CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

761406Orig1s000
761406Orig2s000

MULTI-DISCIPLINE REVIEW

Summary Review
Clinical Review
Non-Clinical Review
Statistical Review
Clinical Pharmacology Review

Office of Therapeutic Biologics and Biosimilars
Clinical, Cross-Discipline Team Leader, and Division Memo

Date	See Electronic Stamp Date
From	Juwaria Waheed, MD (Clinical Reviewer, OTBB) Thomas Herndon, MD (CTL, CDTL, OTBB) Tatiana Oussova, MD (Division Signatory, DDD, OII)
Subject	Request for Approval for Interchangeability - Cross-Discipline Review of amendment to the BLA 761406 Original 2
Application Type	351(k) BLA
BLA/Supplement Number	BLA 761406/Original 2
Received Date	January 15, 2025
Target Action Date	April 30, 2025
Division/Office	Division of Dermatology and Dentistry (DDD)
Proprietary Name	Yesintek
Proper Name	ustekinumab-kfce
Product Code	Bmab1200
Reference Product	US-licensed Stelara (ustekinumab)
Pharmacologic Class	Human interleukin-12 and -23 antagonist
Applicant	Biocon Biologics Inc.
Approved Indication(s)	Adult patients with: • moderate to severe plaque psoriasis (PsO) who are candidates for phototherapy or systemic therapy • active psoriatic arthritis (PsA) • moderately to severely active Crohn's disease (CD) • moderately to severely active ulcerative colitis (UC) Pediatric patients 6 years and older with: • moderate to severe plaque psoriasis, who are candidates for phototherapy or systemic therapy • active psoriatic arthritis (PsA)
Purpose of the Submission	Approval of Yesintek (ustekinumab-kfce) injection as interchangeable with US-Stelara (ustekinumab) as follows per the provisional determination letter for BLA 761406/Original 2 dated November 29, 2024: • Yesintek injection 45 mg/0.5 mL single-dose prefilled syringe for subcutaneous use as interchangeable with US-Stelara injection 45 mg/0.5 mL single-dose prefilled syringe for subcutaneous use • Yesintek injection 45 mg/0.5 mL single-dose vial for subcutaneous use as interchangeable with US-

	Stelara injection 45 mg/0.5 mL single-dose vial for subcutaneous use • Yesintek injection 90 mg/mL single-dose prefilled syringe for subcutaneous use as interchangeable with US-Stelara injection 90 mg/mL single-dose prefilled syringe for subcutaneous use • Yesintek injection 130 mg/26 mL (5 mg/mL) single-dose vial for intravenous use as interchangeable with US-Stelara injection 130 mg/26 mL (5 mg/mL) single-dose vial for intravenous use
Recommendation on Regulatory Action	Approval of the following as interchangeable products: • Approval of Yesintek (ustekinumab-kfce) injection 45 mg/0.5 mL and 90 mg/mL prefilled syringe (PFS) for subcutaneous use • Approval of Yesintek injection 45 mg/0.5 mL single-dose vial for subcutaneous use • Approval of Yesintek (ustekinumab-kfce) injection 130 mg/26 mL (5 mg/mL) single-dose vial for intravenous use

1. Introduction

The subject of this review is the amendment (dated January 15, 2025) to BLA 761406/Original 2 to seek approval for interchangeability of all products under the application that previously received a provisional determination on November 29, 2024.

On November 29, 2023, Biocon Biologics Inc. (hereafter referred to as "the Applicant") submitted a Biologics License Application (BLA) 761406 under section 351(k) of the Public Health Service (PHS) Act seeking licensure of Yesintek (proper name: ustekinumab-kfce; product code: Bmab1200) as a proposed interchangeable biosimilar product to US-Stelara as follows:

- Yesintek injection 45 mg/0.5 mL single-dose prefilled syringe for subcutaneous use as biosimilar to and interchangeable with US-Stelara injection 45 mg/0.5 mL single-dose prefilled syringe for subcutaneous use
- Yesintek injection 45 mg/0.5 mL single-dose vial for subcutaneous use as biosimilar to and interchangeable with US-Stelara injection 45 mg/0.5mL single-dose vial for subcutaneous use
- Yesintek injection 90 mg/mL single-dose prefilled syringe for subcutaneous use as biosimilar to and interchangeable with US-Stelara injection 90 mg/mL single-dose prefilled syringe for subcutaneous use
- Yesintek injection 130 mg/26 mL (5 mg/mL) single-dose vial for intravenous use as biosimilar to and interchangeable with US-Stelara injection 130 mg/26 mL (5 mg/mL) single-dose vial for intravenous use

The data and information in the original BLA supported licensure of Yesintek as a biosimilar product. The Applicant included a scientific justification that Yesintek will produce the same clinical result in any given patient for each condition of use for which licensure is sought and for which US-Stelara has been approved, a scientific justification for extrapolating data and information to support licensure of Yesintek as an interchangeable for each indication for which licensure is sought and for which US-Stelara has been previously approved, and use-related risk analyses and comparative analyses for the PFS platforms. The data and information in the BLA demonstrated that Yesintek can be expected to produce the same clinical result as US-Stelara in any given patient, and that the risk in terms of safety or diminished efficacy of alternating or switching between use of Yesintek and US-Stelara is not greater than the use of US-Stelara without such alternation or switch.

After reviewing the original BLA, FDA did not identify any deficiencies that would justify a complete response action. FDA considered whether any unexpired first interchangeable exclusivity precluded approval of any products in the original application as interchangeable. The Yesintek (ustekinumab-kfce) injection 45 mg/0.5 mL and 90 mg/mL prefilled syringe (PFS) for subcutaneous use, 45 mg/0.5 mL single-dose vial for subcutaneous use, and 130 mg/26 mL (5 mg/mL) single-dose vial for

intravenous use could not be approved as interchangeable due to unexpired first interchangeable exclusivity for Wezlana (ustekinumab-auub) injection 45 mg/0.5 mL and 90 mg/mL for subcutaneous use, and 130 mg/26 mL (5 mg/mL) for intravenous use.

Refer to the Purple Book at https://purplebooksearch.fda.gov for more information about unexpired first interchangeable exclusivity.

BLA 761406 was administratively split to facilitate the following:

- An approval action for BLA 761406/Original 1
    - Yesintek injection 45 mg/0.5 mL single-dose prefilled syringe for subcutaneous use as biosimilar to US-Stelara injection 45 mg/0.5 mL single-dose prefilled syringe for subcutaneous use
    - Yesintek injection 45 mg/0.5 mL single-dose vial for subcutaneous use as biosimilar to US-Stelara injection 45 mg/0.5 mL single-dose vial for subcutaneous use
    - Yesintek injection 90 mg/mL single-dose prefilled syringe for subcutaneous use as biosimilar to US-Stelara injection 90 mg/mL single-dose prefilled syringe for subcutaneous use
    - Yesintek injection 130 mg/26 mL (5 mg/mL) single-dose vial for intravenous use as biosimilar to US-Stelara injection 130 mg/26 mL (5 mg/mL) single-dose vial for intravenous use
- A provisional determination for BLA 761406/Original 2
    - Yesintek injection 45 mg/0.5 mL single-dose prefilled syringe for subcutaneous use would be interchangeable with US-Stelara injection 45 mg/0.5 mL single-dose prefilled syringe for subcutaneous use
    - Yesintek injection 45 mg/0.5 mL single-dose vial for subcutaneous use would be interchangeable with US-Stelara injection 45 mg/0.5 mL single-dose vial for subcutaneous use
    - Yesintek injection 90 mg/mL single-dose prefilled syringe for subcutaneous use would be interchangeable with US-Stelara injection 90 mg/mL single-dose prefilled syringe for subcutaneous use
    - Yesintek injection 130 mg/26 mL (5 mg/mL) single-dose vial for intravenous use would be interchangeable with US-Stelara injection 130 mg/26 mL (5 mg/mL) single-dose vial for intravenous use

The “Biosimilar Multidisciplinary Evaluation and Review” (BMER) documenting the Agency’s review of the original application dated November 27, 2024 is incorporated herein by reference. Refer to the BMER for additional information.

The Original 1 application received an approval letter dated November 29, 2024, and the Original 2 application received a provisional determination letter dated November 29, 2024.

The provisional determination letter instructed the Applicant to submit an amendment no more than six months prior to the date it believed that the application would be eligible

for approval.

To obtain approval of Yesintek (ustekinumab-kfce) injection 45 mg/0.5 mL and 90 mg/mL prefilled syringes for subcutaneous use, 45 mg/0.5 mL single-dose vial for subcutaneous use and 130 mg/26 mL (5 mg/mL) single-dose vial for intravenous use as interchangeable products, the Applicant submitted an amendment, “Request for Approval” on January 15, 2025, which is the subject of this review.

2. Background

Yesintek (proper name: ustekinumab-kfce; product code: BMAB1200) was approved as a biosimilar to US-Stelara (ustekinumab) on November 29, 2024. Refer to the BMER dated November 27, 2024, for background information, including a summary of key regulatory interactions.

3. Product Quality

No new product quality information was submitted nor required for this amendment. There are no product quality issues that would preclude approval of this application. Refer to the BMER dated November 27, 2024. All facilities remain compliant to support approval of this supplement.

The review team considered and determined that there are no new product quality information or updates since the provisional determination letter was issued (November 29, 2024) that would impact the provisional determination of interchangeability. The Applicant also confirmed the same in its request for approval and its April 11, 2025 response to an information request (IR).

4. Clinical and Statistical Evaluation and Recommendations

No new clinical efficacy and safety or statistical information was submitted nor required for this amendment. There are no clinical efficacy and safety or statistical issues that would preclude approval of this application. Refer to the BMER dated November 27, 2024.

The review team considered and determined that there are no new safety information or updates since the provisional determination letter was issued (November 29, 2024) that would impact the provisional determination of interchangeability. The Applicant also confirmed the same in its request for approval and its April 11, 2025 response to an information request (IR).

5. Labeling

Labeling for the original application was reviewed and agreed upon with the Applicant during FDA's review of BLA 761406/Original 1. No changes to the labeling are necessary for the approval of BLA 761406/Original 2. The final labeling will be attached to the approval letter.

The review team determined that there are no new labeling updates since the provisional determination letter was issued (November 29, 2024) that would impact the provisional determination of interchangeability. The Applicant also confirmed the same in its request for approval and its April 11, 2025 response to an IR.

6. Summary Assessment:

The PD letter issued November 29, 2024 states, "In addition to a safety update, the amendment should also identify changes, if any, in the application, i.e., updated labeling; chemistry, manufacturing, and controls data; and risk evaluation and mitigation strategy (REMS)."

In its Request for Approval dated January 15, 2025, the Applicant confirmed that there were no additional changes in the application. An IR was sent to the Applicant on April 9, 2025 to confirm if any changes have occurred to BLA 761406 from FDA's issuance of the PD letter that could impact the provisional determination of interchangeability, specifically addressing the following: safety, labeling changes, chemistry, manufacturing, and controls (CMC) data, and interim supplement approvals or expected supplement approvals.

The review team determined that there are no changes or updates to the application including safety, labeling, and CMC data and interim supplement approvals or expected supplement approvals (when applicable) since the issuance of the PD letter (November 29, 2024) and the expiration of the FIE, April 30, 2025 that would impact the provisional determination of interchangeability. The Applicant confirmed the same in its Request for Approval dated January 15, 2025 and its response to the IR, dated April 11, 2025.

7. Pediatrics

No pediatric studies would be required under PREA for this BLA.

Refer to the BMER dated November 27, 2024 for more information.

8. REMS and Postmarketing Requirements and Commitments

There are no REMS, PMRs, or PMCs associated with this amendment to BLA 761406.

9. Other Regulatory Issues

None.

10. Recommended Regulatory Action

The data and information in BLA 761406, including the information submitted by the Applicant with this amendment, are sufficient to maintain FDA's determination that Yesintek can be expected to produce the same clinical result as US-Stelara in any given patient, and that the risk in terms of safety or diminished efficacy of alternating or switching between use of Yesintek and US-Stelara is not greater than the use of US-Stelara without such alternation or switch. The information submitted by the Applicant, including adequate justification for extrapolation of data and information, demonstrates that:

- Yesintek injection 45 mg/0.5 mL single-dose prefilled syringe for subcutaneous use meets the statutory standards to be interchangeable with US-Stelara injection 45 mg/0.5 mL single-dose prefilled syringe for subcutaneous use
- Yesintek injection 45 mg/0.5 mL single-dose vial for subcutaneous use meets the statutory standards to be interchangeable with US-Stelara injection 45 mg/0.5 mL single-dose vial for subcutaneous use
- Yesintek injection 90 mg/mL single-dose prefilled syringe for subcutaneous use meets the statutory standards to be interchangeable with US-Stelara injection 90 mg/mL single-dose prefilled syringe for subcutaneous use
- Yesintek injection 130 mg/26 mL (5 mg/mL) single-dose vial for intravenous use meets the statutory standards to be interchangeable with US-Stelara injection 130 mg/26 mL (5 mg/mL) single-dose vial for intravenous use

These Yesintek (ustekinumab-kfce) products have met the statutory interchangeability requirements for the following indications for which US-Stelara has been previously approved:

Adult patients with:

- moderate to severe plaque psoriasis (PsO) who are candidates for phototherapy or systemic therapy
- active psoriatic arthritis (PsA)
- moderately to severely active Crohn's disease (CD)
- moderately to severely active ulcerative colitis (UC)

Pediatric patients 6 years and older with:

- moderate to severe plaque psoriasis, who are candidates for phototherapy or systemic therapy
- active psoriatic arthritis (PsA)

As noted in the Purple Book (https://purplebooksearch.fda.gov), the first interchangeable exclusivity expiration date is as follows:

- April 30, 2025 – Wezlana (ustekinumab-auub) injection 45 mg/0.5 mL and 90 mg/mL for subcutaneous use and 130 mg/26 mL (5 mg/mL) for intravenous use.

The recommended regulatory action is approval of the following:

- BLA 761406 Original 2
  - Yesintek injection 45 mg/0.5 mL single-dose prefilled syringe for subcutaneous use is interchangeable with US-Stelara injection 45 mg/0.5 mL single-dose prefilled syringe for subcutaneous use
  - Yesintek injection 45 mg/0.5 mL single-dose vial for subcutaneous use is interchangeable with US-Stelara injection 45 mg/0.5 mL single-dose vial for subcutaneous use
  - Yesintek injection 90 mg/mL single-dose prefilled syringe for subcutaneous use is interchangeable with US-Stelara injection 90 mg/mL single-dose prefilled syringe for subcutaneous use
  - Yesintek injection 130 mg/26 mL (5 mg/mL) single-dose vial for intravenous use is interchangeable with US-Stelara injection 130 mg/26 mL (5 mg/mL) single-dose vial for intravenous use

11. Recommended Comments to the Applicant

None.

12. Division Director or Designated Signatory Comments

I concur with the review team's assessment of the data and information submitted in this amendment and support the regulatory action.

13. Appendices

None.

14. References

None.

This is a representation of an electronic record that was signed electronically. Following this are manifestations of any and all electronic signatures for this electronic record.

/s/

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BIOSIMILAR MULTIDISCIPLINARY EVALUATION AND REVIEW

Application Type	BLA
Application Number	BLA 761406
Received Date	Nov. 29, 2023
BsUFA Goal Date	Nov. 29, 2024
Division/Office	Division of Dermatology and Dentistry (DDD)/Office of Immunology and Inflammation (OII) in collaboration with the Division of Rheumatology and Transplant Medicine (DRTM)/OII and Division of Gastroenterology (DG)/OII
Review Completion Date	See DARRTS stamped date
Product Code Name	Bmab1200
Proposed Nonproprietary Name[1]	ustekinumab- kfce
Proposed Proprietary Name[1]	Yesintek
Pharmacologic Class	IL12/23 Blocker
Applicant	Biocon Biologics Inc.
Applicant Proposed Indication(s)	• moderate to severe plaque psoriasis (PsO) in adult patients and pediatric patients 6 years of age and older who are candidates for phototherapy or systemic therapy; • active psoriatic arthritis (PsA) in adult patients and pediatric patients 6 years of age and older; • moderately to severely active Crohn's disease (CD) in adults; • moderately to severely active ulcerative colitis (UC) in adults
Recommendation on Regulatory Action	Approval of Bmab1200 as biosimilar to US-Stelara. Provisional determination that Bmab1200 is interchangeable with US-Stelara (ustekinumab). Approval for interchangeability is precluded due to unexpired first interchangeable exclusivity for Wezlana.

[1]Section 7 of the Biosimilar Multidisciplinary Evaluation and Review discusses the acceptability of the proposed nonproprietary and proprietary names, which are conditionally accepted until such time that the application is approved.

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Designated Signatory Authority	Tatiana Oussova

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OPDP	Elvy Varghese/James Dvorsky (TL)
OSI	
OSE/DEPI	
OSE/DMEPA	HF Reviewers: Avinash Konkani / Murewa Oguntimein (TL)
OSE/DRISK	

OBP = Office of Biotechnology Products
OPMA = Office of Pharmaceutical Manufacturing Assessment
OPDP = Office of Prescription Drug Promotion
OSI = Office of Scientific Investigations
OSE = Office of Surveillance and Epidemiology
DEPI = Division of Epidemiology
DG = Division of Gastroenterology
DMEPA = Division of Medication Error and Prevention Analysis
DRISK = Division of Risk Management
DPMH = Division of Pediatric and Maternal Health

Glossary

AC	Advisory Committee
ADA	Anti-drug Antibodies
AE	Adverse Event
BLA	Biologics License Application
BMER	Biosimilar Multidisciplinary Evaluation and Review
BMI	Body Mass Index
BPD	Biosimilar Biological Product Development
BsUFA	Biosimilar User Fee Agreements
CDER	Center for Drug Evaluation and Research
CDRH	Center for Devices and Radiological Health
CDTL	Cross-Discipline Team Leader
CFR	Code of Federal Regulations
CI	Confidence Interval
CMC	Chemistry, Manufacturing, and Controls
CRF	Case Report Form
CRO	Contract Research Organization
CRP	C-reactive Protein
CSC	Computational Science Center
CTD	Common Technical Document
CV	Coefficient of Variation
DEPI	Division of Epidemiology
DIA	Division of Inspectional Assessment
DMC	Data Monitoring Committee
DMA	Division of Microbiology Assessment
DMEPA	Division of Medication Error Prevention and Analysis
DPMH	Division of Pediatric and Maternal Health
DRISK	Division of Risk Management
eCTD	Electronic Common Technical Document
EU-Stelara	EU-approved Stelara
FDA	Food and Drug Administration
FISH	Fluorescence In Situ Hybridization
GCP	Good Clinical Practice
GMR	Geometric Mean Ratio
ICH	International Conference on Harmonization
IND	Investigational New Drug
ITT	Intention to Treat
LLOQ	Lower Limit of Quantitation
MAPP	Manual of Policy and Procedure
mITT	Modified Intention to Treat
MOA	Mechanism of Action
NAb	Neutralizing Antibody

NCI-CTCAE	National Cancer Institute – Common Terminology Criteria for Adverse Events
NCT	National Clinical Trial
OBP	Office of Biotechnology Products
OCP	Office of Clinical Pharmacology
OPDP	Office of Prescription Drug Promotion
OSE	Office of Surveillance and Epidemiology
OSI	Office of Scientific Investigations
OSIS	Office of Study Integrity and Surveillance
PD	Pharmacodynamics
PeRC	Pediatric Review Committee
PK	Pharmacokinetics
PMC	Postmarketing Commitments
PMR	Postmarketing Requirements
PREA	Pediatric Research Equity Act
PHS	Public Health Service
PLR	Physician Labeling Rule
PLLR	Pregnancy and Lactation Labeling Rule
REMS	Risk Evaluation and Mitigation Strategies
ROA	Route of Administration
SAE	Serious Adverse Event
SAP	Statistical Analysis Plan
SOC	System Organ Class
SOP	Standard Operating Procedures
TEAE	Treatment-Emergent Adverse Events
ULOQ	Upper Limit of Quantitation
US-Stelara	U.S.-licensed STELARA

Signatures

Discipline and Title or Role	Reviewer Name	Office/Division	Sections Authored/Approved
Nonclinical Reviewer	Renqin Duan	OII/DPTII	4, 13.2
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Nonclinical Supervisor	Barbara Hill	OII/DPTII	4, 13.2
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Biostatistics Team Leader	Somesh Chattopadhyay, Ph.D.	OB/DBVIII	6.1, 6.2
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Clinical Reviewer	Tong Li-Masters, MD	OII/DDD	1, 2, 3, 6.3, 6.4, 6.5, 7, 8, 9, 10, 11, 13.1
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Clinical Team Leader	Snezana Trajkovic, MD		1, 2, 3, 6.3, 6.4, 6.5, 7, 8, 9, 10, 11, 13.1
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Associate Director for Labeling (Optional)			7
	Signature:		
Cross-Discipline Team Leader	Snezana Trajkovic, MD		1, 3, 6.6, 9, 11
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Designated Signatory Authority, DDD Deputy Director for Safety	Tatiana Oussova, MD, MPD	OII/DDD	12
	Signature: Tatiana Oussova -S Digitally signed by Tatiana Oussova -S Date: 2024.11.27 11:34:13 -05'00'		

1. Executive Summary

1.1. Product Introduction

Biocon Biologics Inc. (Biocon; also referred as "the Applicant" in this review) has submitted a biologics license application (BLA) under section 351(k) of the Public Health Service Act (PHS Act) for Bmab1200, a proposed interchangeable biosimilar to US-licensed Stelara (US-Stelara). Bmab1200 is manufactured by recombinant DNA technology and expressed in a murine myeloma (Sp2/0) cell line system.

The Applicant is seeking licensure of Bmab1200 for the same indications approved for US-Stelara:

• Plaque Psoriasis (PsO): Treatment of patients 6 years or older with moderate to severe plaque psoriasis who are candidates for phototherapy or systemic therapy.
• Psoriatic Arthritis (PsA): Treatment of patients 6 years or older with active psoriatic arthritis.
• Crohn's Disease (CD): Treatment of adult patients with moderately to severely active Crohn's disease.
• Ulcerative Colitis (UC): Treatment of adult patients with moderately to severely active ulcerative colitis.

The applicant is seeking licensure for Bmab1200 injection as follows:

- Bmab1200, 45 mg/0.5 mL prefilled syringe (PFS) for subcutaneous use as interchangeable with US-Stelara 45 mg/0.5 mL PFS for subcutaneous use.
- Bmab1200, 45 mg/0.5 mL single-dose vial for subcutaneous use as interchangeable with US-Stelara 45 mg/0.5 mL single-dose vial for subcutaneous use.
- Bmab1200, 90 mg/mL PFS for subcutaneous use as interchangeable with US-Stelara 90 mg/mL PFS for subcutaneous use.
- Bmab1200, 130 mg/26 mL single-dose vial for intravenous (IV) use as interchangeable with US-Stelara 130 mg/26 mL single-dose vial for IV use.

The strengths, dosage form and routes of administration of Bmab1200 will be the same as those approved for US-Stelara.

Although the Division of Dermatology and Dentistry (DDD) is the lead division for this application and provided the written clinical review, clinical input pertaining to the indication of psoriatic arthritis was obtained from the Division of Rheumatology and Transplant Medicine (DRTM), and clinical input pertaining to the indications of Crohn's disease (CD) and ulcerative colitis was obtained from the Division of Gastroenterology (DG) during the course of the review.

1.2. Determination Under Section 351(k)(2)(A)(ii) of the Public Health Service (PHS) Act

Not applicable.

1.3. Mechanism of Action, Route of Administration, Dosage Form, Strength, and Conditions of Use Assessment

Bmab1200 is a recombinant, fully human immunoglobulin G, subclass 1, κ light chain (IgG1κ) monoclonal antibody (mAb) that that belongs to the pharmacologic class of Interleukin-23 (IL-23) and Interleukin-12 (IL-12) antagonists. It binds to the p40 subunit of interleukin IL-12 and IL-23. Binding of the antigen binding fragment (Fab) domain to the p40 protein subunit of both IL-12 and IL-23 inhibits the cytokines from binding to IL-12 and IL-23 receptor complexes on the surface of natural killer (NK) cells or T cells, thereby preventing initiation of downstream immune-response signaling pathways. IL-12 and IL-23 are heterodimeric cytokines secreted by activated antigen presenting cells, such as macrophages and dendritic cells, and both cytokines are involved in inflammatory and immune responses. Among other biological activities, IL-12 activates NK cells to produce and release the interferon gamma (IFN-γ) cytokine and drives CD4+ T cell differentiation toward the T helper 1 (Th1) phenotype; IL-23 induces the T helper 17 (Th17) pathway which are both central to the pathology of certain immune mediated diseases. Bmab1200 has the same mechanism(s) of action as that of US-Stelara.

