TP3. A total of 333 patients entered and were dosed in TP3 and included in the Safety Set for TP3 (SAF3).

For the development of Bmab1200, EMA Scientific Advice was received in March 2020 and Dec 2023. With regard to the BM12H-PSO-03-G-02 study design it was noted that the switch from Stelara to Bmab1200 to assess safety and immunogenicity should be done in such a way that allows follow up of sufficient numbers of patients for one year to compare the safety and immunogenicity of the proposed biosimilar to ustekinumab. Considering that a total of 168 patients who received Bmab1200 completed TP3, this concern seems reasonably addressed.

The safety evaluations were planned according to the known safety profile of ustekinumab, considering the adverse reactions presented in the SmPC and other available clinical information. The safety analyses were performed on the safety analysis sets, consisting of all subjects receiving at least 1 dose of either Bmab1200 or ustekinumab. Overall, the Applicant’s approach to the safety analyses is endorsed.

Study exposure

As mentioned above, the Applicant had received EMA Scientific Advice. With regard to the switch at week 16, the CHMP noted “preserving the study integrity requires establishing robust barriers between the dedicated unmasked team and the masked study personnel, subjects, and investigators. It is essential to ensure that any communication between the unmasked and masked teams is thoroughly documented”. In this context, it was noted that 23 patients were withdrawn from the study due to accidental partial unblinding of a few CRO and site personnel due to the RTSM configuration issue

during re-randomisation (Figure 3). According to the Applicant there was no safety risk to the patient affected. The safety profile, in particular the incidence of treatment-related TEAEs, was comparable between the safety profile for the overall subjects (without excluding these 23 patients) and the subset after excluding the 23 subjects for whom accidental unblinding occurred.

Through Week 52, the overall mean (SD) duration of treatment was 327.7 days (94.82) and the mean (SD) total dose administered was 256.9 mg (99.68). Treatment compliance was 100% for all patients for each treatment period through the study.

The demographic and baseline characteristics were generally balanced, with some small differences observed between the groups.

Adverse events

In study BM12H-PSO-03-G-02, the safety results are presented in 3 separate time periods: TP1 (from baseline to Week 16 predosing, SAF), TP2 (from Week 16 Dosing to Week 28 predosing, SAF2), TP2 + TP3 combined (SAF3). In addition, the overall safety profile was presented from Baseline through Week 52 of patients who remained on the same treatment throughout the study (Bmab 1200 vs Stelara).

During TP1, the incidence of TEAEs was higher in the Bmab 1200 group compared to the Stelara group, which was even more pronounced throughout the study, with 58.1% of patients in the Bmab1200 group experiencing TEAEs compared to 47.5% of patients in the Stelara group. This trend was also seen during the transition period (42.9% in the Stelara-Bmab 1200 group versus 33.3% Stelara-Stelara group). These differences were mainly attributes to the SOC infections and infestations (30.4% vs 20.8%, respectively). Furthermore, it was noted that of the treatment-related TEAEs by SOC, infections and infestations had a higher frequency in the switching group with 9.5% in the Stelara-Bmab1200 group compared to 2.5% group in the Stelara-Stelara group in the SAF3 analysis set (TP2+TP3). None of the baseline subgroups show any association with infections in either group for all three 3-treatment periods (TP1, TP2, and TP3), except for the "baseline and concomitant status of psoriatic arthritis," which is associated with infections (significant p value<0.05). However, since for the "baseline and concomitant status of psoriatic arthritis", the association is seen in both groups, the numerically higher infections in the Bmab-1200 group alone cannot be explained based on this finding. In addition an exploratory analysis to assess the association of infections with the two different doses, i.e., the 45 mg and 90 mg was provided. Based on the p values (>0.05), it was concluded that there is no association of infections with dose level. A similar analysis for treatment-related TEAEs by SOC, infections and infestations was not provided, as the numbers were too small to give any meaningful analysis, which can be followed. Instead, a comprehensive analysis for all possible related TEAEs was conducted. Based on the p values (>0.05), it was concluded that none of the baseline subgroups show any association with possibly related TEAEs of infection in either group.

During TP1, the occurrence of AEs with a suspected causal relationship to study intervention was slightly higher in the Bmab 1200 group compared to the Stelara group. Also after re-randomisation, the proportion of ADRs was higher in the Stelara-Bmab 1200 group (8.7%) and the Bmab 1200-Bmab 1200 group (6.5%) compared to the Stelara-Stelara group (1.1%), but this difference was less pronounced during TP3, with 10.7% of patients in the Stelara-Bmab group and 7.4% of patients in the Stelara-Stelara group experiencing treatment-related TEAEs.

At the SOC level, the most common TEAEs throughout the study belonged to "infections and infestations" in 58 patients (30.4%) in the Bmab 1200 group vs 21 patients (20.8%) in the Stelara group, followed by investigations which were comparable between both treatment groups.

At PT level, nasopharyngitis was the most frequently reported TEAE (9.4% in the Bmab 1200 group vs 5.9% in the Stelara group), followed by alanine aminotransferase increased (6.3% in the Bmab 1200

group vs 5.9% in the Stelara group) and Blood triglycerides increased (5.8% in the Bmab1200 group vs 3.0% in the Stelara group). Overall, the incidence and frequency of the majority of TEAEs by PT was comparable across groups.

Overall, the number of patients who experienced TEAEs leading to study treatment withdrawal and study discontinuation was low. A similar proportion of subjects in both arms experienced TEAEs that led to drug interruption or discontinuation and withdrawn from the study. Of these TEAEs leading to treatment discontinuation, 1 was considered definitely related to study intervention: Angioedema (Stelara); 1 TEAE was considered probably related: Rash Maculo-papular (Stelara) and 1 TEAEs were considered Possibly related to study intervention: Abdominal Pain and Jaundice cholestatic (Bmab 1200).

Serious adverse events were overall infrequent in the clinical PsO study. Seven patients (1.8%) experienced 9 serious TEAEs through the study (baseline through Week 52): 6 patients (3.1%) had 8 serious TEAEs in the Bmab 1200 group and 1 patient had 1 serious TEAE in the Stelara-Bmab 1200 group. No serious TEAEs were reported in the Stelara-Stelara group. Two serious TEAEs occurring in the same patient of the Bamb1200 group, both with Grade 4 intensity (abdominal pain and jaundice cholestatic) were assessed as possible related to study treatment. They occurred on D160 and resolved on D172 and were assessed as SUSAR. All other SAEs were considered as unlikely related or not related to study treatment. Most events were single occurrences, with no clustering discernible.

As mentioned above, throughout the study, AESI were reported more frequently in patients from the Bmab 1200 group compared to patients from the Stelara group mainly due to a higher incidence of patients experiencing Infections in the Bmab 1200 group, however, none of these TEAEs of special interest were assessed as serious TEAEs. No causal relationship was suspected for the occurred malignancies (i.e. 2 events in the Bmab 1200 group). Besides these malignancies no other AESI were assessed as serious. The incidence of hypersensitivity reactions was slightly higher in patients treated with Stelara (3 patients; 3.0%) compared to patients treated with Bmab 1200 (1 patient; 0.5%). Relevant to immunogenicity and ADA formation, the absence of serious systemic hypersensitivity reactions is noted. After re-randomisation (TP2 and TP3 combined), AESI were reported more frequently in Stelara-Bmab 1200 (26.7%) compared to the Stelara-Stelara (12.3%) group, mainly due to an increased number of Infections in that group. Only 2 Hypersensitivity events occurred (urticaria), 1 in the Bmab 1200-Bmab 1200 group and 1 in the Stelara-Bmab 1200 group.

Laboratory findings:

In PsO patients, numerical differences were observed in the incidence of the TEAEs related to abnormal clinical laboratory results. In patients in treatment groups who took the same treatment trough the study (Baseline through Week 52), the incidence of Blood Triglyceride increase/ Hypertriglyceridemia, was numerically higher in patients who remained on Bmab1200 throughout (8.9%) versus those who remained on Stelara throughout (4.0%). In the Phase 1 study, no subject reported adverse event of blood triglyceride increase/ hypertriglyceridemia. In PsO patients, although there were numerical differences in the incidence of blood triglyceride elevation/hypertriglyceridemia between treatment arms, the cases were mostly attributed to an alternative aetiology, were short-lived and/or resolved spontaneously, and were mostly mild or moderate in intensity. None of these events were serious or led to treatment/study withdrawal. The small numerical differences observed during TP1 is probably coincidental. Given the comparable safety profile across the three different treatment arms with respect to Alanine Aminotransferase Increase and associated TEAEs, there do not appear to be any specific concerns with Bmab1200 versus EU Stelara.

A total of 5 TEAEs of neutropenia (4 in the Bmab1200 and 1 in the Stelara treatment group) were observed. No clinically significant signs or symptoms could be attributed to neutropenia in these patients and none of the TEAEs were serious or led to treatment/study withdrawal or another action. It

is unlikely that the difference in treatment (Stelara versus Bmab 1200 group) caused the numerical difference in TEAEs of neutropenia/decreased neutrophil count between the groups.

Immunogenicity:

Study BM12H-NHV-01-G-01

At baseline, 10.5%, 2.3%, and 5.9% of subjects were ADA+ in the Bmab 1200, the US Stelara, and the EU Stelara groups, respectively. The number of ADA+ subjects increased over time and was lower in the Bmab 1200 group (54.7%) compared to the EU-Stelara (75.3%) and the US-Stelara (83.9%) treatment groups.

Study BM12H-PSO-03-G-02

Around 8% of the PsO patients were ADA+ already at baseline. Thereafter the ADA+ incidence and was comparable between the 2 groups throughout the study with no apparent impact of switching from Stelara to Bmab 1200. The overall incidence rate of ADA postbaseline during TP1 (i.e., at any time point from Week 2 to Week 16), irrespective of the baseline status, was observed to be 97.4% in the Bmab 1200 group and 99.0% in the Stelara group and was comparable to the overall incidence in TP2.

The NAb reactive rate was higher in Stelara group vs Bmab 1200 group in TP1. Also, a higher rate was observed in Stelara-Stelara groups compared to Stelara-Bmab 1200 group post-switching in TP2.

As there are concerns on the adequacy/reliability of the ADA assay, the Applicant provided a summary of ADA and NAb data (low vs moderate/high titre levels) in order to identify potentially clinically relevant effects on safety. An analysis of TEAEs from baseline through Week 52 by NAb status has been provided. Overall, the frequency of TEAEs was generally consistent between treatment groups in NAb reactive participants (in Nab reactive participants 54.3%, 47.0% and 53.7% experienced TEAEs in the Bmab1200, Stelara and Stelara-Bmab1200 group, respectively), whereas numerically differences were noted in participants who were NAb negative. However, as the NAb negativity, as such, is not a clinical consideration for safety, the Applicants position that these differences are likely incidental and are not regarded as safety concern can be followed.

To evaluate the course of ADA status and hypersensitivity reaction in ADA-positive patient, visit-wise titres of these patients were provided by the Applicant. Based on these data, it can be concluded that hypersensitivity reactions appeared to be independent of ADA titres and NAb status. However, it remains unclear whether ADA titres and Nab status have an impact on the overall safety profile.