Bmab-1200 product is a sterile liquid solution available in a sterile, single dose, preservative-free solution. Bmab1200 injection is proposed as below:

For subcutaneous injection:
• 45 mg/0.5 mL in a PFS
• 90 mg/mL in a PFS
• 45 mg/0.5 mL in a single-dose vial

For IV infusion:
• 130 mg/26 mL (5 mg/mL) in a single-dose vial

Bmab1200, 45 mg/0.5 mL PFS for subcutaneous use has the same strength, dosage form, and route of administration as US-Stelara, 45mg/0.5 mL PFS for subcutaneous use. Bmab1200, 90 mg/mL PFS for subcutaneous use has the same strength, dosage form, and route of administration as US-Stelara 90 mg/mL PFS for subcutaneous use. Bmab1200, 45 mg/0.5 mL single-dose vial for subcutaneous use has the same strength, dosage form, and route of administration as US-Stelara 45 mg/0.5 mL single-dose vial for subcutaneous use. Bmab1200, 130 mg/26 mL single-dose vial for intravenous (IV) use has the same strength, dosage form, and route of administration as US-Stelara 130 mg/26 mL single-dose vial for IV use. The Bmab1200 45 mg/0.5 mL and 90 mg/mL PFS support the dosing regimens for the proposed indications of adults with PsO and PsA,

and the dosing regimens for the pediatric indications of children 6 years and older with PsO and PsA for patients with body weight (BW) ≥60 kg, and the indications of Crohn's disease and ulcerative colitis for maintenance dosing. The Bmab1200 single dose vial containing 45 mg/0.5 mL supports the dosing regimens for the proposed indications of adults with PsO and PsA, and the dosing regimens for the pediatric indications of children 6 years and older with PsO and PsA for patients with BW <60 kg, and the indications of Crohn's disease and ulcerative colitis for maintenance dosing. The single dose vial containing 130 mg/26 mL (5 mg/mL) supports the indications of Crohn's disease and ulcerative colitis for IV induction.

With respect to Bmab1200, 45 mg/0.5 mL PFS for subcutaneous use, the applicant is seeking licensure as an interchangeable biosimilar for conditions of use that have been previously approved for US-Stelara, 45 mg/0.5 mL PFS for subcutaneous use. With respect to Bmab1200, 90 mg/mL PFS for subcutaneous use, the applicant is seeking licensure as an interchangeable biosimilar for conditions of use that have been previously approved for US-Stelara 90 mg/mL PFS for subcutaneous use. With respect to Bmab1200, 45 mg/0.5 mL single-dose vial for subcutaneous use, the applicant is seeking licensure as an interchangeable biosimilar for conditions of use that have been previously approved for US-Stelara 45 mg/0.5 mL single-dose vial for subcutaneous use. With respect to Bmab1200, 130 mg/26 mL single-dose vial for IV use, the applicant is seeking licensure as an interchangeable biosimilar for conditions of use that have been previously approved for US-Stelara 130 mg/26 mL single-dose vial for IV use.

1.4. Inspection of Manufacturing Facilities

Adequate descriptions of the facilities, equipment, environmental controls, cleaning and contamination control strategy were provided for Biocon Biologics India Limited (FEI 3003981475), proposed for Yesintek (ustekinumab-kfce) drug substance and drug product manufacture. A cGMP and pre-license inspection was performed as a for cause and in support of this BLA from July 15-26, 2024. At the conclusion of the inspection a 10-item FDA Form 483 was issued with a field recommendation of OAI (Official Action Indicated) and a withhold for BLA 761406. At the time of facility review dated 8/10/2024, the compliance status of Biocon Biologics India Limited was not acceptable and a withhold recommendation was initially made for BLA 761406. However, Compliance review by Office of Manufacturing Quality (OMQ) in Office of Compliance (OC) concluded that applicant's responses to 483 were satisfactory and thus, downgraded the facility status from OAI status to VAI (Voluntary Action Indicated) on 11/8/2024. All proposed manufacturing and testing facilities are acceptable based on their current CGMP compliance status and recent relevant inspectional coverage.

1.5. Scientific Justification for Use of a Non-U.S.-Licensed Comparator Product

The Applicant provided adequate data to establish the scientific bridge to justify the relevance of data generated from the comparative clinical study BM12H-PSO-03-G-02, which used EU-Stelara as the comparator, to the assessment of biosimilarity:

- The Office of Pharmaceutical Products (OPQ), CDER has determined, and I agree, that based on the data provided by the Applicant, the analytical component of the scientific bridge between Bmab1200, EU-Stelara, and US-Stelara was established.

- The Office of Clinical Pharmacology (OCP) has determined, and I agree, that based on the data provided by the Applicant, the PK data establish the PK component of the scientific bridge.

1.6. Biosimilarity and Interchangeability Assessment

Table 1. Summary and Assessment of Biosimilarity and Interchangeability

Comparative Analytical Studies[2]	
Summary of Evidence	• Bmab1200 is highly similar to US-Stelara notwithstanding minor differences in clinically inactive components. • Bmab1200 prefilled syringe and single-dose vial for SC injection and single-dose vial for IV infusion have the same strengths as that of US-Stelara. • The strengths, dosage form, and route of administration are the same as those of US-Stelara. • The analytical component of the scientific bridge between Bmab1200, US-Stelara, and EU-Stelara was established to support the relevance of the data generated from studies using EU-Stelara as the comparator to the assessment of biosimilarity.
Assessment of Residual Uncertainties	• There are no residual uncertainties from the product quality assessment.

[2]Refer to the Product Quality Review, including the Comparative Analytical Assessment (CAA) Chapter therein for additional information regarding comparative analytical studies.

Animal/Nonclinical Studies	
Summary of Evidence	• The information in the pharmacology/toxicology assessment supports the demonstration of biosimilarity.
Assessment of Residual Uncertainties	• There are no residual uncertainties from the pharmacology/toxicology assessment.
Clinical Studies	
Clinical Pharmacology Studies	
Summary of Evidence	• A PK similarity study (BM12H-NHV-01-G-01) evaluated PK similarity between Bmab1200, EU-Stelara and US-licensed Stelara in healthy subjects. • PK similarity has been demonstrated between Bmab1200 and US-licensed Stelara and supports a demonstration of no clinically meaningful differences between Bmab1200 and US-licensed Stelara. • PK similarity between Bmab-1200, EU-Stelara and US-licensed Stelara supports the PK component of the scientific bridge to support the relevance of comparative clinical similarity data generated using EU-Stelara to the assessment of biosimilarity. • In Study BM12H-NHV-01-G-01 in healthy subjects, the overall frequency of ADAs and NAbs was slightly higher in the US-Stelara and EU-Stelara groups as compared to the Bmab1200 group. These differences were not considered to be clinically significant. • In comparative clinical study (BM12H-PSO-03-G-02) in patients with PsO, the overall frequency of ADAs was slightly higher in the EU-Stelara group compared to the Bmab1200 group. The slight differences in ADA were not considered to be clinically significant. The overall frequency of NAbs were generally comparable between the two treatment arms, and the single transition from EU-Stelara to Bmab1200 did not result in a change in immunogenicity.

Assessment of Residual Uncertainties	• There are no residual uncertainties from a clinical pharmacology perspective based on the available clinical PK and immunogenicity data.
Additional Clinical Studies	
Summary of Evidence	• In Study BM12H-PSO-03-G-02, there were no meaningful differences in terms of efficacy between Bmab1200 and EU-Stelara. The frequency of treatment-emergent adverse events, serious events, and events leading to discontinuation of the study drug had no meaningful differences between the treatment arms. • Given that the scientific bridge was established (based on the analytical and PK comparisons) between Bmab1200, US-Stelara, and EU-Stelara to justify the relevance of the data generated with EU-Stelara as the comparator, the collective evidence from submitted clinical studies, including the comparative clinical study BM12H-PSO-03-G-02, supports a demonstration of no clinically meaningful differences between Bmab1200 and US-Stelara.
Assessment of Residual Uncertainties	• There are no residual uncertainties from a clinical or statistical perspective.
Switching Study	
Summary of Evidence	• FDA determined that a switching study is not necessary to support a demonstration of interchangeability for Bmab1200. • The Applicant has provided adequate data and information to support a demonstration that the risk in terms of safety or diminished efficacy of alternating or switching between use of Bmab1200 and US-Stelara is not greater than the risk of using US-Stelara without such alternation or switch.
Assessment of Residual Uncertainties	• There are no residual uncertainties from the clinical perspective.
Any Given Patient Evaluation	

Summary of Evidence	• The analytical data and clinical data support a demonstration that Bmab1200 can be expected to produce the same clinical result as that of US-Stelara in any given patient. The Applicant has provided adequate data and information to support a demonstration that Bmab1200 can be expected to produce the same clinical result as that of US-Stelara in any given patient.
Assessment of Residual Uncertainties	• There are no residual uncertainties from the clinical perspective.
Extrapolation	
Summary of Evidence	• DDD, DG, and DRTM teams have determined that the Applicant has provided adequate scientific justification (based on mechanism of action, PK, immunogenicity, and toxicity) to support extrapolation of data and information, including clinical data from the studied population (PsO), to support licensure of Bmab1200 as an interchangeable biosimilar, under section 351(k) of the PHS Act, for the following indications for which US-licensed Stelara has previously been approved: • Plaque Psoriasis (PsO): Treatment of patients 6 years or older with moderate to severe plaque psoriasis who are candidates for phototherapy or systemic therapy. • Psoriatic Arthritis (PsA): Treatment of patients 6 years or older with active psoriatic arthritis. • Crohn's Disease (CD): Treatment of adult patients with moderately to severely active Crohn's disease. • Ulcerative Colitis (UC): Treatment of adult patients with moderately to severely active ulcerative colitis.
Assessment of Residual Uncertainties	• There are no residual uncertainties regarding the extrapolation of data and information to support licensure of Bmab1200 as an interchangeable biosimilar to US-Stelara for the above indications.

1.7. Conclusions on Approvability

In considering the totality of the evidence submitted, the data submitted by the Applicant demonstrate that Bmab1200 is highly similar to U.S.-licensed Stelara, notwithstanding minor differences in clinically inactive components, and that there are no clinically meaningful differences between Bmab1200 and U.S.-licensed Stelara in terms of the safety, purity, and potency of the product. The data and information provided by the Applicant are sufficient to demonstrate that Bmab1200 can be expected to produce the same clinical result as the U.S.-licensed Stelara in any given patient and that the risk in terms of safety or diminished efficacy of alternating or switching between use of Bmab1200 and U.S.-licensed Stelara is not greater than the risk of using U.S.-licensed Stelara without such alternation or switch. The information submitted by the Applicant, including adequate justification for extrapolation of data and information, demonstrates that Bmab1200 is biosimilar to U.S.-licensed Stelara and supports a provisional determination under section 351(k)(4) of the Public Health Service (PHS) Act that Bmab1200 is interchangeable with U.S.-licensed Stelara as follows:

- Bmab1200, 45 mg/0.5 mL PFS for subcutaneous use is an interchangeable biosimilar with US-Stelara 45 mg/0.5 mL PFS for subcutaneous use,
- Bmab1200, 45 mg/0.5 mL single-dose vial for subcutaneous use is an interchangeable biosimilar with US-Stelara 45 mg/0.5 mL single-dose vial for subcutaneous use,
- Bmab1200, 90 mg/mL PFS for subcutaneous use is an interchangeable biosimilar with US-Stelara 90 mg/mL PFS for subcutaneous use, and
- Bmab1200, 130 mg/26 mL single-dose vial for intravenous (IV) use is interchangeable biosimilar with US-Stelara 130 mg/26 mL single-dose vial for IV use

for each of the following indications for which U.S.-licensed Stelara has been previously approved and for which the Applicant is seeking licensure of Bmab1200:

• Plaque Psoriasis (PsO): Treatment of patients 6 years or older with moderate to severe plaque psoriasis who are candidates for phototherapy or systemic therapy.
• Psoriatic Arthritis (PsA): Treatment of patients 6 years or older with active psoriatic arthritis.
• Crohn’s Disease (CD): Treatment of adult patients with moderately to severely active Crohn’s disease.
• Ulcerative Colitis (UC): Treatment of adult patients with moderately to severely active ulcerative colitis.

At this time, FDA is unable to approve Bmab1200 injection 45 mg/0.5 mL PFS for subcutaneous use as interchangeable with US-Stelara injection 45 mg/0.5 mL PFS for subcutaneous use, Bmab1200 injection 45 mg/0.5 mL single-dose vial for subcutaneous use as interchangeable with US-Stelara injection 45 mg/0.5 mL single-dose vial for subcutaneous use, Bmab1200 injection 90 mg/mL PFS for subcutaneous use as interchangeable with US-Stelara injection 90 mg/mL PFS for subcutaneous use, or

Bmab1200 injection 130 mg/26 mL single-dose vial for intravenous use as interchangeable with US-Stelara injection 130 mg/26 mL single-dose vial for intravenous use, because of unexpired First Interchangeable Exclusivity (FIE) for BLAs 761285/761331 for Wezlana (ustekinumab-auub) 45 mg/0.5 mL injection for subcutaneous use, 90 mg/mL injection for subcutaneous use, and 130 mg/26 mL injection for intravenous use (hereinafter "the Wezlana products"). FDA has previously determined that FIE for the Wezlana products will expire on April 30, 2025.[3] Biocon is expected to submit an amendment seeking approval of its Bmab1200 45 mg/0.5 mL injection for subcutaneous use, Bmab1200 90mg/mL injection for subcutaneous use, and 130 mg/26 mL injection for intravenous use products as interchangeable no more than six months prior to the expiration of FIE for the Wezlana products.

Therefore, the FDA review team recommended that BLA 761406 be administratively split to facilitate an approval action for Bmab1200 as a biosimilar product and a provisional determination that Bmab1200 is an interchangeable biosimilar product, as described above.

FDA received a Citizen Petition[4] requesting that "FDA refuse to license any biosimilar version of Ustekinumab as interchangeable with the brand-name reference product that is manufactured using a Chinese hamster ovary ("CHO") cell-line system—and in particular Ustekinumab-ttwe—unless and until the Agency has evaluated and concluded that the differences in sialyation between the proposed interchangeable biosimilar and the reference product, Stelara (ustekinumab), do not have the potential to adversely affect half-life and clinical effectiveness—particularly with respect to therapeutic response durability."[5] The products proposed in this application are not manufactured using a CHO cell-line system and therefore this application is not implicated by the Citizen Petition.

The CDTL and Division Signatory agree with the above assessment and recommendation.

Author:
Tong Li-Masters, MD PhD
Clinical Reviewer
Snezana Trajkovic, MD
CDTL

[3] https://purplebooksearch.fda.gov/
[4] See Docket FDA-2024-P-4538 available at https://www.regulations.gov/docket/FDA-2024-P-4538.
[5] See Citizen Petition from Alvotech USA Inc. dated September 24, 2024 available at https://www.regulations.gov/document/FDA-2024-P-4538-0001.

2. Introduction and Regulatory Background

2.1. Summary of Presubmission Regulatory History Related to Submission

The Division of Dermatology and Dentistry (DDD) had several interactions with the Applicant during the development of Bmab1200. Key discussions are detailed below:

- A Biosimilar Biological Product Development (BPD) Type 2 meeting was held on April 26, 2021, focused on the overall development plan for Bmab1200 and analytical data needed to support the development of Bmab1200 as a proposed biosimilar to US-licensed Stelara. The Agency provided comments on the study designs for the proposed PK bioequivalence and immunogenicity study (BM12H-NHV-01-G-01) and comparative clinical study (BM12H-PSO-03-G-02). The Agency recommended to include EU-approved Stelara as a third 346 arm in the proposed PK similarity study with Bmab1200 and US-licensed Stelara. For the comparative clinical study (BM12H-PSO-03-G-02), the Agency recommended to re-randomize subjects at Week 16 instead of at Week 28, and be conducted with a ratio of 1:1, instead of the proposed (b) (4), as equal randomization allocation would lead to a larger sample size for subjects transitioning from EU-approved Stelara to Bmab1200, which would allow for detecting differences in immunogenicity and safety in this population. The Agency also provided comments on Human Factors Considerations for Biosimilarity and Interchangeability.

- The IND was opened with Protocol BM12H-NHV-01-G-01 (PK similarity study between Bmab1200, US-licensed Stelara, and EU-approved Stelara) on January 31, 2022.

- At a Biosimilar Biological Product Development (BPD) Type 2 meeting held October 6, 2021, the Agency considered the proposed modified study designs for the proposed PK similarity and immunogenicity study (BM12H-NHV-01-G-01) and comparative clinical study (BM12H-PSO-03-G-02) to be reasonable. (b) (4)

(b) (4)

- An iPSP agreement letter was sent to the Applicant on June 12, 2023.

(b) (4)

- On September 1, 2023, the FDA sent an advice/information request letter to the Applicant sharing its updated scientific thinking that a switching study would

generally be considered unnecessary to support a demonstration of interchangeability for proposed ustekinumab interchangeable biosimilar products.

- At a BPD Type 4 meeting on October 26, 2023, the format and content of a complete application for an original biosimilar biological product application under the Program submitted under 351(k) of the PHS Act was discussed.

2.2. Studies Submitted by the Applicant

Refer to the Product Quality review, including the Comparative Analytical Assessment [6](CAA) Chapter for information regarding comparative analytical studies provided to support a demonstration of biosimilarity.

Table 2. BAT2206 Clinical Studies Submitted

Study Identity	National Clinical Trial (NCT) no.		Study Objective	Study Design	Study Population	Treatment Groups
	PK Similarity Study					
BM12H-NHV-01-G-01			Primary Objective: To establish PK similarity between Bmab1200 and US-Stelara, Bmab1200 and EU-Stelara, and EU-Stelara and US-Stelara after single 45 mg SC injection in healthy subjects. Primary Endpoint: AUC0-inf and Cmax of study drugs following a single 45 mg SC injection.	Randomized, double-blind, 3-arm, parallel design study	Healthy Subjects	Bmab1200, US-Stelara and EU-Stelara

[6]

		Comparative Clinical Study(ies)				
BM12H-PSO-03-G-02			Primary Objective: To demonstrate equivalent efficacy between Bmab1200 and EU-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).	Randomized, double blind, active-controlled, parallel group, multicenter study	Adult subjects with moderate to severe chronic plaque psoriasis.	Bmab1200 and EU-Stelara

Source: Clinical Overview Table 1.

Authors:

Tong Li-Masters, MD, PhD
Clinical Reviewer

Snezana Trajkovic, MD
Clinical Team Leader

3. Summary of Conclusions of Other Review Disciplines

3.1. Office of Pharmaceutical Quality (OPQ)

OPQ is recommending approval of BLA 761406 for Bmab1200 manufactured by Biocon. The data submitted in this application are adequate to support a conclusion that the manufacture of Bmab1200 is well-controlled and will lead to a product that is pure and potent.

The data and information provided in the application supports that Bmab1200 is highly similar to US-Stelara, notwithstanding minor differences in clinically inactive components. The Applicant adequately established a three-way scientific bridge between Bmab1200, US-Stelara, and EU-Stelara to support the relevance of the data generated from clinical studies using EU-Stelara as the comparator to the assessment of biosimilarity. The strengths of Bmab1200 45 mg/0.5 mL PFS and 90 mg/mL PFS and 45 mg/0.5 mL vial for SC and 130 mg/ 26mL in single-dose vial for IV are the same as the corresponding strengths of US-Stelara.
Refer to the Executive Summary uploaded in DARRTS on November 19, 2024 for additional details.

3.2. Devices

Bmab1200 injection is a sterile liquid solution with the following proposed strengths in a prefilled syringe (PFS):
• Injection: 45 mg/0.5 mL in a single-dose prefilled syringe
• Injection: 90 mg/mL in a single-dose prefilled syringe

The Bmab1200 PFS container closure system consists of a 1 mL (b) (4) glass syringes containing a 29G½ inch staked needle and rigid needle shield. They are stoppered using (b) (4) plunger stopper.

3.2.1. Center for Devices and Radiological Health (CDRH)

Based on assessment of device constituent parts of the combination product, CDRH recommends approval.

3.2.2. Division of Medication Error Prevention and Analysis (DMEPA)

DMEPA's review of the use-related risk analysis and comparative analyses did not identify any new, differing, or unique risks for the proposed product Bmab1200 PFS as compared to US-licensed Stelara PFS. As such, no further information, or data (e.g., data from a CUHF study) is needed to support this marketing application for Bmab1200, a proposed interchangeable biosimilar to US-licensed Stelara. DMEPA has no HF recommendations for this marketing application.

3.3. Office of Study Integrity and Surveillance (OSIS)

The Division requested that the Office of Study Integrity and Surveillance (OSIS) conduct clinical site inspections at the sites in Table 3. OSIS had the following comments:

Site 01 - At the conclusion of the inspection, investigator Matthew C. Watson did not issue Form FDA 483 to the clinical site. However, there was one discussion item addressed at the inspection close out. Investigator concluded that this discussion item has no impact on data integrity or subject safety.

Site 02 - At the conclusion of the inspection, investigator Matthew C. Watson did not issue Form FDA 483 to the clinical site. However, there was one discussion item addressed at the inspection close out. Investigator concluded that this discussion item has no impact on data reliability.

Site 03 - The Office of Study Integrity and Surveillance (OSIS) determined that an inspection is not needed for the site because OSIS conducted an inspection for the analytical site in (b) (4).

Table 3. Inspection Sites

(Name, Address, Phone number, email, fax#)	Site #	Protocol ID	Purpose	Date of OSIS Review	Date of Previous Inspection	Comments/ Conclusion
Fortrea Clinical Research Unit Ltd. Drapers Yard, Marshall Street, Holbeck Leeds, LS11 9EH, West Yorkshire, UK	01	BM12H-NHV-01-G-01	Clinical; routine inspection	September, 2024	N/A	See text.
Medicines Evaluation Unit Ltd. The Langley Building, Southmoor Road, Wythenshawe, Manchester, M23 9QZ Greater Manchester, UK	02	BM12H-NHV-01-G-01	Clinical; routine inspection	August, 2024	N/A	See text.
(b) (4)	03		Analytical; routine inspection	N/A	(b) (4)	See text.

Refer to memos uploaded in DARRTS on 10/23/2024 and 11/3/2024 for additional details.

3.4. Office of Scientific Investigations (OSI)

An OSI audit was initially requested for Study BM12H-PSO-03-G-02 (Kalowska, Monika Kosiarzy 9a WARSZAWA, N/A 02-953 POL and Daniluk, Stefan Stoleczna Str. 7/200 BIALYSTOK, PODLASKIE 15-879 POL) but later canceled because the two sites that were originally selected for inspection were recently inspected and no problems were found. Because there were no other outliers in evaluation of efficacy and safety and after discussions between the Office of Scientific Investigations (OSI) and the Division of Dermatology and Dentistry were held, it was decided that OSI would not perform clinical inspections for this application.

Author:

Tong Li-Masters, MD, PhD
Clinical Reviewer

Snezana Trajkovic, MD
Clinical Team Leader

4. Nonclinical Pharmacology and Toxicology Evaluation and Recommendations

4.1. Nonclinical Executive Summary and Recommendation

No nonclinical animal studies with Bmab1200 were requested or submitted. In the absence of specific pharmacokinetic, physicochemical, or other identifiable concerns, in vivo assays are not anticipated to provide additional meaningful information to inform the evaluation of toxicity. Animal studies with Bmab1200 are not required to support this 351(k) application. There were no nonclinical safety concerns with excipients or impurities contained in Bmab1200.

This BLA is approvable from a Pharmacology/Toxicology perspective. There is no recommended nonclinical PMC/PMR for this BLA.

4.1.1. Nonclinical Residual Uncertainties Assessment

There were no nonclinical residual uncertainties.

4.2. Product Information

Product Formulation

The quantitative and qualitative composition of the Bmab1200 45 mg/0.5 mL pre-filled syringe (PFS) and 90 mg/mL PFS along with quality standards as well as function of the components are provided in the table below.