6.1.12. Conclusions on clinical safety

The size of the safety database is considered sufficient to enable a comprehensive analysis of comparability between Bmab1200 and ustekinumab (EU). No significant differences in safety have been detected based on the available data and the two products can be concluded to be biosimilar.

In terms of immunogenicity, the assay used in the study was a highly drug tolerant ADA method with a high sensitivity. Hence, high ADA positive rate was observed in PsO patients in both groups and were over 95% at any time point during the study. Nevertheless, given the comparable levels of ADA and NAbs observed between treatment arms and the extensive clinical data collected from patients, the overall body of evidence outweighs concerns regarding the performance of the assay in this context.

7. Risk management plan

7.1. Safety Specification

Summary of safety concerns

The applicant proposed the following summary of safety concerns in the RMP:

Table SVIII.1: Summary of safety concerns

Summary of safety concerns	
Important identified risks	*None*
Important potential risks	• Serious infections (including mycobacterial and salmonella infections) • Malignancy • Cardiovascular events • Serious depression including suicidality • Venous thromboembolism
Missing information	• Long-term safety in paediatric psoriasis patients 6 years and older • Long-term impact on growth and development in paediatric psoriasis patients 6 years and older • Long-term safety in adult patients with moderately to severely active Crohn's disease

7.1.1. Discussion on safety specification

The Applicant has submitted RMP v0.1. within which the summary of safety concerns, and all relevant sections, have been aligned with the most up-to-date RMP for the originator product, Stelara for the important and potential risks. Version 31.2 of the Stelara RMP, dated 27 Feb 2025, contains the following as additional missing information which is absent from the proposed summary of safety concerns; long-term safety in adults with moderately to severely active ulcerative colitis and, long-term safety in paediatric patients weighing at least 40kg with moderate to severely active Crohn's disease. Ulcerative colitis and paediatric Crohn's disease are not proposed indications for Usrenty. The proposed summary of safety concerns is considered acceptable.

7.1.2. Conclusions on the safety specification

Having considered the data in the safety specification, the CHMP agrees that the safety concerns listed by the applicant are appropriate.

7.2. Pharmacovigilance plan

7.2.1.1. Routine pharmacovigilance activities

Routine pharmacovigilance is proposed, which is to include integrated traceability.

The Applicant acknowledges the need for traceability to be fully integrated in different healthcare settings and that infrastructure may vary between countries. A key requirement for pharmacovigilance of biologicals is the need to ensure continuous product and batch traceability in the clinical use. Communication should emphasise the importance of providing the product name (or INN and the name of marketing authorisation holder) and the batch number(s) when reporting suspected adverse reactions. In line with international guidance on biological medicinal products, reporting drug name and batch number is mentioned in appropriate sections of Biocon Biologics ustekinumab product information/labels and included in the product packaging. This information is therefore available to be recorded and reported at all levels in the supply chain from the manufacturer release to prescription, dispensing and patient information.

Ustekinumab will mainly be supplied in the hospital setting. A statement is presented in the product information/label reminding Healthcare Professionals (HCPs) on the type of the medicinal product (Biosimilar) and the need to clearly record both, the trade name and batch number in the patient's healthcare records. For the Biocon Biologics ustekinumab biosimilar, in all countries, no matter if middle or low income, INN and batch number can be found on the package.

According to international guidelines for the use of Biosimilars, Biocon Biologics has a process in place to cover the requirements of traceability. Pharmacovigilance activities of biosimilar ustekinumab follow established standard procedures laid down by Biocon Biologics to collect initial and follow up information. If any missing batch number or product name in the initial report received, then separate follow up will be made to the reporter. Adequacy of the data and proper assessment will be ensured. Biocon Biologics performs diligent follow up on national level to obtain trade name and batch number to distinguish the reports of the Biocon Biologics products to identify batch-related issues and product specific safety concerns.

Other Forms of Routine Pharmacovigilance Activities			
Activity	**Safety Concern(s)**	**Objective/Description**	**Milestones**
For traceability purposes, brand name and batch number of the product received by the patient will be recorded wherever possible.	All safety concerns	To monitor if there are any batch-specific issues in the post marketing environment.	Not applicable

Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection:

Specific Adverse Reaction Follow-up Questionnaires	
Safety Concern	**Purpose/Description**
Serious infections (including mycobacterial and salmonella infections)	Topic of interest (TOI) targeted follow-up questionnaire (TFUQ) to collect information on serious infections and opportunistic infections and TOI TFUQ to collect information on tuberculosis
Malignancy	TOI TFUQ to collect information on malignancies (including lymphoma, second and secondary malignancies)

Cardiovascular events	TOI TFUQ to collect information on cardiovascular events
Venous thromboembolism	TOIQ to collect information on venous thromboembolism

The TOI TFUQs and their content is aligned to the originator, Stelara's.

7.2.1.2. Additional pharmacovigilance activities

7.2.1.2.1. Summary of additional PhV activities

There are no ongoing trials or planned additional pharmacovigilance studies/activities proposed by the applicant.

There are currently four ongoing Category 3 post-authorisation safety studies (PASS) for the originator product Stelara.

Two studies (SWIBREG; PCSIMM002807 and (SNDS; PCSIMM002659) are investigating long-term safety in Ulcerative Colitis and Crohn's patients, utilising population-based, new-user, active comparator prospective cohort studies based on secondary data collection from population registers (France and Sweden). The end of data collection for SNDS; PCSIMM002659 is expected on 31 December 2026, and the expected end of data collection for SWIBREG; PCSIMM002807 is 30 November 2027.