Table 4. Composition of the Bmab1200 SC Drug Product in Prefilled Syringe

Ingredients	45 mg/0.5 mL PFS	90 mg/mL PFS	Quality Standard	Function
	Quantity in 0.5 mL[a] (mg)	Quantity in 1.0 mL[a] (mg)		
Ustekinumab	45	90	In-house specification	Active ingredient/Drug Substance
(b) (4) Histidine		(b) (4)	Ph. Eur./USP-NF	(b) (4)
L-Histidine hydrochloride monohydrate			Ph. Eur.	
Sucrose	38.0	76.0	USP-NF	
Polysorbate 80	0.02	0.04	Ph. Eur./USP-NF	
				(b) (4)
(b) (4) Hydrochloric acid	q.s. to adjust the pH to 6.0±0.3		Ph. Eur./USP-NF	For pH adjustment
Sodium Hydroxide	q.s. to adjust the pH to 6.0±0.3		Ph. Eur./USP-NF	For pH adjustment
				(b) (4)

[a] 45 mg/0.5 mL and 90 mg/mL PFS are filled to a volume (b) (4)

(b) (4)

Source: BLA 761406, Section 2.3.P Drug Product

Bmab1200 drug product composition is the same for 45 mg/0.5 mL vial and 45 mg/0.5 mL PFS presentation.

The quantitative and qualitative composition of the Bmab1200 IV 130 mg/26 mL vial along with quality standards as well as function of the components are provided in the table below.

Table 5. Composition of the Bmab1200 IV Drug Product in Vial

Ingredients	Quantity in 26 mL[a] (mg)	Quantity in mg/mL	Quality Standard	Function
Ustekinumab	130	5	In-house specification	Active ingredient/ Drug Substance
(b) (4) Histidine	20	0.77	Ph. Eur./USP-NF	(b) (4)
L-Histidine hydrochloride monohydrate	27	1.04	Ph. Eur	
L- Methionine	10.4	0.4	Ph.Eur./USP	
EDTA disodium salt dihydrate	(b) (4)		Ph.Eur./USP	
Sucrose	2210	85	USP-NF	
Polysorbate 80	10.4	0.4	Ph. Eur./USP-NF	(b) (4)
(b) (4) Hydrochloric acid	q.s. to adjust the pH to 6.0±0.3		Ph. Eur./USP-NF	For pH adjustment
Sodium Hydroxide	q.s. to adjust the pH to 6.0±0.3		Ph. Eur./USP-NF	For pH adjustment (b) (4)
[a] 130mg/26 mL is filled to a volume (b) (4)				(b) (4)

Source: BLA 761406, Section 2.3.P Drug Product

Comments on Excipients

The excipients in the Bmab1200 are the same and present in the same or similar levels as the excipients in US-Stelara. There are no concerns for the excipients at the proposed levels.

Comments on Impurities of Concern

There are no concerns for potential impurities contained in Bmab1200.

The extractable/leachable studies were conducted with the container closure systems for the Bmab1200 drug substance (b) (4) and Bmab1200 drug product (prefilled syringe and glass vial). No extractables or leachables were identified at a sufficient level to be of toxicological concern. There were no nonclinical safety concerns with the maximum exposures of potential leachables from the container closure systems for the Bmab1200 drug substance (b) (4) and drug product (prefilled syringe and glass vial).

Authors:

Renqin Duan, PhD
Nonclinical Reviewer

Barbara Hill, PhD
Nonclinical Supervisor

5. Clinical Pharmacology Evaluation and Recommendations

5.1. Clinical Pharmacology Executive Summary and Recommendation

Table 6. Clinical Pharmacology Major Review Issues and Recommendations

Review Issue	Recommendations and Comments
Pharmacokinetics	A PK similarity study (BM12H-NHV-01-G-01) evaluated PK similarity between Bmab1200, EU-Stelara and US-licensed Stelara in healthy subjects. PK similarity has been demonstrated between Bmab1200 and US-licensed Stelara and supports a demonstration of no clinically meaningful differences between Bmab1200 and US-licensed Stelara. PK similarity between Bmab1200, EU-Stelara and US-licensed Stelara supports the PK component of the scientific bridge to support the relevance of comparative clinical similarity data generated using EU-Stelara to the assessment of biosimilarity.
Pharmacodynamics	Not applicable
Immunogenicity	In Study BM12H-NHV-01-G-01 in healthy subjects, the overall frequency of ADAs and NAbs was slightly higher in the US-Stelara and EU-Stelara groups as compared to the Bmab1200 group. These differences were not considered to be clinically significant. In comparative clinical study (BM12H-PSO-03-G-02) in patients with PsO, the overall frequency of ADAs was slightly higher in the EU-Stelara group compared to the Bmab1200 group. The slight differences in ADA were not considered to be clinically significant. The overall frequency of NAbs were generally comparable between the two treatment arms, and the single transition from EU-Stelara to Bmab1200 did not result in a change in immunogenicity.

Other (specify)	Not applicable

The clinical development program comprised of two studies (BM12H-NHV-01-G-01 and BM12H-PSO-03-G-02).

> PK similarity study - BM12H-NHV-01-G-01: was a randomized, double blind, 3-arm, parallel design, single dose study in health volunteers to establish PK similarity between Bmab1200 and US--Stelara, Bmab1200 and EU-Stelara, and EU-Stelara and US-Stelara after single 45 mg subcutaneous Injection.
>
> Comparative clinical study - BM12H-PSO-03-G-02: was a randomized, double-blind, active controlled, parallel group, multicenter, multi dose study in patients with moderate to severe chronic plaque psoriasis to demonstrate equivalent efficacy between Bmab1200 and EU-Stelara along with the establishment of safety, tolerability, immunogenicity, and PK of Bmab1200 and EU-Stelara.

The clinical pharmacology review for this BLA primarily focused on the PK similarity study (Study BM12H-NHV-01-G-01) and additional PK and immunogenicity data from the comparative clinical study (Study BM12H-PSO-03-G-02). See Section 6 for results of efficacy and safety.

The three-way PK similarity between Bmab-1200, US-Stelara and EU-Stelara established in the PK similarity study (BM12H-NHV-01-G-01) (Table 7) provides the PK component of the scientific bridge to support the relevance of comparative clinical data generated using EU-Stelara in the comparative clinical study (BM12H-PSO-03-G-02).

The three way PK similarity between Bmab1200, US-Stelara and EU-Stelara was established in the PK similarity study (BM12H-NHV-01-G-01) by using a prespecified criteria of 80 to 125% for the 90% confidence interval (CI) of the least square (LS) geometric means ratios (LS GMRs) for area under the serum drug concentration-time curve (AUC) from time zero to infinity (AUC0-inf)and maximum observed drug concentration (Cmax). The Applicant also calculated the 90% CI for AUC from time zero to the last quantifiable concentration (AUC0-last).

The results indicated that the 90% confidence intervals (CIs) for the geometric mean ratios (GMRs) of Bmab1200 to US-Stelara, Bmab1200 to EU-Stelara, and EU-Stelara to US-Stelara were contained within the prespecified margin of 0.8 to 1.25 for $AUC_{0\text{-inf}}$, C_{max} and AUC_{last} (Table 7).

The results of the PK similarity study demonstrated that PK similarity was established between Bmab1200, US-Stelara and EU-Stelara. The PK similarity study also supported the relevance of use of EU-Stelara in the comparative clinical study (BM12H-PSO-03-G-02).

Table 7. Summary of statistical analyses for assessment of PK similarity (Study BM12H-NHV-01-G-01)

Parameter	Geometric Mean (%CV)			Geometric Mean Ratio* (90% CI)		
	Bmab1200 (n=96)	US-Stelara (n=94)	EU-Stelara (n=97)	Bmab1200 / US-Stelara	Bmab1200 / EU-Stelara	EU-Stelara / US-Stelara
Primary						
$AUC_{0\text{-}inf}$ (h·ng/mL)	192504.40	175945.98	174191.40	109.41 (100.34 - 119.30)	110.51 (101.33 120.53)	99.00 (90.78 - 107.98)
C_{max} (ng/mL)	4459.45	4318.01	4473.14	103.28 (96.16 - 110.91)	99.69 (92.79- 107.11)	103.59 (96.44 - 111.28)
Secondary						
AUC_{last} (h·ng/mL)	183696.45	170171.10	167356.65	107.95 (99.42- 117.21)	106.76 (101.04- 119.24)	98.35 (90.55- 106.81)

*Presented as percent. Source: FDA reviewer analysis

In Study BM12H-NHV-01-G-01, the ADA incidence and nAb incidence in the Bmab1200 treatment group was lower as compared to EU-Stelara and US-Stelara. At baseline, 10.5%, 2.3%, and 5.9% of subjects were ADA+ in the Bmab1200, the US Stelara, and the EU Stelara groups, respectively. Post-treatment, the number of ADA+ subjects increased over time to 44.2% (Day 85), 73.6% (Day 57), and 67.1% (Days 57 and 85) in the Bmab1200, the US-Stelara, and the EUStelara groups, respectively. There was no clinically meaningful impact of immunogenicity on the PK and safety of the study drugs. Furthermore, no meaningful differences were noted in the safety profile based on ADA positivity rate. Overall, it is concluded that the observed differences in the ADA and ADA titer levels are not considered to be clinically significant, and the results support a conclusion of no clinically meaningful differences between Bmab1200 and US-Stelara.

In Study BM12H-PSO-03-G-02, after multiple SC doses, the higher mean ADA titer in the Bmab1200 group compared to the EU-Stelara and the US-Stelara group was majorly attributed to high titers in 2 subjects (Subjects (b) (6)); subject (b) (6) had titers up to 389000 by Day 85 and subject (b) (6) had titers up to 24400 by Day 85. However, these high titers showed a declining trend in the ADA titer values and were not associated with any major safety concerns. Overall, similar median ADA titers were observed across the 3 treatment groups over time. reported. There were no apparent treatment-related differences in the impact of ADA/NAb-positive status on serum concentrations.

The single transition from EU-Stelara to Bmab1200 did not result in a change in immunogenicity; the treatment-emergent ADA incidence was comparable across the Bmab1200/ Bmab1200, EU-Stelara/ Bmab1200 and the EU-Stelara/EU-Stelara groups with no detectable treatment-emergent NAbs in any treatment group. There was no apparent impact of immunogenicity on the PK of the study drugs before or following the

single transition. The totality of immunogenicity data from the study, including following the single transition, support the conclusion that there are no clinically significant differences in immunogenicity between Bmab1200 and EU-Stelara, and do not preclude a conclusion of no clinically meaningful differences between Bmab1200 and US-Stelara.

OSIS inspection: OSIS inspection of the clinical and bioanalytical sites for PK similarity study (BM12H-NHV-01-G-01) are deemed acceptable. See Section 3.

The submitted clinical pharmacology information supports a demonstration that there are of no clinically meaningful differences between Bmab1200 and US-Stelara.

Recommendation: This submission is approvable from a clinical pharmacology perspective.

PMC/PMR: None.

5.1.1. Clinical Pharmacology Residual Uncertainties Assessment

There are no residual uncertainties from the clinical pharmacology assessment.

5.2. Clinical Pharmacology Studies to Support the Use of a Non-U.S.-Licensed Comparator Product

In the PK similarity Study BM12H-NHV-01-G-01, following a single 45 mg SC injection of Bmab1200, EU-Stelara, or US-Stelara, the 90% CIs for the GMRs of Bmab1200 to EU-Stelara, Bmab1200 to US-Stelara, and EU-Stelara to US-Stelara for the tested PK parameters (i.e., $AUC_{0\text{-}inf}$, C_{max} and AUC_{last}) were all within the prespecified margin of 80-125%. These pairwise comparisons met the pre-specified criteria for PK similarity between Bmab1200, EU-Stelara, and US-Stelara; thus, the PK portion of the scientific bridge was established to support the relevance of the data generated using EU-Stelara as a comparator in the comparative clinical study (Study BM12H-PSO-03-G-02). This data supported the use of EU-Stelara in the comparative clinical study.

5.3. Human Pharmacokinetic and Pharmacodynamic Studies

PK Similarity Study Design Features

5.3.1. STUDY BM12H-NHV-01-G-01

The PK similarity study comparing Bmab1200, EU-Stelara and US-Stelara was conducted in healthy subjects (Study BM12H-NHV-01-G-01). This was a multiple-center, randomized, double-blind, 3-arm, parallel group study conducted in 2 sites in the United Kingdom. Subcutaneous route of administration was chosen for this study, as it

is more sensitive compared to IV administration, to detect any potential PK differences during the absorption phase in addition to the distribution and elimination phase. Approximately 258 subjects (86 per group) were planned to be enrolled to ensure that at least 246 subjects completed the study. A subcutaneous dose of 45 mg for Bmab1200, US Stelara, or EU Stelara was administered to the respective treatment groups. A schematic representation of the study design is shown below in Figure 1.

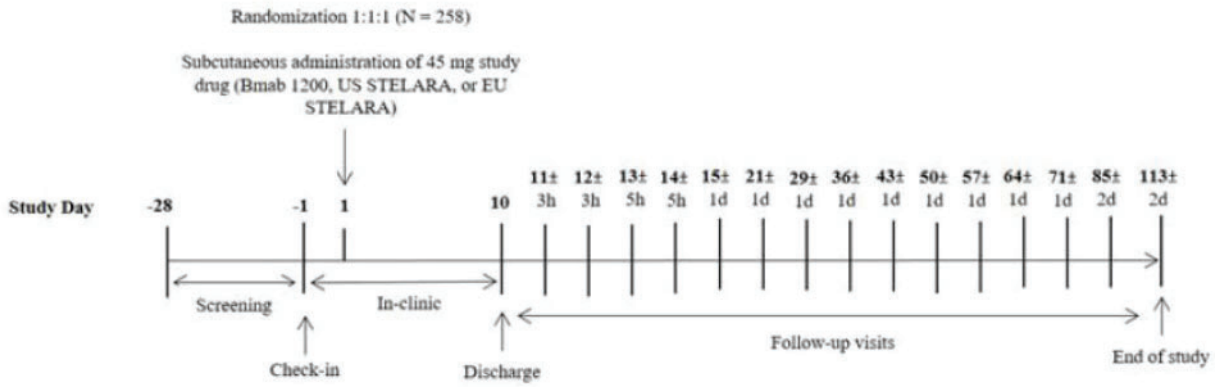


Figure 1. Schematic of study design for Study BM12H-NHV-01-G-01

Source: Applicant's Clinical Study Report

Clinical Pharmacology study endpoints

In Study BM12H-NHV-01-G-01, the primary endpoints selected were maximum serum concentration (Cmax) and total area under the serum concentration-time curve (AUC) from time zero (predose) extrapolated to infinity based on the last quantifiable concentration ($AUC_{0\text{-}inf}$).

The secondary PK parameters to be determined or calculated from the serum concentration-time data were the area under the serum concentration-time curve up to time t ($AUC_{0\text{-}t}$), where t is the last time point with concentrations above the lower limit of quantitation (LLOQ), time to maximum serum concentration (Tmax), elimination rate constant (Kel), elimination half-life (t1/2), volume of distribution (Vz/F) and apparent clearance (CL/F). Other secondary endpoints included safety (incidence and severity of AEs, 12 lead EEG parameters), tolerability, and immunogenicity.

Bioanalytical PK Method and Performance

The quantitation of study drug in human serum was performed with a Sandwich ECLIA method. The assay was validated for the quantitation of study drug in serum of healthy subjects as well as in serum of Ps patients (validation report No. VCA36138-01). During the method validation, Bmab1200, EU-Stelara, and US-Stelara were used as QC samples to assess the suitability of the assay. See Appendix 13.2.1 for detailed information about the assay validation and bioanalysis performance.

Bioanalytical Method and Performance for Immunogenicity samples

See review by Office of Product Quality Assessment III (OPQAIII) for details.

PK Similarity Assessment

PK similarity between Bmab1200, US-Stelara and EU-Stelara has been demonstrated in a 3-arm, parallel PK similarity study in healthy subjects (Study BM12H-NHV-01-G-01).

PK samples were collected pre-dose on pre-dose and within 60 minutes pre-dose and 12 hours post-dose on Day 1, and on Days 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 Days.

The point estimates and 90% CIs of the GMRs of PK parameters ($AUC_{0\text{-}inf}$, C_{max} and AUC_{last}) were all within the pre-defined criteria of 80% to 125 % (7 and Table 8). The mean serum concentration-time profiles were similar between the Bmab1200, US-Stelara and EU-Stelara treatment groups (Figure 2). The PK parameters following a single dose Bmab1200, US-Stelara and EU-Stelara are summarized in Table 8. In general, PK parameters and inter-subject variability were comparable across the three treatment groups. The reviewer reanalyzed the data based on the submitted PK data and determined that the reviewer calculated PK similarity assessment was in line with the applicant submitted data.

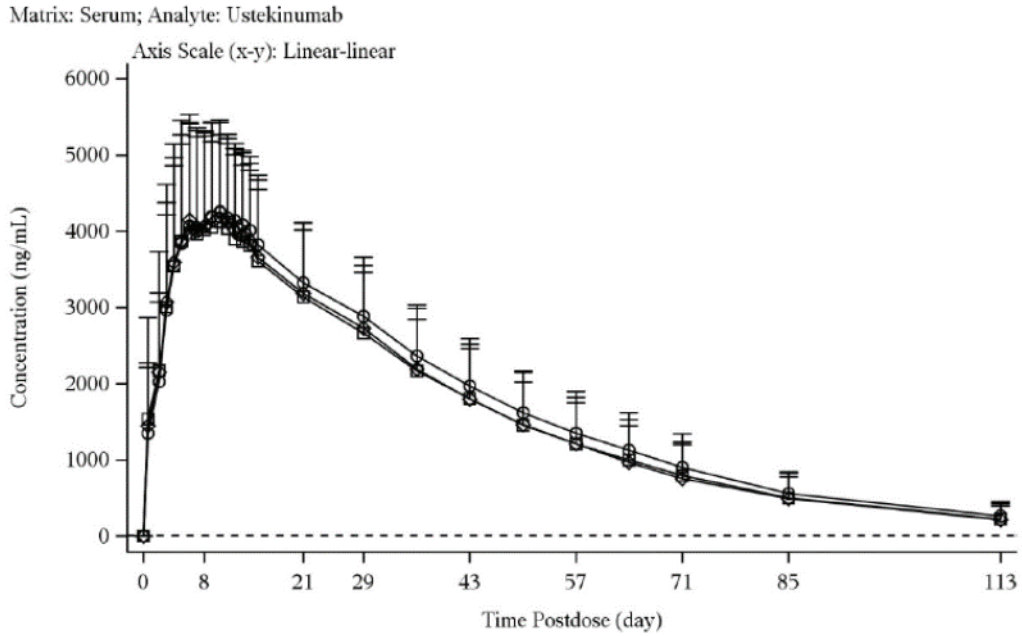


Figure 2. Serum concentration time profile (mean ± SD) of study drug by treatment group

Source: Applicant CSR BM12H-NHV-01-G-01, Figure 2, Page No. 35 of 548

Table 8. Summary of PK Parameters (Study BM12H-NHV-01-G-01) (Reviewer calculated)

PK Parameters	Geometric Mean (Geometric CV%)		
	Bmab1200 (n=86)	**US-Stelara (n=85)**	**EU-Stelara (n=84)**
C_{max} (ng/mL)	4620.35 (25.79)	4508.62 (30.84)	4648.94 (27.37)
AUC_{last} (h*ng/mL)	191154.50 (27.67)	179343.44 (30.86)	177477.12 (34.51)
$AUC_{0\text{-}inf}$ (h*ng/mL)	201429.8 (29.89)	185792.21 (31.17)	186230.57 (37.41)
T_{max} (h)[a]	9.0 (3.0 to 20.0)	9.0 (0.5 to 20.0)	9.0 (3.0 to 20.0)
$T_{1/2}$ (h)[b]	23.32 (7.65)	21.36 (7.11)	20.86 (7.87)

[a]Presented as median (minimum, maximum)
[b]Presented as arithmetic mean ± standard deviation
Source: FDA Analysis

OSIS Inspection of PK Similarity Study
The PK similarity study involved three study sites (2 clinical sites and 1 analytical site). The OSIS determined that inspection for the analytical site (Celerion Switzerland AG) is not needed as they were recently inspected for other applications. The OSIS inspection of the clinical sites is complete and found acceptable. Refer to Section 3.3 for details.

5.3.2. Study BM12H-PSO-03-G-02

Comparative Clinical Study Design Features

The study was a randomized, double-blind, parallel group, active-controlled, multicenter study designed to compare efficacy, safety, immunogenicity, and PK of Bmab1200 with EU-Stelara in adult patients with moderate to severe chronic plaque psoriasis. The study was planned to be conducted in Europe and North America across approximately 42 sites in 6 countries. The study was conducted in an outpatient setting, and the participation for each patient consisted of a screening period (up to 4 weeks/28 days) and a double-blind, active-controlled treatment period (52 weeks) with a re-randomization step for switching therapy at Week 16 (before dosing). The total duration of the study (excluding the screening period) will be 52 weeks.

Selection of study subjects:

- 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.

Patient randomization was stratified by:

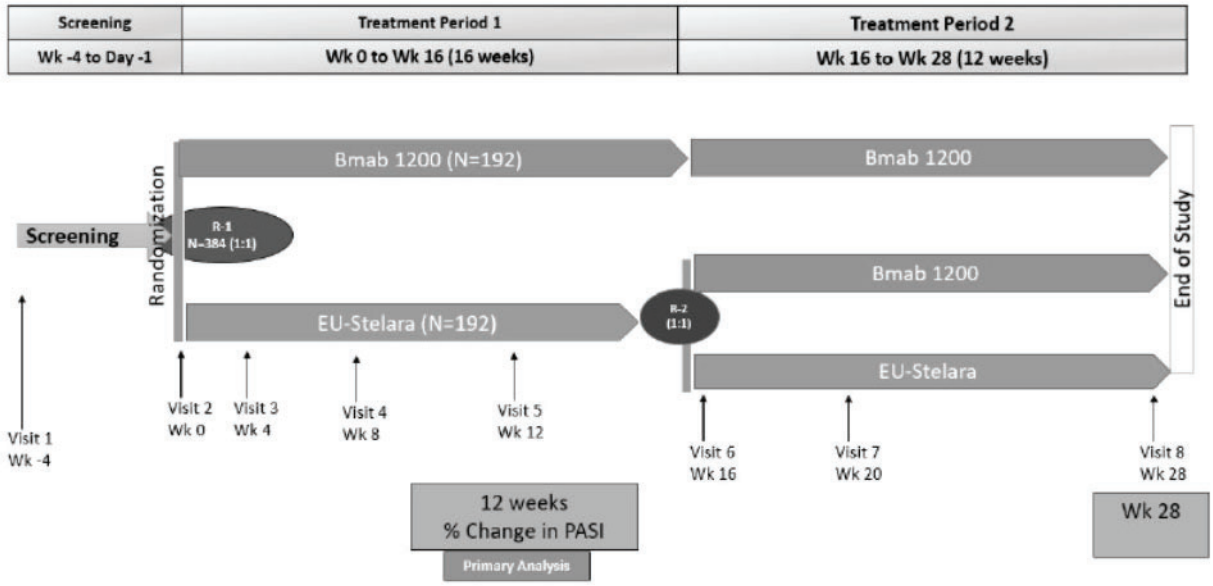
- Geographic region where the patient was enrolled (US vs Europe)
- Body weight (≤100 kg vs >100 kg)
- Prior exposure to biologic therapies for psoriasis or psoriatic arthritis (Yes vs No)
- Concomitant psoriatic arthritis (Yes vs No)

Patients received an initial dose of Bmab1200 or EU-Stelara as shown below at the baseline visit, Week 4, and Week 16 based on the patient's baseline body weight as follows:

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

At Week 16, patients who were initially randomized to receive Bmab1200 continued to receive Bmab1200 45 mg or 90 mg SC every 12 weeks at Weeks 16, 28, and 40 (unless withdrawn from the study). Patients who were initially randomized to EU-Stelara were re-randomized at Week 16 to receive Bmab1200 or continue to receive EU-Stelara in a 1:1 ratio. To maintain the study blinding, the patients in the original Bmab1200 group also went through the rerandomization procedure; however, they were assigned and continued to receive Bmab1200.

Serum trough concentrations (Ctrough) of Bmab1200 and EU-Stelara at steady state were evaluated in all patients with PK sampling at Week 0/Day 1 (pre-dose), and pre-dose at Weeks 4, 16, 28, 40, and at the EoS visit at Week 52 and at Week 3, Week 8, Week, Week 12 and Week 20. Serum samples for immunogenicity assessment (ADA and NAb) were collected pre-dose, Week 0/Day 1 (pre-dose), and pre-dose at Weeks 4, 16, 28, 40, and at the EoS visit at Week 52 and at Week 3, Week 8, Week, Week 12 and Week 20. A schematic representation of the study design is shown in Figure 3 below.



Abbreviations: EU, European Union; PASI, Psoriasis Area and Severity Index; R-1, randomization; R-2, rerandomization; Wk, Week.
Note: Study treatment will be administered at a dose of 45 mg or 90 mg (based on bodyweight category) at baseline visit, Week 4, and Week 16.
To maintain the study blinding, the patients in the original Bmab 1200 group will also go through the rerandomization procedure; however, they will be assigned and continue to receive Bmab 1200.

Figure 3. Schematic of study design for Study BM12H-PSO-03-G-02

Source: Clinical study protocol (BM12H-PSO-03-G-02), Page No.37 of 310

Serum concentrations were similar between Bmab1200 and EU-Stelara groups from Week 4 through Week 28 (**Error! Reference source not found.**). Serum concentrations were also similar across the treatment groups in re-randomized subjects post Week 28 (Table 10).

Table 9. Summary of Serum Concentrations Through Week 28 (Study BM12H-PSO-03-G-02)

Visit	Statistic	Bmab1200	EU-Stelara
Week 4	n Conc. (ng/mL) Geo LS Mean Ratio of Geo LS Mean (90% CI)	150 2673.12 (34.2) 2760.00 (2670.27-2967.47)	148 2207.46 (58.3) 2490.00 (2292.96-2584.55)
Week 12	n Conc. (ng/mL) Geo LS Mean Ratio of Geo LS Mean (90% CI)	148 1651.08 (68.6) 1805.00 (1760.17-2054.20)	140 1191.63 (117.8) 1420.00 (1399.23-1684.03)

Week 28	n Conc. (ng/mL) Geo LS Mean Ratio of Geo LS Mean (90% CI)	142 519.457 (101.20) 539.00 (602.68-752.83)	68 402.668 (140.80) 493.00 487.50-690.72

n = number of subjects with a non-zero concentration
Geo LS = geometric least square
Source: Table 11-1, CSR

Table 10. Summary of Serum Concentrations Post 28 Following Re-randomization (Study BM12H-PSO-03-G-02)

Visit	Statistic	Bmab1200/ Bmab1200 (N=141)	EU-Stelara/ Bmab1200 (N=64)	EU-Stelara/ EU-Stelara (N=64)
Week 40	n Conc. (ng/mL) Geo LS Mean Ratio of Geo LS Mean[a] 90% CI for ratio of Geo LS Mean[a]	128 605.35 (80.2) 667.39-832.42	61 485.46 (103.8) 534.63-741.26	61 465.60 (118.6) 524.28-742.66
Week 52	n Conc. (ng/mL) Geo LS Mean Ratio of Geo LS Mean[a] 90% CI for ratio of Geo LS Mean[a]	127 580.34 (85.1) 644.23-811.82	61 496.31 (107.6) 547.41-760.41	60 548.92 (79.4) 567.25-763.56

n = number of subjects with a non-zero concentration
Geo LS = geometric least square
Source: Table 11-2, CSR

PD Similarity Assessment

Not Applicable

5.4. Clinical Immunogenicity Studies

5.4.1. STUDY BM12H-PSO-03-G-02

Design features of the clinical immunogenicity assessment

Immunogenicity was assessed in patients with plaque psoriasis following multiple doses of Bmab1200 and EU-Stelara in Study BM12H-PSO-03-G-02. See Figure 4 for more details regarding the study design.

Immunogenicity endpoints

Anti-drug antibodies (ADA) and neutralizing antibodies (nAb) were selected as the immunogenicity endpoints. Further, the impact of immunogenicity on PK was compared across both treatment arms and also following a single transition from EU-Stelara to Bmab1200.

> Proportion of patients developing antidrug antibodies (ADAs) and NAbs during Treatment Period 1 (TP1) (time frame: baseline [Day 1] through Week 16)
> Proportion of patients developing ADAs and NAbs during Treatment Period 2 (TP2) (time frame: post rerandomization/dosing on Week 16 through Week 28 predosing)
> Proportion of patients developing ADAs and NAbs during TP3 (time frame: postdosing on Week 28 through Week 52)

Immunogenicity assay validation

The ADA response to study drug was detected using an assay based on MSD electrochemiluminescent method (ECLIA) (validation study No. CA36138-03; document No. VCA36138-03) and the determination of ADA was performed using ECLISA method (Study No. CA36451-02 and Document No. ACA36451-02). Refer to the OBP Immunogenicity review for further details.

The NAb against study drug were detected using a validated MSD-ECL method (Study No. CA36138-03; document No. VCA36138-03).

Both assays appear to have exhibited adequate drug tolerance considering the systemic levels of study drug in the study. Clinical pharmacology defers to the OPQAIII for the acceptability of ADA and NAb bioassay methods. Refer to the OPQAIII Immunogenicity review for further details.

Adequacy of the sampling plan to capture baseline, early onset, and dynamic profile (transient or persistent) of ADA/NAb formation

Serum samples for ADA and NAb assay were collected in Study BM12H-PSO-03-G-02 on Day 1 pre-dose, and at Week 2, Week 4, Week 8, Week 12, Week 16, Week 20, and Week 28 along with serum PK samples at each timepoint. The sampling time points for ADA and NAb were adequate to capture the early onset of immunogenicity as well as assess the impact of immunogenicity on PK. The sampling plans were adequate to capture baseline, early onset, and dynamic profile (transient or persistent) of ADA/NAb formation.

The incidence of ADA- and NAb- positive patients from Baseline up to Week 16 are summarized in Table 5 and from Baseline up to Week 28 in Table 6

Table 11. Immunogenicity results for binding ADA and NAb in Study BM12H-PSO-03-G-02

	N	Anti-Drug antibody		NAb
		Baseline	Treatment-Induced	
Bmab1200	191	15/191 (7.9%)	153/191 (80.1%)	59/191 (30.9%)
EU-Stelara	193	16/193 (8.3%)	168/193 (87.0%)	70/193 (36.3%)

Table 12. Immunogenicity results for binding ADA and NAb in Study BM12H-PSO-03-G-02 at Week 16 and Week 28 following single switch at Week 16.

	Bmab1200/ Bmab1200 **n (%)**	EU-Stelara / Bmab1200 **n (%)**	EU-Stelara/EU-Stelara **n (%)**
Week 16	m=185	m=92	m=92
Binding (ADA)	15 (8.1)	9 (9.8)	7 (7.4)
Neutralizing Antibodies	54 (29.2)	31 (33.7)	42 (44.7)
Week 28	m=182	m=91	m=93
Binding (ADA)	129 (69.7)	70 (76.1)	78 (83.0)
Neutralizing Antibodies	18 (9.7) (m=129)	14 (15.2) (m=70)	24 (25.5) (m=78)

m=number of patients assessed for ADA post-dose up to Week 16 dose.
Source: Applicant analysis (CSR Study BM12H-PSO-03-G-02; Table 14.2.4.2)

The antibody titer was also similar to pre-Week 16, and the titer did not increase in the Stelara-Bmab1200 switching group. The ADA positive rate (%) in patients receiving Bmab1200 was numerically lower than patients receiving EU-Stelara.

At Week 28, the ADA incidence in the group that switched from EU-Stelara to Bmab1200 was generally comparable to the ADA incidence observed in subjects that continued on Bmab1200 and EU-Stelara (Table 12). The overall frequency of NAbs was lower in the Bmab1200 group compared to EU-Stelara group.

Analysis of the immunogenicity incidence including following the single transition, support the conclusion that there are no clinically significant differences in immunogenicity incidence between Bmab1200 and EU-Stelara.

Impact of ADA and NAb on the PK, PD, safety, and clinical outcomes of the proposed product

Impact of ADA on PK

ADA had similar effects on PK of Bmab1200 and EU-Stelara (Table 13, Table 15). Mean study drug serum trough levels of both Bmab1200 and EU-Stelara treatment groups were lower in patients who were ADA positive compared to patients who were ADA negative. Similarly, mean study drug serum trough levels in NAb-positive patients were lower compared to the overall population in both Bmab1200 and EU-Stelara treatment groups (Table 14,Table 16). Overall, Ctrough concentrations were generally comparable between Bmab1200 and EU-Stelara arms in the ADA-positive and NAb-positive subjects.

At week 28, mean study drug serum trough levels of all treatment groups (Bmab1200/ Bmab1200, EU-Stelara/ Bmab1200 and EU-Stelara/EU-Stelara) were higher in those patients who were ADA negative and lower in those patients who were ADA positive compared to the overall population (Table 15).

Table 13. Effect of ADA status on Serum Trough Levels up to Week 16

		Bmab1200		EU-Stelara
	n	Mean (SD) (ng/mL)	n	Mean (SD) (ng/mL)
ADA positive		N=151		N=149
Week 2	104	3942.11 (1196.59)	116	3550.84 (1162.99)
Week 4	113	2788.95 (934.33)	131	2414.55 (927.34)
Week 8	116	4028.71 (1478.87)	129	3477.63 (1405.43)
Week 12	125	1947.54 (931.88)	131	1559.86 (862.77)
Week 16	116	938.09 (561.92)	118	755.25 (496.17)
ADA negative		N=151		N=149
Week 2	47	4176.38 (1305.99)	30	3843.54 (1329.62)
Week 4	37	2910.27 (885.30)	17	2625.29 (609.73)
Week 8	34	4242.09 (1447.76)	18	4111.67 (1439.18)
Week 12	23	1687.83 (720.06)	9	1276.33 (661.25)

Week 16	29	705.28 (519.85)	14	536.07 (489.06)

Source: Created by Reviewer based on data from CSR Study BM12H-PSO-03-G-02

Table 14. Effect of NAb status on Serum Trough Levels up to Week 16

		Bmab1200		EU-Stelara
NAb positive	n	Mean (SD) (ng/mL)	n	Mean (SD) (ng/mL)
Week 2	12	3944.17 (1165.81)	15	3302.00 (1365.77)
Week 4	10	2286.00 (516.57)	18	2382.44 (1092.03)
Week 8	33	3644.24 (1233.38)	40	3018.98 (1350.96)
Week 12	43	2076.40 (967.32)	41	1248.70 (871.42)
Week 16	45	994.20 (579.75)	42	590.83 (505.06)
NAb negative				
Week 2	139	4021.15 (1241.49)	131	3646.36 (1180.43)
Week 4	140	2856.93 (932.83)	130	2446.55 (871.92)
Week 8	117	4199.15 (1512.22)	107	3755.75 (1398.81)
Week 12	105	1837.88 (873.56)	99	1662.94 (818.12)
Week 16	100	845.32 (547.34)	90	797.87 (483.75)

Source: Created by Reviewer based on data from CSR Study BM12H-PSO-03-G-02; Table 14.3.5.3.1

Table 15. Effect of ADA status on Serum Trough Levels up to Week 28 following single switch at Week 16

	Bmab1200/ Bmab1200		EU-Stelara/ Bmab1200		EU-Stelara/EU-Stelara	
	n	Mean (SD) (ng/mL)	n	Mean (SD) (ng/mL)	n	Mean (SD) (ng/mL)
ADA positive						

Week 20	111	3351.18 (1240.15)	60	2879.33 (1125.00)	63	2826.38 (1152.35)
Week 28	99	719.53 (476.45)	17	856.90 (537.88)	57	594.09 (430.44)
ADA negative		N=146		N=71		N=73
Week 20	32	3043.75 (1038.48)	10	3128.00 (1126.21)	9	2930.00 (1019.40)
Week 28	43	581.59 (379.76)	17	660.67 (345.83)	11	563.29 (377.13)

Source: Created by Reviewer based on data from CSR Study BM12H-PSO-03-G-02; Table 14.2.3.11

Table 16. Effect of NAb status on Serum Trough Levels following single switch at Week 16

	Bmab1200/ Bmab1200		EU-Stelara/ Bmab1200		EU-Stelara/EU-Stelara	
	n	Mean (SD) (ng/mL)	n	Mean (SD) (ng/mL)	n	Mean (SD) (ng/mL)
NAb positive		N=146		N=73		N=271
Week 20	41	3407.00 (1192.04)	19	2651.32 (1406.54)	29	2441.38 (1060.36)
Week 28	14	632.66 (513.09)	7	397.51 (309.67)	14	432.94 (537.35)
NAb negative		N=146		N=71		N=73
Week 20	102	3232.29 (1207.34)	51	3013.04 (991.92)	43	3107.72 (1107.94)
Week 28	128	682.68 (447.39)	60	650.86 (390.83)	54	629.60 (379.24)

Source: Created by Reviewer based on data from CSR Study BM12H-PSO-03-G-02; Table 14.2.3.13

Impact of ADA on Efficacy and Safety

ADA status did not appear to have a significant effect on clinical efficacy (Table 17). Similar changes in the Psoriasis Area and Severity Index (PASI) score were observed for both Bmab1200 and EU-Stelara in both ADA-positive and ADA-negative patients (Table 17). Similar trends were observed when comparing NAb positive and NAb negative patients in both Bmab1200 and EU-Stelara groups (Table 18).

Table 17. Percentage Change from Baseline in Psoriasis Area and Severity Index Score at Week 12 by ADA Status (Positive/Negative) Post baseline up to Week 12

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	-

Source: CSR Study BM12H-PSO-03-G-02 GL-301 Table 19

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

Table 18. Percentage Change from Baseline in Psoriasis Area and Severity Index Score at Week 12 by NABs Status (Reactive/Negative) Postbaseline up to week 12

NAbs Status: Reactive up to Week 12	Bmab 1200 (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	**Bmab 1200 (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	-

Source: CSR Study BM12H-PSO-03-G-02 Table 20

Overall, the ADA positive rate was generally comparable between the 2 groups throughout the study, with no apparent impact of switching from Stelara to Bmab1200. Even though, the NAb reactive rate was higher in Stelara group vs Bmab1200 group and Stelara-Stelara group vs Stelara-Bmab1200 group post switching, these differences were not considered as clinically meaningful. For further information, see Section 6.

Further, AEs as recorded (overall AEs, SAEs, TEAEs, AESIs) and particularly hypersensitivity reactions were independent of ADA titers and NAb status with no

injection site reactions being reported. There were no apparent treatment-related differences in the impact of ADA/NAb-positive status on safety. See Section 6 for further details.

Overall, the effect of immunogenicity on PK, efficacy and safety is generally compatible between Bmab1200 and EU-Stelara.

5.4.2. BM12H-NHV-01-G-01

In the PK similarity study BM12H-NHV-01-G-01, immunogenicity of Bmab1200 was compared to US-Stelara and EU-Stelara after a single dose in healthy subjects (Table 19). Blood samples for the immunogenicity assessment were collected at Day 1 pre-dose, and Days 7, 15, 29, 57, 85, and 113. The samples were analyzed in a validated sequential electrochemiluminescence (ECL) immunoassay using an acid capture elution (ACE) method. A drug tolerance of detecting 100 ng/mL ADA in the presence of 240 µg/mL circulating drug across all 3 products (Bmab1200, US Stelara, and EU Stelara) was achieved. The immunogenicity assay used in this study was a sensitive drug tolerant ADA method with a sensitivity of 0.709 ng/mL for the screening assay and 0.839 ng/mL for the confirmatory assay. Therefore, the Applicant has claimed that this sensitive method led to an observation of a generally high ADA+ incidence rate across the 3 study treatment groups.

ADA Incidence and nAb incidence in the Bmab1200 treatment group were slightly lower compared to EU-Stelara and US-Stelara in the PK similarity study. The incidence of anti-drug antibody (ADA) formation at the end of the study (Day 92) in healthy subjects was 26.7 % in the Bmab1200 group compared to 55.3% in the EU-approved Stelara and 60.9% in the US-licensed Stelara groups. There was no apparent impact of immunogenicity on the PK of the study drugs. Overall, we conclude that these differences are not considered to be clinically significant, and the results support a conclusion of no clinically meaningful differences between Bmab1200 and US-Stelara.

Table 19. Summary of ADA incidence in Study BM12H-NHV-01-G-01

	45 mg Bmab 1200 (N = 86)	45 mg US Stelara (N = 87)	45 mg EU Stelara (N = 85)
Overall Subject ADA Status			
ADA-	31 (36.0%)	12 (13.8%)	16 (18.8%)
ADA+	55 (64.0%)	75 (86.2%)	69 (81.2%)
Treatment-emergent ADA+	47 (54.7%)	73 (83.9%)	64 (75.3%)
Number of Subjects with Positive ADA Result at Given Timepoint			
Baseline	9 (10.5%)	2 (2.3%)	5 (5.9%)
Day 7	20 (23.3%)	41 (47.1%)	38 (44.7%)
Day 15	31 (36.0%)	54 (62.1%)	51 (60.0%)
Day 29	34 (39.5%)	51 (58.6%)	54 (63.5%)
Day 57	37 (43.0%)	64 (73.6%)	57 (67.1%)
Day 85	38 (44.2%)	59 (67.8%)	57 (67.1%)
End of Study	29 (33.7%)	55 (63.2%)	51 (60.0%)
Number of Subjects with Negative Result Prior to Baseline and Positive ADA Result at Given Post-baseline Timepoint			
Day 7	14 (16.3%)	39 (44.8%)	33 (38.8%)
Day 15	23 (26.7%)	52 (59.8%)	48 (56.5%)
Day 29	26 (30.2%)	49 (56.3%)	50 (58.8%)
Day 57	32 (37.2%)	62 (71.3%)	52 (61.2%)
Day 85	33 (38.4%)	57 (65.5%)	52 (61.2%)
End of Study	23 (26.7%)	53 (60.9%)	47 (55.3%)

ADA = anti-drug antibody; n = number of subjects with valid observations; N = number of subjects; % = percentage of subjects with valid observations (n/N×100)
n (%) statistics presented.
Reference: Table 14.3.5.1
Program Location: /cvn/projects/prj/ecb/programs/000000226840/dev/tables/t_iss_itt.sas
Program Status: FINAL Program Run: 02OCT2023 Protocol Reference: BM12H-NHV-01-G-01

Table 20. Summary of Summary of Anti-drug Antibody Titer in Study BM12H-NHV-01-G-01

Timepoint	45 mg Bmab 1200 (N = 86) Mean (SD) [n] Median (Min-Max)	45 mg US Stelara (N = 87) Mean (SD) [n] Median (Min-Max)	45 mg EU Stelara (N = 85) Mean (SD) [n] Median (Min-Max)
Baseline	276 (540) [9]	NC (NC) [2]	523 (1030) [5]
	94.0 (60.0-1710)	NC (111-176)	60.0 (60.0-2360)
Day 7	72.7 (22.2) [20]	214 (386) [41]	639 (2470) [38]
	60.0 (60.0-131)	81.3 (60.0-1860)	61.9 (60.0-15000)
Day 15	134 (312) [31]	415 (974) [54]	478 (1380) [51]
	60.0 (60.0-1800)	131 (60.0-6820)	116 (60.0-9430)
Day 29	2730 (15300) [34]	125 (107) [51]	207 (323) [54]
	60.0 (60.0-89200)	69.7 (60.0-581)	73.9 (60.0-1880)
Day 57	10100 (59500) [37]	468 (2010) [64]	549 (1340) [57]
	60.0 (60.0-362000)	73.5 (60.0-15900)	86.1 (60.0-7570)
Day 85	11200 (63100) [38]	688 (3240) [59]	965 (2230) [57]
	60.0 (60.0-389000)	85.2 (60.0-24900)	90.4 (60.0-10600)
End of Study	10100 (49500) [29]	774 (2340) [55]	945 (1660) [51]
	75.3 (60.0-267000)	145 (60.0-16600)	114 (60.0-6870)

Titer results equal to minimum required dilution (MRD) were assigned a value of 60
n = number of subjects with valid observations; N = number of subjects; SD = standard deviation
Reference: Table 14.3.5.2
Program Location: /cvn/projects/prj/ecb/programs/000000226840/dev/tables/t_is_itt.sas
Program Status: FINAL Program Run: 06OCT2023 Protocol Reference: BM12H-NHV-01-G-01

Overall, the incidence of subjects with ADA were higher when treated with the US-Stelara and the EU-Stelara than when treated with Bmab1200. The highest incidence of treatment-emergent ADA+ was found to be 44.2% (Day 85), 73.6% (Day 57), and 67.1% (Day 57) for the Bmab1200, the US-Stelara, and the EU-Stelara treatment groups, respectively.

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6. Statistical and Clinical Evaluation and Recommendations

6.1. Statistical and Clinical Executive Summary and Recommendation

Comparative Efficacy: The comparative efficacy of Bmab1200 and EU-Stelara was evaluated in Study BM12H-PSO-03-G-02 for the FDA's recommended primary endpoint of the percent improvement in PASI at Week 12. The 90% confidence intervals (CI) for the treatment difference for both the Full Analysis Set (FAS) and the Per Protocol Set (PPS) fell within the prespecified margins of ±10% [FAS CI:(-2.602, 1.308); PPS CI: (-3.000, 0.949)]. Thus, the study demonstrated no meaningful differences between Bmab1200 and EU-Stelara regarding the primary efficacy endpoint.

6.1.1. Statistical and Clinical Residual Uncertainties Assessment

There are no residual clinical or statistical uncertainties that impact a demonstration of no meaningful differences between Bmab1200 and EU-Stelara.

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6.2. Review of Comparative Clinical Studies with Statistical Endpoints

Study BM12H-PSO-03-G-02, a comparative clinical study in subjects with moderate to severe plaque psoriasis, was evaluated to assess whether there were no meaningful differences between Bmab1200 and EU-Stelara.

6.2.1. Study BM12H-PSO-03-02

Study Design and Endpoints

Study BM12H-PSO-03-02 was a randomized, double-blind, active-controlled, parallel group, multicenter study designed to compare efficacy, safety, immunogenicity, and PK of Bmab1200 with EU-Stelara in adult subjects with moderate to severe chronic plaque psoriasis.

The study included the following three treatment periods.

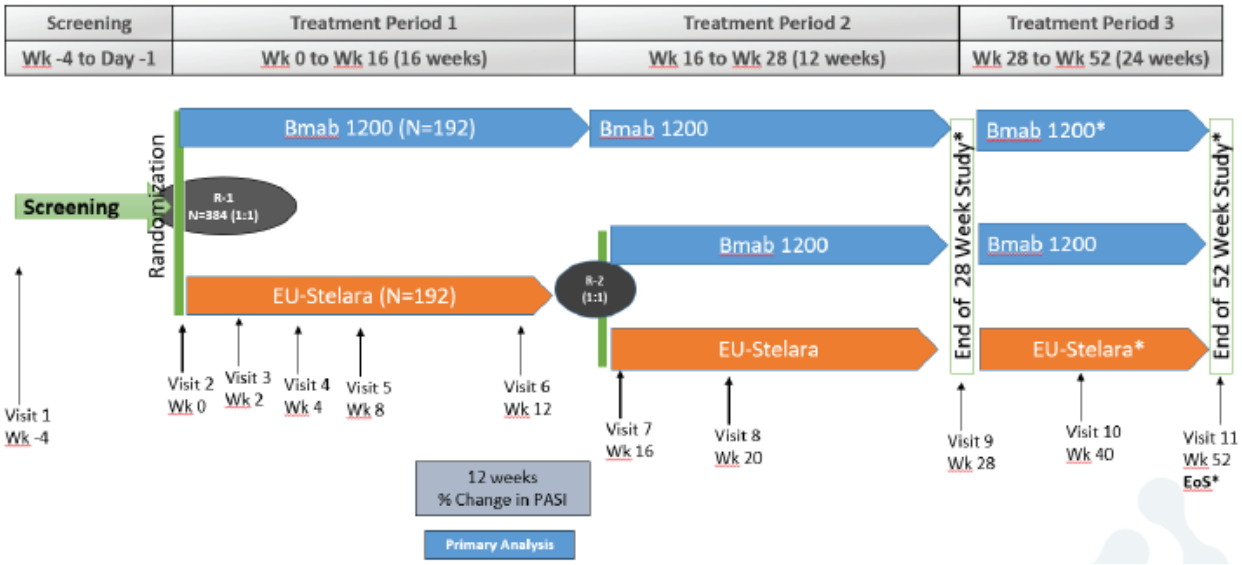
Treatment Period 1 (Baseline to Week 16)
Subjects were randomized in a 1:1 ratio to Bmab1200 or EU-Stelara, and randomization was stratified by geographic region (US vs. Europe), body weight (45 mg: ≤100kg vs. 90 mg: >100 kg), previous exposure to biologic-based therapies (Yes vs. No), and concomitant psoriatic arthritis (Yes vs. No). Subjects received study treatment at baseline and Week 4.