One registry study (CNTO1275PSO4056) is investigating long term safety in paediatric psoriasis patients with the end of data collection due on 31 August 2032. Study CNTO1275ISD3001 (UNITED) LTE is investigating long-term safety in paediatric patients weighing at least 40kg with moderately to severely active Crohn's disease.

Given the protocol for these studies includes the ATC code for 'ustekinumab' in terms of treatment to be captured, it is assumed that data accrued following exposure to all ustekinumab biosimilars including Ursenty will be captured within these studies in addition to the innovator product.

Bearing these ongoing studies in mind, which are being conducted by the originator and are aimed at characterising the long-term safety of ustekinumab, further post-authorisation safety studies are not considered warranted to be undertaken by the applicant. The proposed additional pharmacovigilance plan is therefore considered acceptable.

Table Part III.3: On-going and planned additional pharmacovigilance activities

Study Status	Summary of objectives	Safety concerns addressed	Milestones	Due dates
Category 1 - Imposed mandatory additional pharmacovigilance activities which are conditions of the marketing authorisation				
None				
Category 2 – Imposed mandatory additional pharmacovigilance activities which are Specific Obligations in the context of a conditional marketing authorisation or a marketing authorisation under exceptional circumstances				
None				
Category 3 - Required additional pharmacovigilance activities				
None				

7.2.1.3. Overall conclusions on the PhV Plan

The PRAC and CHMP, having considered the data submitted, is of the opinion that routine pharmacovigilance is sufficient to identify and characterise the risks of the product.

The PRAC and CHMP also considered that routine PhV remains sufficient to monitor the effectiveness of the risk minimisation measures.

7.3. Risk minimisation measures

7.3.1. Summary of Post authorisation efficacy development plan

Table Part IV.1: Planned and on-going post-authorisation efficacy studies that are conditions of the marketing authorisation or that are specific obligations.

Study Status	Summary of objectives	Efficacy uncertainties addressed	Milestones	Due Date
Efficacy studies which are conditions of the marketing authorisation				
None				
Efficacy studies which are Specific Obligations in the context of a conditional marketing authorisation or a marketing authorisation under exceptional circumstances				
None				

7.3.1.1. Risk minimisation measures

7.3.1.2. Routine Risk Minimisation Measures

Safety concern	Routine risk minimisation activities
Serious infections (including mycobacterial and salmonella infections)	**Routine risk communication:** SmPC sections 4.3 (Contraindications), 4.4 (Special Warnings and Precautions for Use), 4.5 (Interaction with Other Medicinal Products and Other Forms of Interaction), 4.6 (Fertility, Pregnancy and Lactation), and 4.8 (Undesirable Effects) PL sections 2 and 4 **Routine risk minimisation activities recommending specific clinical measures to address the risk:** SmPC section 4.4 (Special Warnings and Precautions for Use) • Guidance regarding evaluation of patients for TB infection, treatment of latent TB, and administration of anti-TB therapy in patients with a history of latent or active TB prior to initiation of Usrenty. • Recommendation to monitor patients for signs and symptoms of active TB during and after Usrenty treatment. • Guidance for managing patients who develop a serious infection. • Recommendations regarding the administration of live vaccines to patients receiving ustekinumab and to infants exposed to ustekinumab in utero. (The same recommendations are included in SmPC section 4.5[Interaction with Other Medicinal Products and Other Forms of Interaction]). SmPC section 4.6 (Fertility, Pregnancy and Lactation) • Recommendation regarding the administration of live vaccines to infants exposed to ustekinumab in utero. PL section 2 • Guidance for patients who have recently had or are going to have a vaccination. • Guidance for mothers who received ustekinumab while pregnant and recommendation regarding the administration of live vaccines to infants exposed to ustekinumab in utero. • Guidance for patients who have had a recent infection, have any abnormal skin openings (fistulae), are over 65 years of age, or have recently been exposed to someone who might have TB. PL section 4 • Guidance for patients who develop signs of an infection or have open cuts or sores while using Usrenty. **Other routine risk minimisation measures beyond the Product Information:** Legal status: Restricted medical prescription.

Malignancy	**Routine risk communication:** SmPC sections 4.4 (Special Warnings and Precautions for Use) and 4.8 (Undesirable Effects) PL section2 **Routine risk minimisation activities recommending specific clinical measures to address the risk:** SmPC section 4.4 (Special Warnings and Precautions for Use) • Guidance for monitoring patients for the appearance of skin cancer. **Other routine risk minimisation measures beyond the Product Information:** Legal status: Restricted medical prescription.
Cardiovascular events	**Routine risk communication:** None **Routine risk minimisation activities recommending specific clinical measures to address the risk:** None **Other routine risk minimisation measures beyond the Product Information:** Legal status: Restricted medical prescription.
Serious depression including suicidality	**Routine risk communication:** SmPC section 4.8 (Undesirable Effects) PL section4 **Routine risk minimisation activities recommending specific clinical measures to address the risk:** None **Other routine risk minimisation measures beyond the Product Information:** Legal status: Restricted medical prescription.
Venous thromboembolism	**Routine risk communication:** None **Routine risk minimisation activities recommending specific clinical measures to address the risk:** None **Other routine risk minimisation measures beyond the Product Information:** Legal status: Restricted medical prescription.