Treatment Period 2 (Weeks 16 to 28)
All subjects who received study treatment with EU-Stelara at baseline and Week 4 and achieved at least PASI 50 response by Week 12 were rerandomized in a 1:1 ratio to receive either Bmab1200 or EU-Stelara at Week 16. To maintain blinding, subjects in the original Bmab1200 also went through rerandomization procedure; however, they continued to receive Bmab1200. Original stratification factors were used also for rerandomization.

Treatment Period 3 (Weeks 28 to 52)
Subjects who achieved at least PASI 75 response at Week 28 entered this period to continue the same treatment that they were rerandomized to receive in Treatment Period 2. Note that the results from this treatment period were not included in this submission.

Figure 4 depicts the study design of BM12H-PSO-03-G-02.

Figure 4. Study Design (BM12H-PSO-03-G-02)



Source: Applicant's Figure 1; Clinical Study Report (page 24 of 6093)

The study enrolled subjects ages 18 to 79 years of age with moderate to severe plaque psoriasis who had involved body surface area (BSA) ≥ 10%, Psoriasis Area and Severity Index (PASI) ≥ 12, and static Physician's Global Assessment (sPGA) ≥ 3, with stable disease for at least 2 months before the baseline visit.

The sPGA was calculated by averaging the induration, erythema, and scaling scores that was then rounded to the nearest whole number. The subscales and the sPGA are shown below.

Static Physician's Global Assessment (sPGA)

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

0 = no evidence of plaque elevation
1 = minimal plaque elevation, = 0.25 mm
2 = mild plaque elevation, = 0.5 mm
3 = moderate plaque elevation, = 0.75 mm
4 = marked plaque elevation, = 1 mm
5 = severe plaque elevation, = 1.25 mm or more

Erythema (E) (averaged over all lesions):

0 = no evidence of erythema, hyperpigmentation may be present
1 = faint erythema
2 = light red coloration
3 = moderate red coloration
4 = bright red coloration
5 = dusky to deep red coloration

Scaling (S) (averaged over all lesions):

0 = no evidence of scaling
1 = minimal; occasional fine scale over less than 5% of the lesion

2 = mild; fine scale dominates
3 = moderate; coarse scale predominates
4 = marked thick, non-tenacious scale dominates
5 = severe; very thick tenacious scale predominates

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

Physician's Static Global Assessment based upon the Total Average

0 = Clear, except for residual discoloration
1 = Minimal - majority of lesions have individual scores for I+E+S / 3 that averages 1
2 = Mild - majority of lesions have individual scores for I+E+S / 3 that averages 2
3 = Moderate - majority of lesions have individual scores for I+E+S / 3 that averages 3
4 = Marked - majority of lesions have individual scores for I+E+S / 3 that averages 4
5 = Severe - majority of lesions have individual scores for I+E+S / 3 that averages 5

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

Source: Applicant's Protocol (page 308 of 310)

Statistical Methodologies

The primary analysis population was the Full Analysis Set (FAS) and the Per Protocol Set (PPS) was used for supportive analyses. The Statistical Analysis Plan (SAP) specified PPS as all FAS subjects who received at least 2 study treatment administrations (Baseline and Week 4), and without any important protocol deviations affecting primary efficacy at Week 12. The SAP specified the following important protocol deviations leading to exclusion from PPS:

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

The SAP specified the following intercurrent events.

Table 21 Intercurrent Events (ICE)

Label	ICE
ICE1 (Death)	Death due to any cause prior to PASI assessment
ICE2 (Discontinuation of study treatment due to any reason other than death)	Premature discontinuation of study treatment prior to PASI assessment, for any reason other than death
ICE3 (Prohibited therapy used for treatment of psoriasis)	Use of any prohibited therapies used for treatment of psoriasis prior to PASI assessment, per Section 9.7 of the protocol.
ICE4 (Deviations in dosing)	Errors or deviations in study treatment dosing prior to PASI assessment, including incorrect dose received, incorrect study treatment, incorrect route, or deviation in dosing interval more than 14 days
ICE5 (Data obtained remotely)	Any data obtained from remote assessment due to COVID19 or for any other reason (for example, due to patient not being able to attend the site due to regional lockdown)

Source: Applicant's Statistical Analysis Plan (SAP; page 27 of 87)

The primary endpoint was the percent improvement in PASI at Week 12. The SAP specified the following primary, secondary and tertiary estimands for the primary efficacy endpoint.

Table 22: Estimands for the Primary Endpoint

	Primary Estimand	Secondary Estimand	Tertiary Estimand
Treatment conditions of interest	Bmab 1200 vs EU-Stelara	Bmab 1200 vs EU-Stelara	Bmab 1200 vs EU-Stelara
Population	Patients with moderate to severe chronic plaque psoriasis as defined by the inclusion/exclusion criteria	Patients with moderate to severe chronic plaque psoriasis as defined by the inclusion/exclusion criteria	Patients with moderate to severe chronic plaque psoriasis as defined by the inclusion/exclusion criteria, having received all study treatment administration without deviation up to Week 8 and having available PASI assessment at Week 12
Endpoint	Percent change from baseline in the PASI score at Week 12	Percent change from baseline in the PASI score at Week 12	Percent change from baseline in the PASI score at Week 12
Population-level summary	Difference between treatments (Bmab 1200 minus EU-Stelara) in mean percentage change from baseline in PASI score at Week 12	Difference between treatments (Bmab 1200 minus EU-Stelara) in mean percentage change from baseline in PASI score at Week 12	Difference between treatments (Bmab 1200 minus EU-Stelara) in mean percentage change from baseline in PASI score at Week 12

ICEs and strategies to handle ICEs	• ICE1 (Death): *Composite variable strategy* • ICE2 (Discontinuation of study treatment due to any reason other than death): *Treatment policy strategy* • ICE3 (Prohibited therapy used for treatment of psoriasis): *Treatment policy strategy.* • ICE4 (Deviations in dosing): *Treatment policy strategy* • ICE5 (Data obtained remotely): *Hypothetical strategy*	• ICE1 (Death): *Composite variable strategy* • ICE2 (Discontinuation of study treatment due to any reason other than death): *Treatment policy strategy* • ICE3 (Prohibited therapy used for treatment of psoriasis): *Hypothetical strategy.* • ICE4 (Deviations in dosing): *Hypothetical strategy* • ICE5 (Data obtained remotely): *Hypothetical strategy*	• ICE1 (Death): *Not applicable, patient not considered in population.* • ICE2 (Discontinuation of study treatment due to any reason other than death): *Not applicable, patient not considered in population.* • ICE3 (Prohibited therapy used for treatment of psoriasis): *Not applicable, patient not considered in population.* • ICE4 (Deviations in dosing): *Not applicable, patient not considered in population* ICE5 (Data obtained remotely): *Not applicable, patient not considered in population*

Abbreviations: ICE, intercurrent event; PASI, Psoriasis Area and Severity Index; PFS, prefilled syringe.
Source: Applicant's Table 5; Study Protocol (SAP; pages 286-287 of 310). Font in Red indicate revisions per FDA's feedback (Division of Biometrics III comments).

The protocol-specified strategies for handling the intercurrent events (ICEs) are described below:

- Composite variable strategy: Return-to-baseline multiple imputation (MI) approach was proposed; however, as there were no deaths, this strategy was not implemented.
- Treatment policy strategy: Missing PASI assessment would be imputed by a missing-at-random (MAR) application of SAS Proc MI approach.
- Hypothetical strategy: Available data on "data obtained remotely" would be set to missing, and MAR application of SAS Proc MI would be used.

The SAP specified that subjects with missing PASI would be imputed using the Markov Chain Monte Carlo (MCMC) approach (10 imputations, seed=436987) including factors for study treatment, stratification factors, baseline PASI score, and binary variables for ICE occurrence at the visit. Then the point estimates and standard errors would be obtained using the Rubin's rules (SAS PROC MIANALYZE).

All estimands were analyzed with ANCOVA including terms for treatment and the stratification factors (region, body weight at baseline, baseline psoriatic arthritis status, and previous biologic use) used for the randomization at baseline as fixed factors. Two-sided 90% confidence intervals for the treatment difference were calculated using least squares means and compared to margins of ±10%.

The protocol specified that that all inferential analyses of the primary efficacy endpoint would be conducted during the Treatment Period 1 only with the primary timepoint of Week 12. Consequently, the handling of estimands only applied up to Week 16.

Several secondary efficacy endpoints were included in the study:

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

For the secondary efficacy endpoints, the protocol specified that "no margins of equivalence are applied to secondary efficacy endpoints". Therefore, analyses of the secondary endpoints were descriptive in nature.

Subject Disposition

Study BM12H-PSO-03-G-02 randomized a total of 384 subjects: 191 to Bmab 1200 and 193 to EU-Stelara. Of the 384 subjects, 382 (99.5%) completed Treatment Period 1 (TP1; Week 16), and 2 subjects (0.5%) discontinued TP1 due to adverse events (1 in Bmab 1200, 1 in EU-Stelara). Reasons for discontinuation in Treatment Period 2 (TP2) included adverse events (AEs), withdrawal of consent, principal investigator's (PI) decision, use of prohibited medication, lack of response (<PASI50) at Week 12, pregnancy, and others (change in residency). See Table 23.

Table 23. Subject Disposition for Treatment Period 1

	Bmab 1200	EU-Stelara	Total
Randomized	**191**	**193**	**384**
Full Analysis Set (FAS)	**191 (100%)**	**193 (100%)**	**384 (100%)**
Applicant's Per Protocol (PP)	**189 (99.0%)**	**189 (97.9%)**	**378 (98.4%)**
Excluded from Applicant's PP	2	4	6
Did not receive 2 study treatment dose (baseline; Week 4)	1 (b) (6)	1 (b) (6)	2
Major protocol deviation leading to exclusion	1 (b) (6)	3 (b) (6)	4
FDA's FAS (FFAS)	**191 (100%)**	**192 (99.5%)**	**383 (99.7%)**
Excluded from FFAS	0	1	0
Baseline sPGA of mild severity	0	1 (b) (6)	1

FDA's PP Set (FPP)	**186 (97.4%)**	**186 (96.4%)**	**372 (96.9%)**
Excluded from FPP	5	7	12
Baseline sPGA of mild severity	0	1 (b) (6)	1
Did not receive 2 study treatment dose (baseline; Week 4)	1 (b) (6)	1 (b) (6)	2
Use of prohibited medication	1 (b) (6)	3 (b) (6)	4
Washout period (exclusion criterion 2c) not followed	2 (b) (6)	1 (b) (6)	3
Incorrect randomization stratification (lack of reporting)	1 (b) (6)	1 (b) (6)	2

Source: Reviewer Analysis

Demographics and Baseline Characteristics

The demographic characteristics were generally balanced across treatment groups. The mean age was about 43 years and approximately 8% of subjects were of age 65 years and older. The majority of subjects were male (67%), and all subjects except 2 subjects in the study were white. Fourteen percent of the subjects had prior use of biologics. Approximately 22% of the subjects weighed >100 kg at baseline.

Subjects were to have PASI ≥ 12, sPGA ≥ 3 and BSA ≥ 10% at baseline; however, there was one subject in the EU-Stelara arm that had a baseline sPGA of 2 (mild). Subjects had a mean PASI score of approximately 23 and baseline 29.9% BSA. Approximately 53% of subjects had a sPGA score of 3 (moderate), and the baseline disease characteristics were generally balanced across treatment arms. See Table 24

Table 23. Demographics and Baseline Disease Characteristics

	Bmab 1200 N=191	**EU-Stelara N=193**	**Total N=384**
Age			
Mean (SD)	42.53 (13.09)	43.87 (13.58)	43.20 (13.34)
Median	41.0	40.0	42.0
Min, Max	18, 74	18, 73	18, 79
<65 years	178 (93.2%)	176 (91.2%)	354 (92.2%)	
≥65 years	13 (6.8%)	17 (8.8%)	30 (7.8%)
[redacted]			
Female	70 (36.7%)	57 (29.5%)	127 (33.1%)
Male	121 (63.3%)	136 (70.5%)	257 (66.9%)
Race			
Black or African American	1 (0.5%)	1 (0.5%)	2 (0.5%)
White	190 (99.5%)	192 (99.5%)	382 (99.5%)
Weight			
Mean (SD)	84.69 (17.88)	86.99 (17.37)	85.85 (17.64)
Median	84.2	86.7	85.0

Min, Max	48.0, 128.7	46.0, 128.4	46.0, 128.7
≤100 kg	151 (79.1%)	150 (77.7%)	301 (78.4%)
>100kg	40 (20.9%)	43 (22.3%)	83 (21.6%)
Prior biologic for psoriasis			
Yes	27 (14.1%)	26 (13.5%)	53 (13.8%)
No	164 (86.9%)	167 (86.5%)	331 (86.2%)
PASI			
Mean (SD)	23.39 (9.13)	22.98 (9.29)	23.19 (9.20)
Median	20.1	20.2	20.1
Min, Max	12.2, 59.5	12.2, 68.4	12.2, 68.4
sPGA			
Mild	0 (0%)	1 (0.5%)	1 (0.26%)
Moderate	93 (48.7%)	112 (58.0%)	205 (53.4%)
Severe	69 (36.1%)	56 (29.0%)	125 (32.6%)
Very severe	29 (15.2%)	24 (12.5%)	53 (13.8%)
%BSA			
Mean (SD)	29.91 (16.29)	29.93 (16.31)	29.92 (16.28)
Median	26.00	25.00	25.0
Min, Max	10.0, 90.0	10.0, 93.0	10.0, 93.0

Source: Reviewer Analysis

As Stelara is a weight-based treatment, we evaluated the baseline disease characteristics by baseline weight group. See Table 25. While the number of subjects is small for those that weigh > 100 kg, it appears that there were more sPGA of Severe subjects in Bmab 1200 arm (20%) compared to that in the EU-Stelara (14%) arm.

Table 24. Baseline Disease Characteristics by Baseline Body Weight

Baseline Body Weight	**≤100 kg**		**>100kg**	
Treatment	**Bmab 1200 45 mg N=151**	**EU-Stelara 45 mg N=150**	**Bmab 1200 90 mg N=40**	**EU-Stelara 90 mg N=43**
PASI				
Mean (SD)	23.17 (9.46)	22.46 (8.59)	24.24 (7.78)	24.82 (11.33)
Median	19.8	19.9	22.7	20.7
Min, Max	12.2, 59.5	12.2, 51.4	14.2, 44.4	12.8, 68.4
sPGA				
Mild	0 (0%)	1 (0.7%)	0 (0%)	0 (0%)
Moderate	76 (50.3%)	91 (60.7%)	17 (42.5%)	21 (48.8%)
Severe	54 (35.8%)	40 (26.6%)	15 (37.5%)	16 (37.2%)
Very severe	21 (13.9%)	18 (12.0%)	8 (20.0%)	6 (14.0%)
%BSA				
Mean (SD)	30.16 (17.08)	29.22 (15.79)	28.98 (13.00)	32.40 (17.98)
Median	24.0	24.5	27.0	27.0
Min, Max	10, 90	10, 86	13, 60	12, 93

Source: Reviewer Analysis

Analysis of Primary Clinical Endpoint(s)

The primary efficacy endpoint was the percent improvement in PASI from baseline to Week 12 in the FAS with the analysis in the PPS as supportive. The treatment difference was estimated using ANCOVA including terms for treatment and the randomization stratification factors (region, body weight at baseline, baseline psoriatic arthritis status, and previous biologic use) as fixed factors. Two-sided 90% confidence intervals for the treatment difference are calculated using least squares means and compared to margins of ±10%.

The 90% confidence intervals for the difference in the percent improvement in PASI at Week 12 for both the FAS and PPS fell within the margins of ±10%, indicating no meaningful differences between Bmab 1200 and EU-Stelara. See Table 26.

Table 25. Applicant's and Reviewer's Results for the Analysis of the Primary Endpoint

	Applicant's			FDA		
	Bmab 1200	**EU-Stelara**	**LS Mean Difference $_{B-S}$ (SE) 90% CI**	**Bmab 1200**	**EU-Stelara**	**LS Mean Difference $_{B-S}$ (SE) 90% CI**
FAS	**191**	**193**		**191**	**192**	
Primary Estimand	79.872 (2.818)	80.552 (2.783)	-0.680 (1.186) (-2.631, 1.271)	79.906 (2.821)	80.553 (2.785)	-0.647 (1.189) (-2.602, 1.308)
Secondary Estimand	80.152 (2.841)	80.758 (2.801)	-0.607 (1.193) (-2.569, 1.356)	80.177 (2.841)	80.760 (2.801)	-0.583 (1.194) (-2.547, 1.381)
Tertiary Estimand	79.911 (2.788)	80.575 (2.755)	-0.664 (1.202) (-2.641, 1.313)	79.945 (2.791)	80.576 (2.757)	-0.630 (1.205) (-2.612, 1.351)
PPS	189	189		186	186	
Primary Estimand	76.669 (3.062)	77.594 (2.998)	-0.925 (1.188) (-2.878, 1.028)	76.444 (3.077)	77.470 (3.008)	-1.025 (1.201) (-3.000, 0.949)
Secondary Estimand	77.046 (3.080)	77.970 (3.011)	-0.924 (1.187) (-2.877, 1.029)	76.822 (3.094)	77.848 (3.022)	-1.025 (1.201) (-3.000, 0.949)
Tertiary Estimand	76.815 (3.011)	77.704 (2.947)	-0.889 (1.196) (-2.856, 1.079)	76.608 (3.026)	77.578 (2.957)	-0.970 (1.208) (-2.957, 1.017)

Source: Applicant's study report (Table 14) and Reviewer Analysis; LS Mean = Least squares mean, B = Bmab 1200, S= Stelara, SE = standard error, FAS = Full Analysis Set, PPS = Per Protocol Set. ANCOVA model included the treatment group and randomization stratification variables (region, body weight at baseline category, baseline psoriatic arthritis status, and previous biologic use) as fixed factors.

Potential Effects of Missing Data

The applicant reported 4 ICEs affecting the primary analysis and concluded that the incidence of missing data for the efficacy analyses was low. See Table 27.

Table 26. Intercurrent Events (ICE)

	Bmab 1200 N=191	EU-Stelara N=192
ICE1: death	0	0
ICE2: discontinuation of study treatment due to any reason other than death	1 (b) (6)	1 (b) (6)
ICE3: prohibited therapy used for treatment of Ps	0	2

		(b) (6)
ICE4: deviations in dosing	0	0
ICE5: data obtained remotely	0	0

Source: Applicant's study report (Table 14.2.1.1.1.1)

The following table lists the subjects with ICE along with their percent change in PASI from baseline at their last available visit prior to Week 12.

Table 27. List of ICE Subjects and Their Percent Change in PASI from Baseline at Previous Visits

Subject ID	Treatment	ICE	Available Visits	Percent Change from Baseline
(b) (6)	Bmab 1200	ICE2	Baseline, Week 4	70.41% at Week 4
	EU-Stelara	ICE2	Baseline, Weeks 4, 8	100% at Week 8
	EU-Stelara	ICE3	Baseline, Weeks 4, 8, 12	84.62% at Week 12
	EU-Stelara	ICE3	Baseline, Weeks 4, 8, 12	95.98% at Week 12

Source: Reviewer analysis; ICE = intercurrent event

As a sensitivity analysis for handling missing data, to assess whether the conclusions could be impacted by even more extreme outcomes, we considered two extreme scenarios where missing data were imputed with the following:

- 100% improvement in PASI for Bmab 1200 and 0% improvement in PASI for Stelara,
- 0% improvement in PASI for Bmab 1200 and 100% improvement in Stelara.

Table 29 shows that the confidence intervals under both scenarios remain inside the margins of ±10%. Therefore, the conclusion of no clinically meaningful differences remains unchanged under both extreme cases.

Table 28. Sensitivity Analysis of the Primary Endpoint Using Extreme Case Imputation

Percent Improvement in Psoriasis Area and Severity Index (PASI) from Baseline to Week 12				
Sensitivity				
Extreme Case	**LS Mean (SE)**	N=191	N=192	**LS Mean Difference $_{B-S}$ 90% CI**
	PASI 100 for Stelara **PASI 0 for Bmab 1200**	81.280 (3.431)	84.118 (3.372)	-2.838 (-5.326, -0.349)
	PASI 0 for Stelara **PASI 100 for Bmab 1200**	74.306 (3.510)	72.557 (3.450)	1.748 (-0.798, 4.294)

Source: Reviewer Analysis; LS Mean = Least squares mean, SE = standard error, B= Bmab 1200, S= Stelara. ANCOVA model included the treatment group and randomization stratification variables (region, body weight at baseline category, baseline psoriatic arthritis status, and previous biologic use) as fixed factors.

Assay Sensitivity and Constancy

Study BM12H-PSO-03-G-02 was a comparative clinical study of Bmab 1200 and EU-Stelara; it did not include a placebo arm. The following published placebo-controlled trials of Stelara in subjects with moderate to severe plaque psoriasis included the

percent improvement in PASI at Week 12 as a secondary endpoint. The key design criteria and results for these published Stelara trials are presented in Table 30

All trials below had similar inclusion criteria (BSA ≥ 10%, PASI ≥ 12, and sPGA ≥ Moderate or Marked). The percent improvement in PASI for the Stelara arm in Study BM12H-PSO-03-G-02 was generally consistent with the results from the published Stelara studies at Week 12. Given the low placebo response rates in the previous studies, and the consistent response rates of Stelara across the published studies, the assumption of assay sensitivity may be reasonable for Study BM12H-PSO-03-G-02.

Table 29. Study Characteristics and Results of Published Stelara Studies

	Leonardi (2008)	Papp (2008)	Tsai (2011)	Study BM12H-PSO-03-G-02
Selected inclusion criteria	BSA ≥ 10% PASI ≥ 12 sPGA ≥ Marked (3)	BSA ≥ 10% PASI ≥ 12 sPGA ≥ Moderate (3)	BSA ≥ 10% PASI ≥ 12 sPGA ≥ Moderate (3)	BSA ≥ 10% PASI ≥ 12 sPGA ≥ Moderate (3)
Region/Country	USA, Canada, Belgium	Austria, Canada, France, Germany, Switzerland, UK, USA	Korea, Taiwan	Estonia, Georgia, Latvia, Poland, USA
Baseline PASI Mean Stelara 45 mg Stelara 90 mg Placebo	 20.5 19.7 20.4	 19.4 20.1 19.4	 25.2 - 22.9	 22.5 24.8 -
% Imp. In PASI Stelara 45 mg Stelara 90 mg Placebo	 75.6 77.2 7.0	 77.0 82.1 4.9	 78.5 - 3.1	 78.5 85.2 -

Source: Reviewer Table

Analysis of Secondary Clinical Endpoint(s) of Interest

Secondary efficacy endpoints included PASI response endpoints (PASI50, PASI 75, PASI 90, PASI 100), success on the sPGA (0 or 1). These endpoints were evaluated at a variety of timepoints. The response rates for some secondary endpoints of interest including the PASI response endpoints and sPGA at Week 12 for FAS and PPS are presented in Table 31. For both FAS and PPS, the response rates were generally similar across the treatment arms.

Table 30. Selected Secondary Endpoint Response Rates at Week 12

	FAS		PPS	
Week 12	**Bmab 1200 N=191**	**EU-Stelara N=192**	**Bmab 1200 N=186**	**EU-Stelara N=186**
PASI50	186 (97.4%)	185 (96.4%)	182 (97.9%)	181 (97.3%)
PASI75	168 (88.0%)	169 (88.0%)	164 (88.2%)	165 (88.7%)
PASI90	107 (56.0%)	118 (61.5%)	104 (55.9%)	116 (62.4%)

PASI100	41 (21.5%)	48 (25.0%)	39 (21.0%)	48 (25.8%)
sPGA 0 or 1	161 (84.3%)	166 (86.5%)	156 (83.9%)	161 (86.6%)

Source: Reviewer analysis. Non-responder imputation was implemented.

Table 32 below shows the selected secondary endpoint response rates at Week 12 by weight group (≤100 kg, >100 kg). For subjects ≤ 100 kg as well as for subjects > 100 kg, the response rates were generally comparable across the two arms. Given the small number of subjects in the subgroup of subjects with bodyweight > 100 kg at baseline, it would be difficult to draw a meaningful conclusion based on these findings.

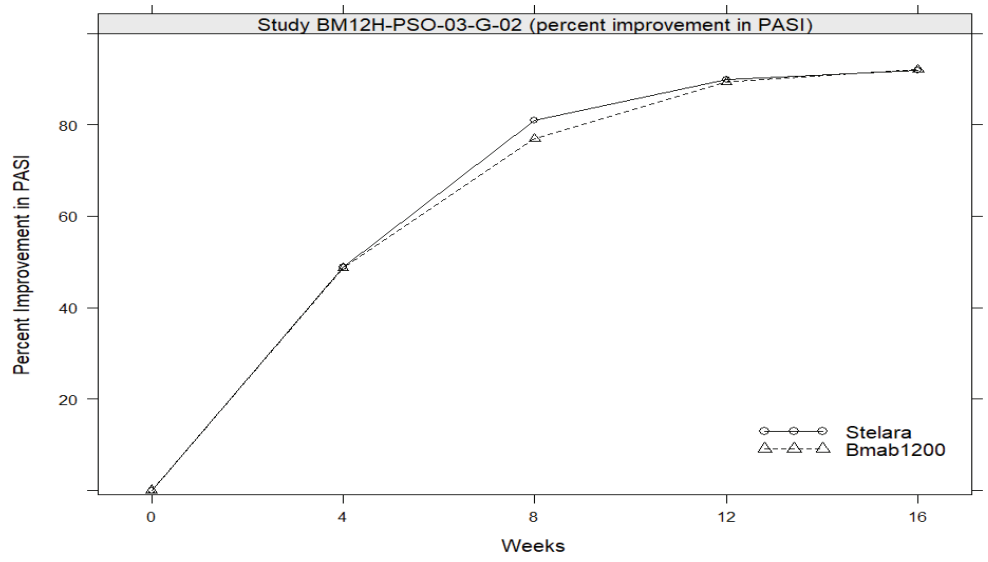
Table 31. Selected Secondary Endpoint Response Rates at Week 12 by Weight Group

	FDA's FAS (≤100 kg)		FDA's FAS (>100kg)	
Week 12	**Bmab 1200 N=151**	**EU-Stelara N=149**	**Bmab 1200 N=40**	**EU-Stelara N=43**
PASI50	147 (97.4%)	142 (95.3%)	39 (97.5%)	43 (100%)
PASI75	132 (87.4%)	132 (88.6%)	36 (90.0%)	37 (86.1%)
PASI90	81 (53.6%)	94 (63.1%)	26 (65.0%)	24 (55.8%)
PASI100	34 (22.5%)	38 (25.5%)	7 (17.5%)	10 (23.3%)
sPGA 0 or 1	127 (84.1%)	128 (85.9%)	34 (85.0%)	38 (88.4%)

Source: Reviewer Analysis. Non-responder imputation was implemented.

The average percent changes in PASI for Bmab 1200 and EU-Stelara were similar at each visit through Week 16. See Figure 5.

Figure 5. Average Percent Improvement in PASI by Visit (FAS)



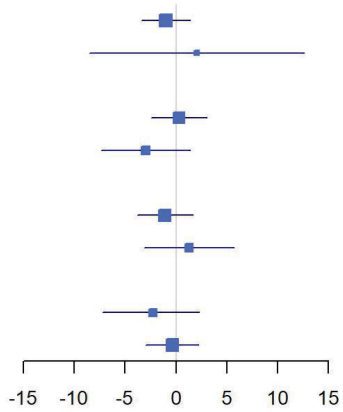
Source: Reviewer figure

Subgroup Analyses

Figure 6presents subgroup analysis by age group (<65 or ≥65 years of age), sex (male or female), body weight at baseline (≤100 kg, >100 kg), and prior biologic use (yes or no) along with 95% CIs for the difference in LS Means. The subgroups of ≥ 65 years of age, with prior biologic use, baseline weight >100 kg in Bmab 1200 were small. Therefore, it is difficult to make meaningful comparisons across age, prior biologic use, and baseline bodyweight classifications. For the sex subgroups, the percent improvement in PASI showed that females in Bmab 1200 were numerically lower than those in the EU-Stelara arm whereas the males showed similar results. However, given that the female subgroup was smaller than that of the males, it might be difficult to make a meaningful comparison across the sex subgroup. Note that all but two subjects in the study were white, so subgroup analysis by race was not possible.

Figure 6. Percent Improvement in PASI at Week 12 by Age, , Weight, Prior Biologic for Psoriasis Groups

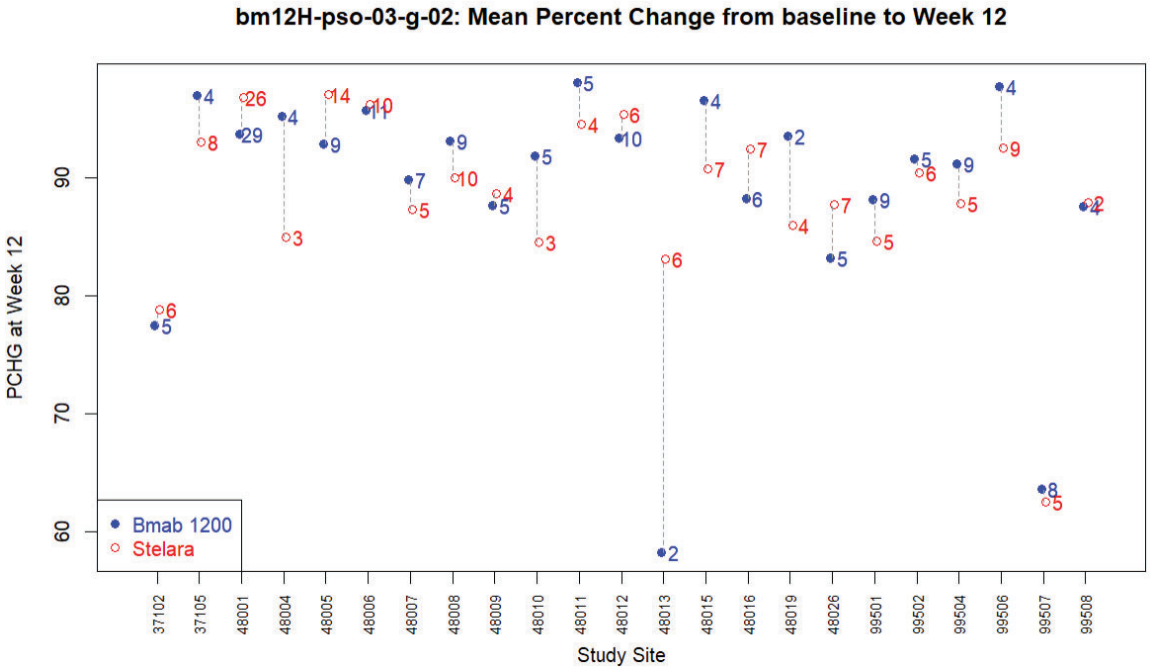
Subgroups (n[B], n[A])	Bmab1200 (N=194)	EU-Stelara (N=387)	LSM diff
Age			
<65 years (178, 176)	78.32	79.32	-1.00
>=65 years (13, 17)	82.78	80.71	2.07
Sex			
Male (121, 136)	75.96	75.65	0.31
Female (70, 57)	89.01	91.98	-2.98
Weight			
<=100 kg (151, 150)	77.47	78.54	-1.07
>100 kg (40, 43)	86.48	85.18	1.30
Prior Biologic for Ps			
Yes (27, 26)	90.79	93.05	-2.26
No (164, 167)	78.95	79.31	-0.36



Source: Reviewer Figure; Two-sided 95% CI for the difference in LS Means plotted above. ANCOVA model

Subgroup analyses for the primary endpoint by site is presented in Figure 7. As there were many small sites, only those sites with a minimum of 6 subjects were included in the analysis.

Figure 7. Percent Improvement in PASI by Site



Source: Reviewer Figure

6.3. Review of Safety Data

6.3.1. Methods

To evaluate comparative safety, adverse events, laboratory examination, vital signs, hypersensitivity, and immunogenicity were reviewed. The primary study used to evaluate comparative safety was the comparative clinical study, BM12H-PSO-03-G-02, as it provided comparisons between EU-Stelara and Bmab 1200 in subjects with moderate to severe plaque psoriasis for up to 12 weeks (primary efficacy assessment). Additionally, a portion of subjects with PASI 50 response or better by Week12 in Study BM12H-PSO-03-G-02 who received EU-Stelara were transitioned to Bmab 1200 at Week 16 in order to assess for potential safety issues after transitioning from EU-Stelara to Bmab 1200 for an additional 12 weeks. Subjects who achieved ≥ PASI 75 response at Week 28 continued the same treatment that they were rerandomized to receive at Week 16 until Week 40 (last dose), with follow-up until Week 52. Safety data from the PK similarity study (BM12H-NHV-01-G-01) in healthy volunteers were also reviewed as supportive of the primary safety assessment.

Clinical Studies Used to Evaluate Safety

The Applicant collected safety data from two clinical studies, as listed in Section 2.2 and summarized below. In both studies, the safety analysis population is the 'as treated' population, i.e., all subjects who took at least one dose of the investigational product

they actually received. See Section 5.3 and Section 6.2.1 for the study schemas for Study BM12H-NHV-01-G-01 and Study BM12H-PSO-03-G-02 respectively.

In the PK similarity study (BM12H-NHV-01-G-01), a total of 258 subjects received a single dose of 45 mg SC of either Bmab 1200 (86 subjects), US-Stelara (87 subjects), or EU-Stelara (85 subjects) with a follow-up period of 16 weeks (112 days). This study was conducted in healthy subjects and had limited follow-up. Therefore, only limited safety information could be obtained from this study and are not captured in this review.

The primary safety data was derived from the comparative clinical study (BM12H-PSO-03-G-02), which was conducted in three treatment periods. In the Treatment Period 1 (TP1, from baseline visit to Week 16 [pre-dosing]), 384 subjects were randomized in a 1:1 ratio to receive either Bmab 1200 (191 subjects) or EU-Stelara (193 subjects). Subjects were dosed according to weight (45mg for subjects weighing <100kg and 90 mg for subjects weighing ≥100kg) according to the standard dosing schedule for US-Stelara: 45mg or 90mg initially and 4 weeks later, followed by 45mg or 90mg at Week 16. The primary efficacy endpoint (percentage of PASI improvement from baseline to Week 12) was evaluated at Week 12.

During Treatment Period 2 (TP2, Week 16 dosing to Week 28 [pre-dosing]), subjects initially randomized to EU-Stelara who achieved PASI ≥ 50 by Week 12 were rerandomized in a 1:1 ratio to continue EU-Stelara (EU-Stelara/EU-Stelara, 94 subjects) or switch to Bmab 1200 (EU-Stelara/ Bmab 1200, 92 subjects). Subjects in the Bmab 1200 arm were continued on Bmab 1200 (Bmab 1200/ Bmab 1200, 185 subjects). At Week 16, subjects who had less than PASI 50 response were discontinued.

Treatment Period 3 (TP3) was from Week 28 dosing to Week 52. A total of 333 subjects (EU-Stelara/EU-Stelara-81 subjects, EU-Stelara/ Bmab 1200-84 subjects, Bmab 1200/ Bmab 1200-168 subjects) who completed TP2 and achieved PASI ≥ 75 response at Week 28 continued the same treatment that they were rerandomized to receive at Week 16 until Week 40 (last dose), with follow-up until Week 52.

The size and adequacy of the safety database from the perspective of demonstration of no clinically meaningful differences is sufficient.

Categorization of Adverse Events

A Serious Adverse Events (SAE) is defined as any event that
• results in death
• is immediately life-threatening*
• requires inpatient hospitalization or prolongation of existing hospitalization**
• results in persistent or significant disability/incapacity
• is a congenital anomaly/birth defect
• important medical events that may not result in death, be life-threatening, or require hospitalization may be considered SAEs when, based upon appropriate medical judgment, they may jeopardize the patient or may require medical or surgical

intervention to prevent one of the outcomes listed in this definition. Examples of such medical events include allergic bronchospasm requiring intensive treatment in an emergency room or at home, blood dyscrasias or convulsions that do not result in inpatient hospitalization, or the development of drug dependency or drug abuse.

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

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

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

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

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

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

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

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

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

The following events will be considered as AESIs: infections, malignancies, hypersensitivity reactions, posterior reversible encephalopathy syndrome (PRES), and noninfectious pneumonia.

Infections
All AEs related to infection, including TB and sepsis, are reported.

Malignancies
AEs related to malignancy including but not limited to cutaneous and non-cutaneous malignancies are reported.

Hypersensitivity reactions
All AEs related to hypersensitivity reactions, including anaphylaxis and angioedema, are reported.

Anaphylactic reactions
Anaphylaxis are identified according to Sampson criteria. Anaphylaxis is likely when any 1 of the 3 criteria are fulfilled.

1. Acute onset of an illness (minutes to several hours) with involvement of the skin, mucosal tissue, or both (eg, generalized hives, pruritus or flushing, swollen lips-tongue-uvula) and at least one of the following:
   a) Respiratory compromise (eg, dyspnea, wheeze or bronchospasm, stridor, reduced peak expiratory flow, hypoxemia)
   b) Reduced blood pressure or associated symptoms of end-organ dysfunction (eg, hypotonia [collapse], syncope, incontinence)

2. Two or more of the following that occur rapidly after exposure to a likely allergen for that patient (minutes to several hours):
   a) Involvement of the skin-mucosal tissue (eg, generalized hives, itch-flush, swollen lips-tongue-uvula)

b) Respiratory compromise (eg, dyspnea, wheeze-bronchospasm, stridor, reduced peak expiratory flow, hypoxemia)
c) Reduced blood pressure or associated symptoms (eg, hypotonia [collapse], syncope, incontinence)
d) Persistent gastrointestinal symptoms (eg, crampy abdominal pain, vomiting)

3. Reduced blood pressure after exposure to known allergen for that patient (minutes to several hours):
a) Adults: Systolic blood pressure of less than 90 mm Hg or greater than 30% decrease from that person's baseline.

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

Noninfectious Pneumonia
All AEs of noninfectious pneumonia are reported. Clinical presentations may include cough, dyspnea, and interstitial infiltrates.

Safety Analyses

To evaluate comparative safety, adverse events, laboratory examination, vital signs, hypersensitivity, and immunogenicity were reviewed. The primary study used to evaluate comparative safety was the comparative clinical study, BM12H-PSO-03-G-02, as it provided comparisons between EU-Stelara and Bmab 1200 in subjects with moderate to severe plaque psoriasis for up to 12 weeks (primary efficacy assessment). Additionally, a portion of subjects with PASI ≥ 50 response in Study BM12H-PSO-03-G-02 who received EU-Stelara were transitioned to Bmab 1200 at Week 16 in order to assess for potential safety issues after transitioning from EU-Stelara to Bmab 1200 for an additional 12 weeks. Subjects who completed TP2 and achieved PASI ≥ 75 response at Week 28 continued the same treatment that they were rerandomized to receive at Week 16 for additional 24 weeks.

Safety data from the PK similarity study (BM12H-NHV-01-G-01) in healthy volunteers was reviewed as supportive of the primary safety assessment.

6.3.2. Major Safety Results

Relevant Characteristics of the Population Evaluated for Safety

Table 32. Population Demographics of Study BM12H-PSO-03-G-02

	Bmab 1200 (N=191)	EU-Stelara (N=193)	Total (N=384)
Age (years)			
Mean (SD)	42.5 (13.09)	43.9 (13.58)	43.2 (13.34)
Median (Min, Max)	41.0 (18, 74)	42.0 (20, 79)	42.0 (18, 79)
Sex / Childbearing Potential			
F	70 (36.6)	57 (29.5)	127 (33.1)
N	22 (11.5)	22 (11.4)	44 (11.5)
Postmenopausal	20 (10.5)	20 (10.4)	40 (10.4)
Surgically Sterile	2 (1.0)	2 (1.0)	4 (1.0)
Y	48 (25.1)	35 (18.1)	83 (21.6)
M	121 (63.4)	136 (70.5)	257 (66.9)
Region			
Europe	189 (99.0)	189 (97.9)	378 (98.4)
EST	10 (5.2)	9 (4.7)	19 (4.9)
GEO	45 (23.6)	35 (18.1)	80 (20.8)
LVA	11 (5.8)	18 (9.3)	29 (7.6)
POL	123 (64.4)	127 (65.8)	250 (65.1)
US	2 (1.0)	4 (2.1)	6 (1.6)
Ethnicity			
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			
BLACK OR AFRICAN AMERICAN	1 (0.5)	1 (0.5)	2 (0.5)
WHITE	190 (99.5)	192 (99.5)	382 (99.5)
Height (cm) at Baseline			
Mean (SD)	172.8 (8.80)	174.2 (8.65)	173.5 (8.74)
Median (Min, Max)	172.5 (143, 192)	175.0 (149.7, 198)	174.8 (143, 198)
Weight (kg) at Baseline			
Mean (SD)	84.7 (17.88)	87.0 (17.37)	85.8 (17.64)
Median (Min, Max)	84.2 (48, 128.7)	86.7 (46, 128.4)	85.0 (46, 128.7)
BMI (kg/m^2)			
Mean (SD)	28.2 (5.06)	28.7 (5.44)	28.4 (5.25)
Median (Min, Max)	27.3 (18.73, 41.55)	28.4 (17.71, 50.16)	27.9 (17.71, 50.16)
Smoker Status			
Ex-Smoker	22 (11.5)	19 (9.8)	41 (10.7)
Never Smoked	108 (56.5)	122 (63.2)	230 (59.9)
Smoker	61 (31.9)	52 (26.9)	113 (29.4)
Alcohol Status			
Current drinker	74 (38.7)	73 (37.8)	147 (38.3)

Light drinker (less than 2 drinks per day)	73 (38.2)	71 (36.8)	144 (37.5)
Moderate drinker (2-4 drinks per day)	1 (0.5)	2 (1.0)	3 (0.8)
Ex-drinker	1 (0.5)	0	1 (0.3)
Non drinker	116 (60.7)	119 (61.7)	235 (61.2)
Unknown	0	1 (0.5)	1 (0.3)
Previous exposure to biologic-based therapies			
No prior exposure to biologics	165 (86.4)	166 (86.0)	331 (86.2)
Prior exposure to biologics	26 (13.6)	27 (14.0)	53 (13.8)
Concomitant psoriatic arthritis			
Concomitant psoriatic arthritis	30 (15.7)	32 (16.6)	62 (16.1)
No Concomitant psoriatic arthritis	161 (84.3)	161 (83.4)	322 (83.9)

Source: Reviewer's analysis
SD = Standard Deviation.

Other Product-Specific Safety Concerns

Deaths
There were no deaths reported in BM12H-PSO-03-G-02.

Treatment Emergent Adverse Events

Serious adverse events (SAE)s
Overall, 7 subjects (1.8%) experienced 9 serious treatment emergent adverse events (TEAEs) through the study.

In TP1, four subjects reported 5 SAEs, none of which was considered related to study drug treatment.

Table 33. SAEs in Subjects with Psoriasis in TP1 (Up to Week 16)

Preferred Term	Bmab 1200 N = 191 n (%)	EU-Stelara N = 193 n (%)
Any SAE	3 (1.6)	1 (0.5)
Endometrial adenocarcinoma	1 (0.5)	0 (0.0)
Squamous cell carcinoma of the tongue	1 (0.5)	0 (0.0)
Acute myocardial infarction	1 (0.5)	0 (0.0)
Cardiac failure	1 (0.5)	0 (0.0)
Cholecystitis acute	0 (0.0)	1 (0.5)

Source: Reviewer's analysis

Selected narratives for subjects taking Bmab 1200 in TP1:

Subject (b) (6), a 72-year-old female with a history of smoking, angina pectoris, hypertension, coronary artery disease, obesity, chronic obstructive pulmonary disease, hypercholesterolaemia, and psoriatic arthropathy suffered Grade 3 serious adverse events (SAEs) of cardiac failure and acute myocardial infarction on Study Day 7 after receiving her first dose of Bmab 1200 group in TP1 (45 mg) that required hospitalization. She was treated medically and received a a drug-eluting stent. The SAEs of cardiac failure and acute myocardial infarction were considered resolved on Study Day 15 after treatment with medications and drug-eluting stent, and the patient was discharged from the hospital on the same day. The dose of the study drug was not changed because of the SAEs of cardiac failure and acute myocardial infarction. The subject continued to receive Bmab 1200 at 45 mg during TP2 and TP3. She completed the study on Study Day 366.

This reviewer agrees with the investigator and the Applicant that the SAEs are not likely related to the study drug, as the patient's history of angina pectoris, hypertension, coronary artery disease, obesity, psoriasis, hypercholesterolemia, and smoking provided a plausible alternate etiology for the events; additionally, the events resolved despite ongoing treatment with the study drug.

Table 34. SAEs in Subjects with Psoriasis in TP2 (Week 16-28)

	Bmab 1200-Bmab 1200	EU-Stelara-EU-Stelara	EU-Stelara-Bmab 1200
	N = 185	N = 94	N = 92
Preferred Term	n (%)	n (%)	n (%)
Any SAE	1 (0.5)	0 (0.0)	0 (0.0)
Abdominal pain	1 (0.5)	0 (0.0)	0 (0.0)
Jaundice cholestatic	1 (0.5)	0 (0.0)	0 (0.0)

Source: Reviewer's analysis

Subject (b) (6), a 66-year-old female with no history of significant alcohol use had mildly elevated gamma glutamyltransferase (GGT) levels at 69 U/L (reference range: 5-32 U/L) at Screening and on Study Day 1 (83 U/L, reference range: 5-32 U/L). See table below for the relevant laboratory values. Subject developed mild increase in other liver enzymes (AST/ALT /ALP), in addition to worsening GGT level, starting from Week 8, all of which much worsened at Week 20, after her third injection of Bmab 1200 (45 mg) at Week 16. No concomitant medications were reported.

On Day 160, the subject was admitted to the hospital for abdominal pain and jaundice. On Study Day 162, ultrasound and computed tomography (CT) scans showed cholestasis and dilation of the intrahepatic biliary tract ducts; no mechanical cause of cholestasis was identified. On Study Day 170, endoscopic cholangiopancreatography

(ERCP) showed a tight stenosis of the common hepatic duct with post-stenotic dilation of the bile ducts. The patient underwent sphincterotomy of Vater papilla and stenting of the common bile duct. The events were considered resolved on Study Day 172, and the patient was discharged from the hospital on the same day.

The study drug was permanently discontinued because of the SAEs of abdominal pain and jaundice cholestatic. The subject had received 3 doses in the original Week 28 study and the last dose of the study drug was on Study Day 108. She was withdrawn early from the study on Study Day 199 at the discretion of the investigator because of medical or administrative reasons.

This reviewer agrees with the investigator and the Applicant that possible causality of the SAEs to the study drug could not be excluded, due to the temporal association, though 'cholestasis of the intrahepatic biliary tract' and tight stenosis of the bile duct could have contributed to them as well.

Table 35. Relevant Laboratory Values

Visit	Study Day	Date	ALT (U/L) (RR: 10 to 33)	AST (U/L) (RR: 10 to 36)	GGT (U/L) (RR: 5 to 32)	ALP (U/L) (RR: 30 to 115)	Direct Bilirubin (µmol/L) (RR: 0 to 6.8)
Screening	-18	(b) (4)	31	28	**69**	107	3.4
Baseline	1		24	23	**83**	**117**	3.4
Week 4	31		24	23	**79**	**118**	3.4
Week 8	66		**51**	**51**	**143**	**119**	3.4
Week 12	87		**72**	**47**	**431**	**197**	3.4
Week 16	108		**45**	**40**	**628**	**281**	4.1
Week 20	143		**566**	**347**	**837**	**419**	**10.9**
			ALT (U/L) (RR: <55)[a]	AST (U/L) (RR: 5 to 34)[a]	GGT (U/L) (RR: 9 to 36)[a]	ALP (U/L) (RR: 40 to 150)[a]	Bilirubin (mg/dL) (RR: 0.2 to 1.2)[a]
	160	(b) (4)	**328**	**166**	**622**	**341**	**3.86**
	164		**218**	**122**	—	—	**4.43**

Source; Cinical Study Report.
Abbreviations: ALP, alkaline phosphatase; ALT, alanine aminotransferase; AST, aspartate aminotransferase; GGT, gamma glutamyltransferase; RR, reference range
Note: Bolded text denotes that the laboratory value was out of the RR.

During TP3, two subjects reported two SAEs. Neither of these SAEs were considered related to study drug treatment.