Long-term safety in paediatric psoriasis patients 6 years and older	**Routine risk communication:** None **Routine risk minimisation activities recommending specific clinical measures to address the risk:** None **Other routine risk minimisation measures beyond the Product Information:** Legal status: Restricted medical prescription.
Long-term impact on growth and development in paediatric psoriasis patients 6 years and older	**Routine risk communication:** None **Routine risk minimisation activities recommending specific clinical measures to address the risk:** None **Other routine risk minimisation measures beyond the Product Information:** Legal status: Restricted medical prescription.
Long-term safety in adult patients with moderately to severely active Crohn's disease	**Routine risk communication:** None **Routine risk minimisation activities recommending specific clinical measures to address the risk:** None **Other routine risk minimisation measures beyond the Product Information:** Legal status: Restricted medical prescription.

The proposed routine Risk Minimisation Measures are aligned with those of the reference product, and are sufficient to minimise the risks of the product in the proposed in indications.

7.3.2. *RMP summary and RMP annexes overall conclusion*

The public summary of the RMP does not require revision.

7.4. Overall conclusion on the Risk Management Plan

The CHMP and PRAC considered that the risk management plan version 0.1 is acceptable.

8. Pharmacovigilance

8.1. Pharmacovigilance system

The CHMP considers that the pharmacovigilance system summary submitted by the applicant fulfils the requirements of Article 8(3) of Directive 2001/83/EC.

8.2. Periodic Safety Update Reports submission requirements

The requirements for submission of periodic safety update reports for this medicinal product are set out in the list of Union reference dates (EURD list) provided for under Article 107c(7) of Directive 2001/83/EC and any subsequent updates published on the European medicines web-portal.

9. Product information

9.1. User consultation

A justification for not performing a full user consultation with target patient groups on the package leaflet has been submitted by the applicant and has been found acceptable for the following reasons:

The Applicant confirmed that with the exception of differences based on scientific grounds, no deviations from the reference medicinal product's package leaflet have been introduced. Accordingly, no user testing consultation with target patient groups has been conducted on the package leaflet for Usrenty Solution for Injection and Solution for Intravenous Infusion as per Articles 59(3) and 61(1) of Directive 2001/83/EC, as amended by Directive 2004/27/EC and in line with the QRD general principles regarding the SmPC information for a generic/ hybrid/biosimilar product (EMA/627621/2011).

9.2. Additional monitoring

Pursuant to Article 23(1) of Regulation No (EU) 726/2004, Usrenty (ustekinumab) is included in the additional monitoring list since:

- It is a biological product that is not covered by the previous category and authorised after 1 January 2011.

Therefore, the summary of product characteristics and the package leaflet include a statement that this medicinal product is subject to additional monitoring and will allow quick identification of new safety information. The statement is preceded by an inverted equilateral black triangle.

10. Biosimilarity assessment

10.1. Comparability exercise and indications claimed

Bmab1200 has been developed as a biosimilar candidate to Stelara (ustekinumab). The applicant proposes the following indications for Bmab1200:

Adult patients with:

- Moderate to severe plaque psoriasis (Ps) who are candidates for phototherapy or systemic therapy. who failed to respond to, or who have a contraindication to, or are intolerant to other systemic therapies including ciclosporin, methotrexate (MTX) or PUVA (psoralen and ultraviolet A)
- Active psoriatic arthritis (PsA), alone or in combination with MTX, with inadequate response to non-biological disease-modifying anti-rheumatic drug (DMARD) therapy
- Moderately to severely active Crohn's disease with inadequate response, lost response to, or intolerance to either conventional therapy or a TNFα antagonist

Paediatric patients 6 years and older with:

- Moderate to severe plaque psoriasis, who are inadequately controlled by, or are intolerant to, other systemic therapies or phototherapies

The dosage form and route of administration for Bmab1200 is identical to Stelara (EU).

Quality programme

A comprehensive similarity exercise following the general principles outlined in "Guideline on similar biological medicinal products containing biotechnology-derived proteins as active substance: quality issues" (EMA/CHMP/BWP/247713/2012) was performed. Received CHMP scientific advice has been followed in the presented similarity exercise. Bmab1200 DP, US-licensed Stelara® and EU-approved Stelara® have been compared.

Bmab1200 has the same amino acid sequence, formulations, dosage forms, presentations, and product strengths as the reference medicinal product (RMP) Stelara.

Clinical studies BM12H-NHV-01-G-01 and BM12H-PSO-03-G-02 included the use of SC DP PFS presentations only. A detailed risk assessment based on formulation, container closure, DP manufacturing process etc. was performed and a product quality comparison between the different Bmab1200 SC DP presentations was conducted for US-licensed Stelara® and EU-approved Stelara® separately. Based on the outcome of this risk assessment, it was concluded that a single Comparative analytical assessment (CAA) for all three Bmab1200 SC DP presentations would be sufficient.

Batches of vial presentations were not used in clinical studies. The SC DP 45 mg vial has the same formulation, dosage, and recommended administration as the SC DP 45 mg PFS presentation. The IV DP 130 mg vial has the same DS but different formulation and administration route compared to SC DP PFS presentations. Consequently, two separate comparative analytical assessments (CAA) were performed for Bmab1200 SC DP and IV DP presentations.

The quality range (standard deviation multiplier) used for comparative analytical assessment was defined as mean RMP Stelara ± 3SD.

The comparative testing included analysis of biological activity, primary structure, higher order structure, particles and aggregates, product-related substances and impurities, general properties and thermal stability studies. Appropriate analytical methods have been utilised to ensure an understanding of Stelara (EU/US) product profile and Bmab1200 DP.