Table 36. SAEs in Subjects with Psoriasis in TP3 (Week 28-52)

Preferred Term	Bmab 1200-Bmab 1200 N = 168 n (%)	EU-Stelara-EU-Stelara N = 81 n (%)	EU-Stelara-Bmab 1200 N = 84 n (%)
Any SAE	1 (0.6)	0 (0.0)	0 (0.0)
Right hemisphere ischemic stroke	1 (0.6)	0 (0.0)	0 (0.0)
Uterovaginal prolapse	1 (0.6)	0 (0.0)	0 (0.0)

Source: Reviewer's analysis

Selected narratives for subjects taking Bmab 1200 in TP3:

Subject (b) (6), a 57-year-old female with a history of smoking, hypercholesterolaemia, and ischaemic stroke (left-sided ischemic stroke) suffered a SAE of right hemisphere ischemic stroke on Study Day 339 during TP3, 60 days after her 5th dose of Bmab 1200 at 45 mg. She was admitted to the hospital for weakness and loss of sensation in the left side of her body. CT head showed right hemisphere ischemia, CT angiography showed a short segment narrowing of the initial section of the right internal carotid artery, up to 60% a congenital structural defect, which was associated with the present stroke.

The event was considered resolved on Study Day 347, and the patient was discharged on the same day in good general condition; neurologically, the patient had persistent hypoesthesia left-sided humeral.

This reviewer agrees with the investigator and the Applicant that the SAEs are not likely related to the study drug, as the patient's history of hypercholesterolemia, ischemic stroke (in 2019), right internal carotid artery stenosis, congenital structural defect of the intracerebral artery, and smoking provided a plausible alternate etiology for the events.

Dropouts and/or Discontinuations

TEAEs that led to study treatment discontinuation or study withdrawal are listed in the tables below.

Table 37. Study Treatment Discontinuation or Study Withdrawal in Subjects with Psoriasis in TP1 (Up to Week 16)

Preferred Term	Bmab 1200 N = 191 n (%)	EU-Stelara N = 193 n (%)
Any AE	2 (1.0)	3 (1.6)
Endometrial adenocarcinoma	1 (0.5)	0 (0.0)
Squamous cell carcinoma of the tongue	1 (0.5)	0 (0.0)

Alcohol poisoning	0 (0.0)	1 (0.5)
Hypersensitivity*	0 (0.0)	2 (1.0)

Source: Reviewer's analysis
*Hypersensitivity includes: Angioedema, Rash maculo-papular

Table 38. Study Treatment Discontinuation or Study Withdrawal in Subjects with Psoriasis in TP2 (Week 16-28)

Preferred Term	Bmab 1200-Bmab 1200 N = 185 n (%)	EU-Stelara-EU-Stelara N = 94 n (%)	EU-Stelara-Bmab 1200 N = 92 n (%)
Any AE	1 (0.5)	0 (0.0)	0 (0.0)
Abdominal pain	1 (0.5)	0 (0.0)	0 (0.0)
Jaundice cholestatic	1 (0.5)	0 (0.0)	0 (0.0)

Source: Reviewer's analysis

No subject had TEAEs that led to study treatment discontinuation or study withdrawal from the study during TP3.

Overall, there were very few discontinuations at any point during the study in any arm. No clinically significant differences were found between Bmab 1200 arm and EU-Stelara arm.

Common Adverse Events

Common TEAEs are listed in the tables below. During TP1, the incidences of upper respiratory infections and hyperlipidemia were higher in the Bmab 1200 arm compared to EU-Stelara arm.

Table 39. TEAEs in ≥ 1% Subjects with Psoriasis in TP1 (Up to Week 16)

Preferred Term	Bmab 1200 N = 191 n (%)	EU- Stelara N = 193 n (%)
Any AE	81 (42.4)	66 (34.2)
Upper respiratory tract infection*	23 (12.0)	17 (8.8)
Hyperlipidemia*	21 (11.0)	7 (3.6)
Elevated liver function tests*	9 (4.7)	8 (4.1)
Hypertension*	5 (2.6)	3 (1.6)
Influenza	4 (2.1)	6 (3.1)
Urinary tract infection	4 (2.1)	1 (0.5)

Hyperglycaemia	3 (1.6)	0 (0.0)
Hypersensitivity*	3 (1.6)	5 (2.6)
Proteinuria	3 (1.6)	2 (1.0)
Anaemia	2 (1.0)	0 (0.0)
Arthralgia	2 (1.0)	2 (1.0)
Covid-19	2 (1.0)	0 (0.0)
Creatinine renal clearance decreased	2 (1.0)	1 (0.5)
Dizziness	2 (1.0)	0 (0.0)
Somnolence	2 (1.0)	1 (0.5)
Blood glucose increased	1 (0.5)	2 (1.0)
Headache	1 (0.5)	2 (1.0)
C-reactive protein increased	0 (0.0)	3 (1.6)
Leukocytosis	0 (0.0)	2 (1.0)
Obesity	0 (0.0)	2 (1.0)
Oral herpes	0 (0.0)	2 (1.0)
Toothache	0 (0.0)	2 (1.0)

Source: Reviewer's analysis
*Elevated liver function tests includes: Alanine aminotransferase increased, Aspartate aminotransferase increased, Blood bilirubin increased, Gamma-glutamyltransferase increased
*Hyperlipidemia includes: Blood cholesterol increased, Blood triglycerides increased, Hyperlipidaemia, Hypertriglyceridaemia, Lipids increased, Acquired mixed hyperlipidaemia
*Hypersensitivity includes: Angioedema, Pruritus, Rash maculo-papular, Urticaria
*Hypertension includes: Blood pressure increased, Hypertension, Essential hypertension
*Upper respiratory tract infection includes: Nasopharyngitis, Pharyngitis, Pharyngitis streptococcal, Respiratory tract infection viral, Rhinitis, Sinusitis, Upper respiratory tract infection, Viral upper respiratory tract infection, Upper respiratory tract inflammation

During TP2, the incidences of hyperlipidemia and elevated liver function tests were higher in the Bmab 1200-Bmab 1200 arm compared to EU-Stelara-Bmab 1200 arm or EU-Stelara-EU-Stelara arm.

Table 40. TEAEs in ≥ 1% Subjects with Psoriasis in TP2 (Week 16-28)

Preferred Term	Bmab 1200-Bmab 1200 N = 185 n (%)	EU-Stelara-EU-Stelara N = 94 n (%)	EU-Stelara-Bmab 1200 N = 92 n (%)
Any AE	46 (24.9)	20 (21.3)	24 (26.1)
Upper respiratory tract infection*	9 (4.9)	3 (3.2)	6 (6.5)
Hyperlipidemia*	7 (3.8)	1 (1.1)	1 (1.1)
Elevated liver function tests*	6 (3.2)	1 (1.1)	1 (1.1)
Covid-19	1 (0.5)	0 (0.0)	3 (3.3)
Influenza	0 (0.0)	3 (3.2)	1 (1.1)

Urinary tract infection	1 (0.5)	1 (1.1)	2 (2.2)
Bronchitis	1 (0.5)	0 (0.0)	2 (2.2)
Neutropenia	3 (1.6)	0 (0.0)	0 (0.0)
Arthralgia	0 (0.0)	2 (2.1)	0 (0.0)
Eosinophilia	2 (1.1)	0 (0.0)	0 (0.0)
Proteinuria	0 (0.0)	0 (0.0)	2 (2.2)
Vaginal infection	2 (1.1)	0 (0.0)	0 (0.0)
Weight increased	2 (1.1)	0 (0.0)	0 (0.0)

Source: Reviewer's analysis
*Elevated liver function tests includes: Alanine aminotransferase increased, Aspartate aminotransferase increased, Blood bilirubin increased, Gamma-glutamyltransferase increased
*Hyperlipidemia includes: Blood cholesterol increased, Blood triglycerides increased, Hyperlipidaemia, Hypertriglyceridaemia, Lipids increased, Acquired mixed hyperlipidaemia
*Hypersensitivity includes: Angioedema, Pruritus, Rash maculo-papular, Urticaria
*Hypertension includes: Blood pressure increased, Hypertension, Essential hypertension
*Upper respiratory tract infection includes: Nasopharyngitis, Pharyngitis, Pharyngitis streptococcal, Respiratory tract infection viral, Rhinitis, Sinusitis, Upper respiratory tract infection, Viral upper respiratory tract infection, Upper respiratory tract inflammation

It is noticed that hyperlipidemia occurred more frequently in the Bmab 1200 arm than that in the EU-Stelara arm during TP1. However, none of the TEAEs of hyperlipidemia was serious and none led to study treatment discontinuation or study withdrawal. In addition, most of the TEAEs of hyperlipidemia were mild or moderate in severity. No clinical significance was found in the frequency of severe hyperlipidemia between Bmab 1200 arm and EU-Stelara arm during TP1. Furthermore, very few cases of lipidemia occurred during TP2, no clinically significant difference was found between the different treatment arms.

Overall, no clinically significant differences in common TEAEs were found between Bmab 1200 arm and EU-Stelara arm.

Adverse Reactions (ADRs)

The TEAEs considered related to treatments are listed in the tables below.

Table 41. ADRs in Subjects with Psoriasus in TP1 (Up to Week 16)

Preferred Term	Bmab 1200 N = 191 n (%)	EU-Stelara N = 193 n (%)
Any AE	17 (8.9)	12 (6.2)
Elevated liver function tests*	4 (2.1)	2 (1.0)
Upper respiratory tract infection*	4 (2.1)	3 (1.6)
Dizziness	2 (1.0)	0 (0.0)
Hypersensitivity*	2 (1.0)	3 (1.6)

Somnolence	2 (1.0)	0 (0.0)

Source: Reviewer's analysis
*Elevated liver function tests includes: Alanine aminotransferase increased, Aspartate aminotransferase increased, Gamma-glutamyltransferase increased
*Hyperlipidemia includes: Hypertriglyceridaemia, Lipids increased
*Hypersensitivity includes: Angioedema, Pruritus, Rash maculo-papular, Urticaria
*Hypertension includes: Blood pressure increased
*Upper respiratory tract infection includes: Nasopharyngitis, Pharyngitis, Rhinitis, Sinusitis

Table 42. ADRs in Subjects with Psoriasus in TP2 (Week 16-28)

Preferred Term or CMQ	Bmab 1200-Bmab 1200 N = 185 n (%)	EU-Stelara- EU-Stelara N = 94 n (%)	EU-Stelara-Bmab 1200 N = 92 n (%)
Any AE	12 (6.5)	1 (1.1)	8 (8.7)
Upper respiratory tract infection*	3 (1.6)	0 (0.0)	2 (2.2)
Elevated liver function tests*	2 (1.1)	0 (0.0)	0 (0.0)
Neutropenia	2 (1.1)	0 (0.0)	0 (0.0)

Source: Reviewer's analysis
*Hyperlipidemia includes: Lipids increased
*Upper respiratory tract infection includes: Nasopharyngitis, Rhinitis

Overall, very few TEAEs of ADR occurred at any point during the study in any arm. No clinically significant differences were found between Bmab 1200 arm and EU-Stelara arm.

No injection site reactions were reported in Study BM12H-PSO-03-G-02.

Adverse Events of Special Interest (AESIs)

The prescribing information for US-licensed Stelara carries the following warnings and precautions: infections (including cellulitis, pneumonia, sepsis, zoster, abscess, and tuberculosis), malignancies, hypersensitivity reactions, posterior reversible encephalopathy syndrome (PRES), and noninfectious pneumonia.

The Applicant identified the following AEs as Events of Interest: infections, malignancies, hypersensitivity reactions, posterior reversible encephalopathy syndrome (PRES), and noninfectious pneumonia.

AESIs are listed in the tables below. Infection was the most frequent AESI for both TP1 and TP2. No serious infection was reported in either treatment period.

Table 43. AESIs in Subjects with Psoriasis in TP1 (Up to Week 16)

AESI Type	Bmab 1200	EU-Stelara

Preferred Term	N = 191 n (%)	N = 193 n (%)
Infections	**38 (19.9)**	**32 (16.6)**
Hypersensitivity reactions	**1 (0.5)**	**3 (1.6)**
Pruritus	0 (0.0)	1 (0.5)
Urticaria	1 (0.5)	0 (0.0)
Angioedema	0 (0.0)	1 (0.5)
Rash maculo-papular	0 (0.0)	1 (0.5)
Malignancy	**2 (1.0)**	**0 (0.0)**
Endometrial adenocarcinoma	1 (0.5)	0 (0.0)
Squamous cell carcinoma of the tongue	1 (0.5)	0 (0.0)

Source: Reviewer's analysis

Table 44. AESIs in Subjects with Psoriasis in TP2 (Week 16-28)

AESI Type Preferred Term	Bmab 1200-Bmab 1200 N = 185 n (%)	EU-Stelara-EU-Stelara N = 94 n (%)	EU-Stelara-Bmab 1200 N = 92 n (%)
Infections	**18 (9.7)**	**8 (8.5)**	**17 (18.5)**
Hypersensitivity reaction	**1 (0.5)**	**0 (0.0)**	**1 (1.1)**
Urticaria	1 (0.5)	0 (0.0)	1 (1.1)

Source: Reviewer's analysis.

Other than infections, very few AESIs occurred at any point during the study in any arm. Overall, no clinically significant differences were found between Bmab 1200 arm and EU-Stelara arm.

6.3.3. Additional Safety Evaluations

Laboratory Evaluations

No clinically significant changes over time or differences between treatment arms were observed for hematology or clinical chemistry parameters (including liver function tests and creatinine) in Study BM12H-PSO-03-G-02. Across treatment periods, the proportions of subjects with newly occurring clinically notable values of clinical chemistry parameters were low and there were no clinically significant differences among groups.

Vital Signs

In Study BM12H-PSO-03-G-02, no clinically significant changes were observed in any of the vital signs variables.

ECGs

In Study BM12H-PSO-03-G-02, no clinically significant changes were observed in any of the parameters of the ECGs.

Pregnancies

Two pregnancies were reported during Study BM12H-PSO-03-G-02, one during TP1 and the other one during TP3. The first pregnancy (Subject (b) (6)) occurred on Study Day 95, at the end of TP1, thus completing TP1 and not counted in the tables above for TEAEs, but she did not continue to TP2. The subject received 2 doses of Bmab 1200 before the event. She underwent an elective artificial abortion. No complications or adverse events were reported for the procedure.

Subject (b) (6), who was on EU-Stelara during all TPs, became pregnant after receiving all 5 doses of the study drug, thus completing the study and not counted in the tables above for TEAEs. The patient did not experience any events or illness during the pregnancy, other than some nausea related to the pregnancy during the first trimester. The clinical condition of the fetus at the time of this report was normal.

Overall, there are no residual uncertainties related to the safety analysis.

6.4. Clinical Conclusions on Immunogenicity

The immunogenicity evaluation included qualitative and quantitative measurement of anti-drug antibody (ADA) and neutralizing antibody (NAb) in healthy subjects (from single dose PK studies) and in subjects with plaque psoriasis (multiple doses up to 52 weeks), and an assessment of the impact of ADA on PK, efficacy and safety.
In addition to the evaluation of TEAEs across treatment arms in Study BM12H-PSO-03-G-02, the safety analyses included an evaluation of the frequencies of hypersensitivity, immune mediated reactions, and injection site reactions for all treatment periods. The incidence of hypersensitivity and immune-mediated reactions were infrequent, and there were no injection site reactions. Overall, TEAEs between the two arms were also balanced. The results regarding TEAEs by ADA and NAb positivity status during TP2 were consistent with those in TP1, showing no meaningful differences between treatment arms. ADA positivity was not associated with increased reporting of hypersensitivity and injection site reactions.

Overall, in Study BM12H-PSO-03-G-02, there were no meaningful differences between the frequency of TEAEs in the Bmab 1200/Bmab 1200 arm versus the other treatment arms (EU-Stelara/ Bmab 1200 and EU-Stelara/EU-Stelara), regardless of NAb status. It is concluded that the totality of immunogenicity data from the study, including following

the single transition, support the conclusion that there are no clinically significant differences in immunogenicity between Bmab 1200 and EU-approved Stelara, and do not preclude a conclusion of no clinically meaningful differences between Bmab 1200 and US-licensed Stelara.

Refer to Section 5.4 Clinical Immunogenicity Studies for results of the immunogenicity assessments.

Authors:

Tong Li-Masters, MD, PhD
Clinical Reviewer

Snezana Trajkovic, MD
Clinical Team Leader

6.5. Risk in Terms of Safety or Diminished Efficacy of Switching Between Products and the Any Given Patient Evaluation (to Support a Demonstration of Interchangeability)

The Applicant has developed Bmab 1200 as a proposed interchangeable biosimilar to US-licensed Stelara and is seeking licensure of Bmab 1200 for the same indications, same dosage form, strengths, and routes of administration as US-licensed Stelara.

The Applicant provided sufficient justification that Bmab 1200 can be expected to produce the same clinical results as US-licensed Stelara in any given patient. The scientific justification considered the factors that are described in the FDA guidance for industry, Considerations in Demonstrating Interchangeability with a Reference Product (refer also to Section 6.6 Extrapolation).

The Applicant also provided sufficient scientific justification that the risk in terms of safety or diminished efficacy of alternating or switching between use of Bmab 1200 and US-licensed Stelara is not greater than the risk of using US-licensed Stelara without such alteration or switch. The Applicant referenced the comparative analytical data provided in their application that evaluated and compared critical quality attributes of Bmab 1200 and US-licensed Stelara and the results from the comparative clinical study (Study BM12H-PSO-03-G-02) to support their justification. The Applicant also described that the results from the single transition included in Study BM12H-PSO-03-G-02 provided supportive evidence of a low immunogenic risk and no safety concerns with switching between Bmab 1200 and US-licensed Stelara.

FDA considers the risk of a clinically impactful immunogenic response when alternating or switching between Bmab 1200 and US-licensed Stelara to be low. Thus, a switching study that compares immunogenicity and PK and/or PD to assess whether the risk in terms of safety or diminished efficacy of alternating

or switching between use of Bmab 1200 and US-licensed Stelara is not greater than using US-licensed Stelara without such alternation or switch was considered unnecessary to support a demonstration of interchangeability for Bmab 1200.

The data and information provided by the Applicant are sufficient to demonstrate that Bmab 1200 can be expected to produce the same clinical result as US-licensed Stelara in any given patient and that the risk in terms of safety or diminished efficacy of alternating or switching between use of Bmab 1200 and US-licensed Stelara is not greater than the risk of using US-licensed Stelara without such alternation or switch.

6.6. Extrapolation

The Applicant submitted data and information in support of a demonstration that Bmab1200 is highly similar to U.S.-Stelara notwithstanding minor differences in clinically inactive components and that there are no clinically meaningful differences between Bmab1200 and U.S.-Stelara in terms of safety, purity and potency. In addition, the totality of evidence submitted in the application sufficiently demonstrates that Bmab1200 can be expected to produce the same clinical results as US-licensed Stelara in any given patient and that, the risk in terms of safety or diminished efficacy of alternating or switching between use of Bmab1200 and US-licensed Stelara is not greater than the risk of using US-licensed Stelara without such alteration or switch.

The Applicant is seeking licensure of Bmab1200 for the following indication(s) for which U.S.- Stelara has been previously licensed and for which Bmab1200 has not been directly studied:

- Moderate to severe plaque psoriasis in pediatric patients 6 years and older, who are candidates for phototherapy or systemic therapy.
- Active psoriatic arthritis in adult patients and pediatric patients 6 years and older
- Moderately to severely active Crohn's disease in adults
- Moderately to severely active ulcerative colitis in adults

The Applicant provided a justification for extrapolating data and information submitted in the application to support licensure of Bmab1200 as a biosimilar for each such indication for which licensure is sought and for which U.S.- Stelara has been previously approved. This Applicant's justification was evaluated and considered adequate, as summarized below.

Therefore, the totality of the evidence provided by the Applicant supports licensure of Bmab1200 for each of the following indication(s) for which Biocon Biologics Inc. is seeking licensure of Bmab1200:

- Moderate to severe plaque psoriasis in pediatric patients 6 years and older, who are candidates for phototherapy or systemic therapy.
- Active psoriatic arthritis in adult patients and pediatric patients 6 years and older
- Moderately to severely active Crohn's disease in adults
- Moderately to severely active ulcerative colitis in adults.

6.6.1. Division of Gastroenterology

Executive Summary: Consistent with the principles of the FDA guidance for industry *Scientific Considerations in Demonstrating Biosimilarity to a Reference Product* (April 2015),[7] the Division of Gastroenterology (DG) concludes that the Applicant has provided sufficient scientific justification to support extrapolation of data submitted in the application to support licensure of Bmab1200 as an interchangeable biosimilar to US licensed Stelara, under section 351(k) of the PHS Act, for the non-studied indications of Crohn's disease (CD), and ulcerative colitis (UC) in adults. The scientific justification based on the mechanism of action, pharmacokinetics (PK), immunogenicity, and safety supporting this conclusion are summarized in the following paragraphs.

Mechanism of Action: The mechanisms of action of ustekinumab that are relevant to moderate to severe active plaque psoriasis (PsO; the studied clinical study population) are also relevant to inflammatory bowel disease (IBD) (i.e., CD and UC). The Applicant provided data to support that Bmab1200 has the same known and potential mechanisms of action as US-Stelara, which supports extrapolation to indications not directly studied in the Bmab1200 clinical program. Ustekinumab belongs to the pharmacologic class of interleukin (IL)-23 and IL-12 antagonists. It is a human IgG1κ monoclonal antibody that binds with specificity to the p40 protein subunit used by both the IL-12 and IL-23 cytokines that are involved in inflammatory and immune responses, such as natural killer cell activation and CD4+ T-cell differentiation and activation. In the *in vitro* models, ustekinumab was shown to disrupt IL-12 and IL-23 mediated signaling and cytokine cascades by disrupting the interaction of these cytokines with a shared cell-surface receptor chain, IL-12Rβ1. The cytokines IL-12 and IL-23 have been implicated as important contributors to the chronic inflammation that is a hallmark of CD and UC.[8]

The biological activities of Bmab1200 and US-Stelara were evaluated by a comprehensive set of comparative functional and binding assays. The product quality reviewers concluded the acceptability of the comparative analytical assessments. Biological activities relevant to the primary mode of action i.e., IL-12 and IL-23 binding and neutralization, were similar across Bmab1200 and US-Stelara. Furthermore, inhibition of cytokine release and STAT3/STAT4 signaling, Fc mediated functions, as well as absence of effector functions were similar across Bmab1200 vs. US- Stelara. Overall, these data support the determination that Bmab1200 and US-Stelara are highly similar. Data support the conclusion that Bmab1200 and US-Stelara utilize the same mechanism(s) of action, to the extent such mechanism(s) are known.

Pharmacokinetics (PK): Study BM12H-NHV-01-G-01 was a randomized, double-blind, parallel group, single dose, 3-way, PK similarity study conducted in healthy volunteers. The clinical pharmacology reviewers concluded that the data from this study support a demonstration of PK similarity between Bmab1200 vs. US-Stelara, Bmab1200 vs. EU-Stelara, and EU-Stelara vs. US-Stelara in healthy volunteers (refer to Section 5 Clinical

[7] Guidance for Industry – Scientific Considerations in Demonstrating Biosimilarity to a Reference Product.
[8] Stelara USPI approved 03/06/2023, available on Drugs@FDA.

Pharmacology Evaluation and Recommendations). Available data on US-Stelara do not indicate any major differences in PK based on disease state. It is reasonable to conclude that PK for Bmab1200 is expected to be similar between the studied populations and those with IBD.

Immunogenicity: In the Bmab1200 development program, immunogenicity was evaluated in populations that were considered sensitive for detecting meaningful differences (healthy subjects and PsO). While some differences were noted in the ADA incidence across the treatment groups in both study populations, per the Clinical Pharmacology reviewers, the impact of immunogenicity on PK, efficacy, and/or safety between Bmab1200 and US-/EU-Stelara was generally comparable and not considered to be clinically meaningful. Additionally, there were no meaningful differences in the rates of ADA in those subjects that underwent a single transition from EU-Stelara to Bmab1200 in Study BM12H-PSO-03-G-02 compared to those that remained on EU-Stelara. Therefore, it is reasonable to conclude that the impact of immunogenicity in patients with IBD receiving Bmab1200 would be similar to that observed in patients with Ps receiving US-Stelara. Refer to Section 5 Clinical Pharmacology Evaluation and Recommendations of this review for further details.