Non-clinical programme

The non-clinical programme supporting the similarity of Bmab1200 to Stelara (ustekinumab) includes a comprehensive battery of in vitro pharmacodynamic characterisation studies comparing key biological activities of Bmab1200 and RMP Stelara (EU/US). In general, a step-wise approach following the

general principles outlined in "Guideline on similar biological medicinal products containing monoclonal antibodies – non-clinical and clinical issues" (EMA/CHMP/BMWP/403543/ 2010) was performed.

Clinical programme

The clinical programme supporting the similarity of Bmab to Stelara (ustekinumab) includes one completed randomised, double-blind, single-dose, 3-arm, parallel-group PK similarity study in healthy adult subjects comparing Bmab1200 to ustekinumab (Study BM12H-NHV-01-G-01); and one completed randomised, double-blind, active-controlled clinical study in adult subjects with moderate to severe PsO (Study BM12H-PSO-03-G-02).

The Phase I PK study in healthy volunteers evaluated PK bioequivalence between Bmab 1200 and reference products. PK similarity of multiple dosing was assessed descriptively in the Phase 3 study in patients.

Comparability in efficacy between Bmab 1200 and Stelara was evaluated in Study BM12H-PSO-03-G-02 conducted in patients with moderate-to-severe plaque psoriasis with dosing at baseline, at week 4 and every 12 weeks thereafter according to the Stelara labelling. The study population represents the most sensitive population to demonstrate biosimilarity.

The safety profiles of Bmab1200 and the reference product were assessed in the clinical PK study as well as the clinical PsO study through a comparative, descriptive analysis of adverse events, laboratory data and immunogenic potential. For both clinical studies, the safety analyses were performed on the safety analysis set which included all randomised subjects who received any investigational product.

The clinical development followed the applicable guidelines Guideline on similar biological medicinal products (EMEA/CHMP/42832/2005 Rev. 1) and Guideline on Similar Biological Medicinal Products Containing Monoclonal Antibodies - Non-Clinical and Clinical Issues (EMA/CHMP/BMWP/403543/2010).

10.2. Results supporting biosimilarity

Quality aspects

General similarity between Bmab1200 and RMP Stelara (EU/US) has been demonstrated for the following physicochemical and biological properties:

- Primary structure (including N-glycosylation)
- Higher order structure
- Particles and aggregates
- Product-related substances and impurities
- Thermal stability
- General properties (including protein concentration)
- Biological activity:
  - p40 protein binding
  - IL-23 and IL-12 binding
  - IL-23 and IL-12 binding kinetics (affinity)
  - Inhibition of IL-23 and IL 12-mediated signalling (STAT3/4 activation, IL-17/IFNγ release)

- Lack of binding to receptor-bound IL-23 and IL-12
- Lack of binding to IL-6 and IL-10
- FcRn binding
- FcγRIa, FcγRIIa, FcγRIIb, FcγRIIIb, and FcγRIIIa binding
- C1q Binding
- Lack of ADCC and CDC activity

Non-clinical aspects

See biological activity under quality bullet point above.

Clinical aspects

PK:

Two clinical studies were conducted to demonstrate PK bioequivalence, a Phase 1 PK study in healthy volunteers (BM12H-NHV-01-G-01) and a Phase 3 confirmatory study in moderate-to-severe chronic plaque psoriasis (BM12H-PSO-03-G-02).

In the pivotal PK study, the study design, dose and route of administration were acceptable and in accordance with the relevant EMA guidance (EMA/CHMP/BMWP/403543/2010). Demographics and baseline characteristics are acceptable and well balanced between treatment arms. All but one subject from the US Stelara cohort completed the study. This subject and two participants (one EU-Stelara, one US-Stelara) were excluded from the PK analysis set, the latter due to sample mix-up on 3 consecutive days.

The study met its co-primary endpoints of C_{max} and $AUC_{0\text{-}inf}$ as the 90% CIs of the GLSM ratios for both co-primary endpoints were within the acceptable bioequivalence range (0.80 - 1.25) for each of the three pairwise comparisons. Subgroup/sensitivity analyses and secondary endpoints as well as partial AUC analyses supported the primary analysis.

The Phase 3 study provided supportive PK data in patients. The results showed comparable mean trough serum ustekinumab concentrations in patients treated with Bmab 1200 and EU-Stelara for 52 weeks.

Data provided indicate that ADA formation have no substantial effect on the PK of Bmab 1200 and Stelara.

Efficacy:

Data from study BM12H-PSO-03-G-02 conducted in patients with moderate-to-severe plaque psoriasis were provided to compare efficacy between Bmab 1200 and EU-Stelara. The primary efficacy endpoint was the percentage change in PASI score between baseline and 12 weeks. Three different estimand strategies (primary, secondary, tertiary) were applied. The predefined equivalence margin for EMA was ±13% for the 95% CI. The Full Analysis Set (FAS) consisting of all patients who signed the ICF and were randomised into TP1 was used for the primary analyses of efficacy. Additional analysis for the Per-Protocol-Set were provided.

The percentage change from baseline in the PASI Score at Week 12 (primary endpoint) was comparable between Bmab 1200 and Stelara (LS mean change: -79.87 vs. -80.55) in the FAS. The LS mean difference for the primary estimand was 0.6800 (95% CI: 1.64, 3.00). Very similar results are also observed for the secondary and tertiary estimands. For all estimands, the 95% CI was within a very narrow range, thus clinical comparability can be concluded. The Week 12 analysis based on the

PPS yielded overall similar changes in PASI in both groups and do support the results seen for the FAS. Efficacy data from the 45 mg dosing subgroup (n=301) at Week 12 were also similar and support the clinical comparability as concluded for the total patient population.

Results for the secondary endpoints (including change in PASI score at earlier and later time points until 52 weeks, sPGA scores and DLQI evaluation) overall support clinical comparability.

Despite a very high rate of ADA positive patients during the phase 3 trial, the analysis provided did not reveal major effects on Bmab1200 exposure and efficacy measures (e.g. PASI score) as compared to Stelara. Overall, the ADA and nAb profile for Bmab1200 appears similar to the comparator.

Safety:

- Single dose PK study in healthy subjects

In general, the safety profile reported in Study BM12H-NHV-01-G-01 for Bmab 1200 was comparable to the EU and US Stelara treatment groups. Numerical differences were overserved; however, small sample size makes it difficult to interpret this data. Overall, the safety profile is consistent with the known safety profile of Stelara.

The number of subjects who were ADA- at baseline and ADA+ post-dose at any given timepoint until the EOS visit was lower in the Bmab 1200 group (54.7%) compared to the EU-Stelara (75.3%) and the US-Stelara (83.9%) treatment groups. However, it was noted that at baseline, 10.5%, 2.3%, and 5.9% of subjects were ADA+ in the Bmab 1200, the US Stelara, and the EU Stelara groups, respectively.

- Study in PsO patients:

In Study BM12H-PSO-03-G-02 in patients with moderate to severe plaque psoriasis, overall, no major differences in the safety profile between Bmab1200 and EU-Stelara were reported. However, throughout the study, TEAEs were reported more frequently in patients from the Bmab 1200 group compared to patients from the Stelara group, mainly due to a higher incidence of patients experiencing Infections in the Bmab1200 groups. However, these differences were not associated with any of the baseline characteristics, including the received dose level of ustekinumab. Therefore, and as no unusual clustering of events was observed, the differences are likely incidental. In line with this observation, also slightly more treatment-related TEAEs were observed in the Bmab1200 group compared to the Stelara group but these differences were less pronounced. However, the overall incidence was low and no unexpected clustering of events was seen. The incidence of ≥3 TEAEs was generally low and comparable between both treatment groups. Numerical differences in TEAEs such as increased blood triglycerides and neutropenia in patients treated with Bmab 1200 have been detected but the cases were mostly attributed to an alternative aetiology, were short-lived and/or resolved spontaneously, and were mostly mild or moderate in intensity. It is therefore unlikely that the difference in treatment (Stelara versus Bmab 1200 group) caused the numerical difference.

Seven patients (1.8%) experienced 9 serious TEAEs trough the study: 6 patients had 8 serious TEAEs in the Bmab1200 group compared to 1 patient that had 1 serious TEAE in the Stelara group. Of those, 2 serious TEAEs occurring in the same patient of the Bamb1200 group, both with Grade 4 intensity (abdominal pain and jaundice cholestatic) were assessed as possible related to study treatment. They occurred on D160 and resolved on D172 and were assessed as SUSAR.

Throughout the study, AESI were reported more frequently in patients from the Bmab 1200 group (31.9%) compared to patients from the Stelara group (22.8%) mainly due to a higher incidence of patients experiencing Infections (30.4% vs 20.8%) in the Bmab 1200 group. No causal relationship was suspected for the occurred malignancies (i.e. 2 events in the Bmab 1200 group). Besides these malignancies no other AESI were assessed as serious. The incidence of hypersensitivity reactions was

slightly higher in patients treated with Stelara compared to patients treated with Bmab 1200. Relevant to immunogenicity and ADA formation, the absence of serious systemic hypersensitivity reactions is noted. After re-randomisation (TP2 and TP3 combined), AESI were reported more frequently in Stelara-Bmab 1200 compared to the Bmab 1200-Bmab 1200 and the Stelara-Stelara group, mainly due to an increased number of Infections in that group.

In healthy subjects as well as PsO patients, around 8% of the study participants were ADA positive already at baseline. In the Phase 3 study, over 90% of the participants were ADA positive at any timepoint during the study and was comparable between the treatment groups. Overall, the ADA incidence and nAb reactive rate were generally comparable between the Stelara and Bmab 1200 groups and the Stelara-Stelara and Stelara Bmab 1200 groups throughout the study, with no apparent impact of switching from Stelara to Bmab 1200. The nAb reactive rate was higher in Stelara group versus Bmab 1200 group and the Stelara-Stelara group versus Stelara-Bmab 1200 group post switching. Hypersensitivity reactions were independent of ADA titres and nAb status with no injection site reactions being reported. Furthermore, the frequency of TEAEs was generally consistent between treatment groups in nAb reactive participants. Overall, no major safety concerns have arisen from the safety assessment of Bmab1200 studies.

10.3. Uncertainties and limitations about biosimilarity

Uncertainties and limitations to be addressed:

Quality

None

Non-clinical

None

Clinical

Clinical PK

Partial AUC analyses revealed some differences in the elimination phase between Bmab 1200 and EU-Stelara, however this do not appear to have translated to clinically meaningful effects in efficacy outcomes.

In the Phase 3 study in patients with plaque psoriasis, C_{trough} levels were slightly higher with Bmab 1200 compared to EU-Stelara. However, comparative C_{trough} values stratified by body weight category (<100 kg and >100 kg) do not suggest important differences in PK between treatments for each BW group separately.

Although no effect of ADA on PK is indicated for both Bmab 1200 and EU-Stelara, no definite conclusions can be drawn from the subgroup analyses presented due to the small sample sizes in the ADA negative subgroups. Overall, the PK results in healthy volunteers and in the target population support biosimilarity of Bmab1200 and EU-or US-Stelara.

Clinical Efficacy

There was a notable difference in the percentage change from baseline in PASI at Week 8 between the Bmab 1200 and Stelara 4.0296 (95% CI: 0.43; 7.63). This difference was also reflected in the other efficacy measures used as secondary endpoint. Still, with regard to the primary objective, the size of the difference is not considered to principally question the comparability of efficacy and the difference

was contained within the pre-specified equivalence margin. The 45 mg dosing subgroup showed a similar response pattern.

Clinical Safety

Overall, no major safety differences have been observed between the proposed biosimilar Bmab1200 and Stelara treatment groups. The differences observed in the SoC infections and infestations in the Bmab1200 group were not associated with any baseline characteristics, including the received dose level of ustekinumab. Therefore, and as no unusual clustering of events were observed, the differences are likely incidental. Numerically differences have also been detected for increased blood triglycerides and neutropenia in patients treated with Bmab 1200. The trends observed are modest and small sample size in the subgroups may contribute to the slight imbalance. Apart from that, it should be kept in mind that due to a relatively small sample size, the study was insensitive to detect differences in safety, other than for very common AEs.

Immunogenicity

Uncertainties in adequately assessing the impact of ADA on PK, safety and efficacy exist, primarily due to the unusually high false positive rates and high number of confirmed positive subjects with the ADA assay. The overall body of evidence appears to outweigh concerns about the performance of the assay in this context.

10.4. Discussion on biosimilarity

Quality

The presented biological and physiochemical comparability data support the claim of biosimilarity for Bmab1200 and RMP Stelara (EU/US). All biological activities relevant to the primary mechanism of action, including IL-12/IL-23 binding and inhibition of IL-12/IL-23 mediated signalling, are similar.

Minor differences in N-glycan profile were observed between Bmab1200 and RMP Stelara (EU/US) such as lower sialylation, lower terminal galactosylation, higher terminal GlcNAc, lower afucosylation, and lower alpha galactosylation. Similar to Stelara, Bmab1200 is also expressed in murine myeloma cell line. Therefore, observed differences in N-glycans cannot be attributed to a different expression cell line. However, N-glycans in Bmab1200 are located in the Fc region only. As Bmab1200 does not comprise any Fc effector function such as ADCC or CDC, observed differences in N-glycans are not expected to have any clinically meaningful effect. Due to the murine expression cell line, Bmab1200 contains non-human glycans, such as N-glycolylneuraminic acid (NGNA) and alpha 1,3 Galactose. However, no risk to safety or immunogenicity is perceived because levels of both glycan species are lower in Bmab1200 compared to RMP Stelara and enclosed in a cavity in the Fc region.

Additionally, minor differences in charge and size variants were observed, which are caused by lower contents of C terminal lysine variant and HMWP in Bmab1200, respectively. As these differences are rather small and not shown to affect biological function related to the mechanism of action they are not expected to be clinically meaningful.

A lower binding affinity of Bmab1200 to FcγRIIIa (V158 and F158) and FcγRIIIb compared to RMP Stelara (EU/US) is attributed to lower levels of afucosylated glycans in Bmab1200. No clinical impact is expected from this difference because Bmab1200 does not induce Fc effector functions such as ADCC and CDC.

Overall, all observed differences in Bmab1200 compared to RMP Stelara (EU/US) were adequately discussed and shown not to affect the biological function related to the mechanism of action. Therefore, the presented quality data generally support the biosimilarity of Bmab1200 to Stelara

(EU/US).

Non-clinical

The presented *in vitro* pharmacology data investigating the functional activity of Bmab1200 compared to Stelara (EU/US) demonstrates generally biosimilarity of products.

Clinical

Clinical pharmacology

The clinical development programmeme for Bmab1200 and the design of the studies are considered adequate to assess the PK bioequivalence of Bmab1200 and its reference product Stelara. The clinical studies were adequately designed and in accordance with the relevant EMA guidance. Overall, the PK results support bioequivalence between Bmab 1200 and Stelara.

Clinical efficacy

The efficacy analysis conducted in study BM12H-PSO-03-G-02 support clinical comparability between Bmab 1200 and Stelara up to 52 weeks. Based on the data provided similar immunogenicity can be assumed.

Clinical safety and immunogenicity

Overall, the Bmab1200 clinical development programmeme and design of the studies is considered adequate to evaluate the comparability of Bmab1200 and its reference product Stelara in terms of safety and immunogenicity. Whilst no major differences in safety profile between Bmab1200 and Stelara have been identified based on the available data.

The immunogenicity assay used in this study has a highly sensitive drug tolerant ADA method with a high sensitivity. Hence, high ADA positive rate was observed in PsO patients in both groups and were over 95% at any time point during the study. The potential impact of NAbs on comparative clinical outcomes, including the relationship between NAbs and the primary efficacy endpoint of PASI percentage improvement and the safety endpoint of hypersensitivity reactions were analysed. Overall, the immunogenicity did not seem to have an effect on efficacy, or on hypersensitivity reactions which were independent of ADA titres and NAb status with no injection site reactions being reported.

10.5. Extrapolation of safety and efficacy

The clinical data up to 52 weeks support the comparability of efficacy in the indication of plaque psoriasis using SC administration. As the mechanism of action for ustekinumab is similar in each of the originator indications (including adult and paediatric psoriasis, psoriatic arthritis and Crohn's disease) extrapolation to the indications proposed by the applicant is deemed principally possible. Based on the partial AUC analyses, extrapolation of SC administration to the IV administration can also be granted.

10.6. Additional considerations

10.7. Conclusions on biosimilarity and benefit risk balance

Based on the review of the submitted data, Usrenty can be considered biosimilar to Stelara and a benefit/risk balance comparable to the reference product can be concluded.