Safety: The safety of Bmab1200 compared to EU-Stelara was assessed in the comparative clinical study BM12H-PSO-03-G-02 conducted in patients with PsO. Safety assessments included adverse events (AEs), physical examinations, vital signs, 12-lead ECGs, clinical laboratory testing, and immunogenicity assessments. The frequency of TEAEs, SAEs and discontinuations due to AEs were generally comparable between the Bmab1200 and EU-Stelara groups in the clinical study. In addition, as previously noted, a single transition from EU-Stelara to Bmab1200 was assessed as part of the study. No meaningful differences in the incidence of adverse events, were observed in patients with Ps that underwent a single transition, compared to those that remained on their randomized treatment (Bmab1200 or EU-Stelara). Refer to the Section 6.3. Review of Safety Data, for further details. In controlled clinical studies of US-licensed Stelara, as described in the approved labeling, the types of adverse events and their rates were similar across indications. The safety profile of Bmab1200 has been shown to be similar to that of EU-Stelara in patients with PsO. When combined with the adequate PK bridging between US-Stelara and EU-Stelara from the healthy volunteer study BM12H-NHV-01-G-01 as well as similar product quality attributes, PK, and immunogenicity, the safety profile in the IBD population is expected to be generally comparable to that observed in patients with PsO, and overall, the data support extrapolation to the non-studied IBD population.

Regulatory Recommendations: DG concludes that sufficient scientific justification was provided to support licensure of Bmab1200 for the following indications:

- For the treatment of adult patients with moderately to severely active Crohn's disease.
- For the treatment of adult patients with moderately to severely active ulcerative colitis.

Authors:

Sandhya Apparaju, PhD	Suna Seo, MD, MSc	Juli Tomaino, MD, MS
Senior Clinical Analyst	Clinical Team Leader	Deputy Division Director

6.6.2. Division of Rheumatology and Transplant Medicine

The Applicant is seeking licensure of Bmab1200 for the following indication under the purview of DRTM:

- Active Psoriatic Arthritis (PsA) in adults and pediatric patients (6 years or older)

In their application, the Applicant has provided justification for extrapolation of data and relevant supportive information for licensure of Bmab1200 as a biosimilar for the above indication for which licensure is sought and for which US-Stelara has been previously licensed and Bmab1200 has not been directly studied.

First, as summarized above, the Applicant submitted data and information to demonstrate that Bmab1200 is highly similar to US-Stelara notwithstanding minor differences in clinically inactive components and that there are no clinically meaningful differences between Bmab1200 and US-Stelara in terms of safety, purity, and potency based on similar clinical pharmacokinetics (PK) in healthy volunteers (Study BM12H-NHV-01-G-01) and similar efficacy, safety, and immunogenicity in patients with moderate-to-severe chronic plaque psoriasis (PsO) (Study MB12H-PSO-03-G-02).

Further, the additional points considered in the scientific justification for extrapolation of data and information to support licensure of Bmab1200 for the treatment of PsA are described below. The Applicant's justification was evaluated and considered adequate, as summarized below.

Therefore, the toality of the evidence provided by the Applicant supports licensure of Bmab1200 for the following indication for which Biocon is seeking licensure: the treatment of adults and pediatric patients 6 years of age and older with active psoriatic arthritis

Mechanism of Action (MOA)
In comprehensive *in vitro* comparative testing, Bmab1200 has been shown to be functionally similar to ustekinumab. These data demonstrate that the biologic activity and potency of Bmab1200 have a high degree of similarity to ustekinumab and provide additional evidence that the MOA of the two products, binding to the p40 subunit of the IL-23 and IL-12 and, subsequently, preventing the interaction of IL-23 and IL-12 with IL-12Rb1, is the same.

The Applicant provided adequate justification to support that Bmab1200 has the same known and potential mechanisms of action as US-Stelara for PsA.

Pharmacokinetics (PK)
PK similarity was demonstrated between Bmab1200 and US-Stelara in Study BM12H-NHV-01-G-01, a randomized, double-blind, 3-arm, single-dose, parallel-group PK similarity study to evaluate PK, safety, tolerability, and immunogenicity in healthy adult volunteers, as reviewed in the section on Clinical Pharmacology. Importantly, Bmab1200 was also demonstrated to be analytically similar to EU-Stelara and US-Stelara, as discussed in the section on CMC/Product Quality; therefore, there are no product-related attributes that would increase the uncertainty that the PK/biodistribution may differ between Bmab1200 and US-Stelara in the rheumatology indication for licensure (PsA). Thus, a similar PK profile would be expected between Bmab1200 and US-Stelara in patients with PsA.

The Applicant provided adequate justification that a similar PK profile is expected between Bmab1200 and US-Stelara for PsA.

Immunogenicity
Immunogenicity of Bmab1200 was examined in the PK similarity study (BM12H-NHV-01-G-01, healthy participants) and comparative clinical study (MB12H-PSO-03-G-02, participants with PsO), and, as reviewed by the clinical pharmacology team, there were no meaningful differences in the development of binding and neutralizing ADAs for the Bmab1200 treatment group compared with US-Stelara and EU-Stelara. The clinical PK and safety data further supported that the immunogenicity was generally comparable. The clinical pharmacology review team has concluded that there are sufficient data to support similar immunogenicity between Bmab1200 and US-Stelara with repeat dosing in participants with PsO and after a single dose in healthy participants. Accordingly, similar immunogenicity would be expected between Bmab1200 and US-Stelara in patients with PsA. In addition, DRTM notes that similar rates of antibodies to US-Stelara were seen in clinical studies of patients with PsO and PsA.

The Applicant provided adequate justification that similar immunogenicity is expected between Bmab1200 and US-Stelara for PsA.

Toxicity
The Applicant demonstrated that there are no clinically meaningful differences in safety between Bmab1200 and EU-Stelara in participants with PsO and between Bmab1200, EU-Stelara, and US-Stelara following single doses in healthy participants. Additionally, in controlled clinical studies of US-Stelara submitted to support its approval, as described in the approved labeling,[9] the types of adverse events and their rates were similar across indications. Coupled with the demonstration of analytical and PK similarity between Bmab1200, US-Stelara, and EU-Stelara, a similar safety profile would be expected between Bmab1200 and US-Stelara in patients with PsA.

[9] Ibid.

The Applicant provided adequate justification that a similar safety profile would be expected between Bmab1200 and US-Stelara for PsA.

Additional factors considered (if applicable)
None

Conclusions
Based on the above considerations, DRTM concludes that the Applicant has provided sufficient scientific justification (based on the mechanism of action, pharmacokinetics, immunogenicity, and toxicity profile) for extrapolation of the data and information in the application to support licensure of Bmab1200 for the treatment of adults and pediatric patients 6 years of age and older with active psoriatic arthritis.

Authors:

Suzette Peng, MD	Rachel Glaser, MD
Clinical Reviewer, DRTM	Associate Director for Therapeutic Review, DRTM

7. Labeling Recommendations

7.1. Nonproprietary Name

The Applicant's proposed nonproprietary name**, ustekinumab-xxxx.** The Agency assigned the four-letter suffix -kfce for inclusion in the proper name designated in the license at such time as the Agency approves the BLA (DMEPA Nonproprietary Name Suffix Advice Letter dated 8/12/2024).

7.2. Proprietary Name

The proposed proprietary name for Bmab 1200 is conditionally approved as Yesintek. The name has been reviewed by DMEPA, who concluded the name was acceptable (DMEPA review dated February 23, 2024).

7.3. Other Labeling Recommendations

It was determined that the proposed labeling is compliant with Physician Labeling Rule (PLR) and Pregnancy and Lactation Labeling Rule (PLLR), is clinically meaningful and scientifically accurate, and conveys the essential scientific information needed for safe and effective use of the product.

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8. Human Subjects Protections/Clinical Site and other Good Clinical Practice (GCP) Inspections/Financial Disclosure

The data quality and integrity of the studies were acceptable. The BLA submission was in electronic common technical document (eCTD) format and was adequately organized.

Documented approval was obtained from institutional review boards (IRBs) and independent ethics committees (IECs) prior to study initiation. All protocol modifications were made after IRB/IEC approval. The studies were conducted in accordance with good clinical practice (GCP), code of federal regulations (CFR), and the Declaration of Helsinki.

The Applicant has adequately disclosed financial interests and arrangements with the investigators. Form 3454 is noted in Section 14.2 and verifies that no compensation is linked to study outcome. The Principal Investigators (PIs) did not disclose any proprietary interest to the sponsor.

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9. Advisory Committee Meeting and Other External Consultations

No Advisory Committee was held for this biosimilar application, as it was determined that there were no issues where the Agency needed input from the Committee.

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10. Pediatrics

Under the Pediatric Research Equity Act (PREA) (section 505B of the FD&C Act), all applications for new active ingredients, new indications, new dosage forms, new dosing regimens, or new routes of administration are required to contain a pediatric assessment to support dosing, safety, and effectiveness of the product for the claimed indication unless this requirement is waived, deferred, or inapplicable. Section 505B(l) of the FD&C Act provides that a biosimilar product that has not been determined to be interchangeable with the reference product is considered to have a "new active ingredient" for purposes of PREA, and a pediatric assessment is generally required unless waived or deferred or inapplicable. Under the statute, an interchangeable product is not considered to have a "new active ingredient" for purposes of PREA.

At the time of this review, another ustekinumab product, Wezlana, has been approved as an interchangeable biosimilar and has qualified for a period of FIE. FDA has previously determined that FIE for the Wezlana products will expire on April 30, 2025.[10] Therefore, because Bmab1200 will be approved first as a biosimilar (and not as interchangeable), this biologic will be considered to have a new active ingredient.

This application included the January 20, 2023, Agreed Initial Pediatric Study Plan (Agreed iPSP).

In this application, the Applicant included assessment via extrapolation for pediatric patients ages 6-17 years with moderate to severe plaque psoriasis and psoriatic arthritis. See Section 6.6 for review of the assessments.

The proposed 45 mg/0.5 mL single-dose vial presentation will allow for weight-based dosing of plaque psoriasis and psoriatic arthritis patients 6 years and older.

The Applicant referenced the guidance for industry, "Questions and Answers on Biosimilar Development and the BPCI Act," and noted that the labeling for US-licensed Stelara does not include adequate pediatric information and is not licensed for the treatment of:

- Plaque psoriasis in pediatric patients < 6 years of age
- Psoriatic arthritis in pediatric patients < 6 years of age
- Crohn's disease in pediatric patients 0-17 years of age
- Ulcerative colitis in pediatric patients 0-17 years of age

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[10] https://purplebooksearch.fda.gov/

11. REMS and Postmarketing Requirements and Commitments

11.1. Recommendations for Risk Evaluation and Mitigation Strategies

None.

Authors:

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11.2. Recommendations for Postmarket Requirements and Commitments

None.

Authors:

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12. Division Director Comments

12.1. Division Director (OND – Clinical) Comments

I concur with the team's assessment of the data and information submitted in this BLA. The data and information submitted by the Applicant, including adequate justification for extrapolation of data and information, demonstrate that Bmab1200 is biosimilar to US-Stelara. I also concur with the team's recommendation to provisionally determine that the following Bmab1200 products would be interchangeable with US-Stelara products:

- Bmab1200, 45 mg/0.5 mL PFS for subcutaneous use with US-Stelara 45 mg/0.5 mL PFS for subcutaneous use,
- Bmab1200, 45 mg/0.5 mL single-dose vial for subcutaneous use with US-Stelara 45 mg/0.5 mL single-dose vial for subcutaneous use,
- Bmab1200, 90 mg/mL PFS for subcutaneous use with US-Stelara 90 mg/mL PFS for subcutaneous use, and
- Bmab1200, 130 mg/26 mL single-dose vial for intravenous (IV) use with US-Stelara 130 mg/26 mL single-dose vial for IV use.

These Bmab1200 products have met the statutory interchangeability requirements for the following indications for which US-Stelara has previously been approved:

Treatment of:

- moderate to severe plaque psoriasis (PsO) in adult patients and pediatric patients 6 years and older, who are candidates for phototherapy or systemic therapy,
- active psoriatic arthritis (PsA) in adult patients and pediatric patients 6 years and older,
- moderately to severely active Crohn's disease (CD) in adults, and
- moderately to severely active ulcerative colitis in adults.

When action is taken for this BLA, it will be administratively split to facilitate an approval action for Bmab1200 as a biosimilar product ("Original 1") and a provisional determination that Bmab1200 is an interchangeable biosimilar product, as described in Section 1.1 above ("Original 2").

This provisional determination is appropriate because at this time, FDA is unable to approve Bmab1200 injection 45 mg/0.5 mL PFS for subcutaneous use as interchangeable with US-Stelara injection 45 mg/0.5 mL PFS for subcutaneous use, Bmab1200 injection 45 mg/0.5 mL single-dose vial for subcutaneous use as interchangeable with US-Stelara injection 45 mg/0.5 mL single-dose vial for subcutaneous use, Bmab1200 injection 90 mg/mL PFS for subcutaneous use as interchangeable with US-Stelara injection 90 mg/mL PFS for subcutaneous use, or Bmab1200 injection 130 mg/26 mL single-dose vial for intravenous use as interchangeable with US-Stelara injection 130 mg/26 mL single-dose vial for intravenous use, because of unexpired FIE for the Wezlana products. FDA has previously determined that FIE for the Wezlana products will expire on April 30, 2025.[11] As described in the provisional determination letter, Biocon is expected to submit an amendment seeking approval of its Bmab1200 45 mg/0.5 mL injection for subcutaneous use, Bmab1200 90mg/mL injection for subcutaneous use, and 130 mg/26 mL injection for intravenous use products as interchangeable no more than six months prior to the expiration of FIE for the Wezlana products.

Author:
Tatiana Oussova, MD, MPH
Deputy Director for Safety

[11] https://purplebooksearch.fda.gov/

13. Appendices

13.1. Financial Disclosure

Covered Clinical Study: BM12H-NHV-01-G-01

Was a list of clinical investigators provided:	Yes	
Total number of investigators identified: 16		
Number of investigators who are Sponsor employees (including both full-time and part-time employees): 0		
Number of investigators with disclosable financial interests/arrangements (Form FDA 3455): 0		
If there are investigators with disclosable financial interests/arrangements, identify the number of investigators with interests/arrangements in each category (as defined in 21 CFR 54.2(a), (b), (c) and (f)): Compensation to the investigator for conducting the study where the value could be influenced by the outcome of the study: 0 Significant payments of other sorts: 0 Proprietary interest in the product tested held by investigator: 0 Significant equity interest held by investigator in S Sponsor of covered study: 0		
Is an attachment provided with details of the disclosable financial interests/arrangements:	Yes	No (Request details from Applicant)
Is a description of the steps taken to minimize potential bias provided:	Yes	No (Request information from Applicant)
Number of investigators with certification of due diligence (Form FDA 3454, box 3) 0		
Is an attachment provided with the reason:	Yes	No (Request explanation from Applicant)

Covered Clinical Study: BM12H-PSO-03-G-02

Was a list of clinical investigators provided:	Yes	
Total number of investigators identified: 172		
Number of investigators who are Sponsor employees (including both full-time and part-time employees): 0		
Number of investigators with disclosable financial interests/arrangements (Form FDA 3455): 0		
If there are investigators with disclosable financial interests/arrangements, identify the number of investigators with interests/arrangements in each category (as defined in 21 CFR 54.2(a), (b), (c) and (f)): Compensation to the investigator for conducting the study where the value could be influenced by the outcome of the study: 0 Significant payments of other sorts: 0 Proprietary interest in the product tested held by investigator: 0 Significant equity interest held by investigator in S Sponsor of covered study: 0		
Is an attachment provided with details of the disclosable financial interests/arrangements:	Yes	No (Request details from Applicant)
Is a description of the steps taken to minimize potential bias provided:	Yes	No (Request information from Applicant)
Number of investigators with certification of due diligence (Form FDA 3454, box 3) 0		
Is an attachment provided with the reason:	Yes	No (Request explanation from Applicant)

13.2. Nonclinical Appendices

13.2.1. Nonclinical Pharmacology

No data were provided.

13.2.2. Nonclinical Pharmacokinetics

No data were provided.

13.2.3. General Toxicology

No data were provided.

13.2.4. Other Toxicology

Extractables/Leachables

The Bmab1200 formulated drug substance (DS) [redacted]

An extensive extractable study was conducted [redacted]

The risk assessment performed indicates that the extractables identified in all extraction solutions are well within the permitted daily exposure (PDE) calculated for individual extractable compounds including those extracted under worst case harsh conditions (100% ethanol).

A few extractables were identified by compound functionality such as [redacted] and these had levels below SCT of 1.5 µg/day.

Based on the risk assessment it was concluded that a separate leachable study for Bmab1200 is deemed not necessary, due to the following reasons:

(a) The extractables levels in the studies have been determined at worst case harsh conditions (40°C, 112 days) whereas actual storage of the product [redacted] is [redacted] and the product [redacted] is exposed to room temperature for not more than 3-5 days.

(b) Risk of extractables becoming leachable of concern is further mitigated by valuation and screening of leachable in Bmab1200 DP conducted for SC PFS and vial as well as IV vial presentations after exposing the products to temperature stress of 40°C for one month.

Bmab1200 drug product (DP) is filled into sterile 1 mL [(b) (4)] glass syringe fitted with a staked needle and stoppered with a [(b) (4)] plunger stopper. A plunger rod is assembled onto the plunger stopper on the side that does not come in contact with the product and helps in extruding the product out from the syringe. Bmab1200 DP is not in direct contact with the assembly components of plunger rod and needle safety guard (NSG) at any point of manufacturing, shipping and recommended use conditions. Additionally, plunger rod and NSG assembly process is not expected to have any impact on product quality parameters.

An extractable study for Bmab1200 SC PFS was conducted using primary container closure components: Glass Syringe (PFS) Barrel, PFS stoppers and PFS needle shield.

Screening leachables study was performed at [(b) (4)] for the SC PFS (45 mg/0.5 mL), SC vial (45 mg/0.5 mL) and IV vial (90 mg/1 mL). No volatile, semi-volatile or non-volatile compounds, [(b) (4)], or relevant elements were found at or above the respective Analytical Evaluation Threshold (AET) levels in the Bmab1200 drug products stored in the PFS and SC vial. The results from this leachable study demonstrate that the risks to patient safety from leachables originating from the manufacturing process and the Bmab1200 DP PFS and SC vial container closure systems is not of concern.

Based on the evaluation of the data from the stability, screening-leachable and [(b) (4)] spiking studies, it can be concluded that the chosen primary container closure system is compatible for storing Bmab1200 SC PFS, SC vial (45 mg/0.5 mL) and IV vial (90 mg/1 mL).

Overall, the applicant's assessment for potential extractables/leachables appeared reasonable. There were no nonclinical safety concerns with the maximum exposures of potential leachables from the container closure systems for the Bmab1200 drug substance [(b) (4)] and drug product (prefilled syringe and glass vial).

14.2.5. Nonclinical Labeling Review

The applicant proposed the same labeling for nonclinical potions of the drug label as the approved US-STELARA label. The applicant proposed nonclinical labeling is acceptable.

13.3. Clinical Pharmacology Appendices

13.3.1. Summary of Bioanalytical Method Validation and Performance

Pharmacokinetics

For the PK similarity study (Study BM12H-NHV-01-G-01), serum Bmab1200, US-Stelara, and EU-Stelara concentrations measured using a validated Sandwich ECLIA method. The same bioanalytical method was used for PK samples obtained from the

comparative clinical study (Study BM12H-PSO-03-G-02). Both the method validation reported entitled “Validation of an ECLIA method for the determination of Ustekinumab in human serum” and sample analysis for the study were performed at Celerion Switzerland AG. Table 53 shows the summary of ECLIA method validation and performance in quantification of Bmab1200, US-Stelara, and EU-Stelara during the method validation. Both the method validation and in-study performance were acceptable.

Table 53. Summary of the bioanalytical method validation and in-study performance for measurement of Bmab1200, US-Stelara, and EU-Stelara

Bioanalytical method validation report name, amendments, and hyperlinks	Method Validation Report No. VCA36138-01 (\\CDSESUB1\EVSPROD\bla761406\0001\m5\53-clin-stud-rep\531-rep-biopharm-stud\5314-bioanalyt-analyt-met\vca36138-01\vca36138-01-report-body.pdf)	
Method description	ECLIA method for the determination of Bmab 1200 in human serum according to the method standard operating procedure (SOP) SM3-552, using MESO QuickPlex SQ 120 detection devices.	
Materials used for calibration curve & concentration	Bmab 1200 (Lot No. BS21006806; Exp: 05/31/2023 4.00, 8.00, 16.0, 30.0, 50.0, 70.0, 90.0, 130, 170, 220 ng/mL (4.00 ng/mL and 220 ng/mL were used as anchor points)	
Validated assay range	8.00 to 170 ng/mL	
Material used for QCs & concentration	EU-Stelara (Lot No. LJS3MMD; Exp: 10/30/2024) US-Stelara (ustekinumab) (Lot No. 21A121MA.A; Exp: 01/30/2024) LLOQ: 8.00 ng/mL; LOQ: 24.0 ng/mL; MQC: 85.0 ng/mL; HQC: 128 ng/mL; ULQC: 170 ng/mL 1000 ng/mL (DQC 1), 10000 ng/mL (DQC 2), 20000 ng/mL (DQC3)	
Minimum required dilutions (MRDs)	4	
Source & lot of reagents (LBA)	Refer to the Validation report	
Regression model & weighting	5-PL, weighting $1/y^2$	
Validation Parameters	**Method Validation Summary**	**Acceptability**

Calibration curve performance during accuracy & precision	No of standard calibrators from LLOQ to upper limit of quantitation (ULOQ)	10	Yes
	Cumulative accuracy (%bias) from LLOQ to ULOQ Bmab 1200	1.9 to 5.7	Yes
	Cumulative precision (%CV) from LLOQ to ULOQ Bmab 1200	0.0 to 2.7	Yes
QCs performance during accuracy & precision LBA QCs: ±20% bias (±25% at LLOQ), ≤ 20%CV and ≤ 30% total error (≤ 40% at LLOQ)	Cumulative accuracy (%bias) in QCs Bmab 1200 EU-Stelara US-Stelara	-4.5 to -12.2 1.1 to 8.4 -0.3 to 5.0	Yes
	Inter-batch %CV Bmab 1200 EU-Stelara US-Stelara	3.5 to 5.9 4.9 to 8.2 5.6 to 7.4	Yes
	Percent total error (TE) Bmab 1200 EU-Stelara US-Stelara	8.5 to 27.4 7.2 to 29.2 4.5 to 14.3	Yes
Selectivity & matrix effect	No matrix effect observed in normal healthy human serum or disease state serum (plaque psoriasis) lots prepared with Bmab 1200, US-Stelara, or EU-Stelara		Yes
Hemolysis effect	No effect from hemolysis up to 2% of pre-frozen whole blood on the quantitation of Bmab 1200 or Stelara		Yes
Lipemic effect	No effect from lipemia on the quantitation of Bmab 1200. Acceptance criteria are not met for EU-Stelara and US-Stelara. (Note: Lipemic samples are not suitable for this assay)		Yes (Bmab 1200)
Dilution linearity & hook effect	100,000 ng/mL of Bmab 1200, US-Stelara and EU- Stelara diluted 200, 400, and 800-fold; No apparent hook effect observed at concentrations up to 20,000 ng/mL of Bmab 1200, US-Stelara and EU- Stelara		Yes

	For Bmab 1200: Bias between 8.0% 9.5% and mean precision (DF200-800) at 3.0% For EU-Stelara: Bias between 2.9% 9.6% and mean precision (DF200-800) at 5.4% For US-Stelara: Bias between 4.4% 6.7% and mean precision (DF200-800) at 5.4% No hook effect observed (signal up to 20000 ng/mL above ULOQ)	
Bench-top/process stability	Up to 17 hours for LQC and HQC prepared with Bmab 1200, US-Stelara, and EU-Stelara For Bmab 1200: Demonstrated for 19 hours at ambient temperature for samples previously stored at -20°C and -80°C For EU-Stelara: Demonstrated for 19 hours at ambient temperature for samples previously stored at -20°C and -80°C For US-Stelara: Demonstrated for 18 hours at ambient temperature for samples previously stored at -20°C and -80°C Working Stock Solution Stability: For Bmab 1200, US Sterala and EU Stelara: Demonstrated for 28 days at -80°C	Yes
Freeze-Thaw stability	For Bmab 1200: Demonstrated for 6 cycles at -80°C For EU-Stelara: Demonstrated for 6 cycles at -80°C For US-Stelara: Demonstrated for 6 cycles at -80°C	Yes
Long-term storage	Long term srotage stability was demonstrated for 398 days at -20°C and -80°C for LQC, HQC and DQC prepared with Bmab 1200, US-Stelara and EU-Stelara. (\\CDSESUB1\EVSPROD\bla761406\0019\m5\53-clin-stud-rep\531-rep-biopharm-stud\5314-bioanalyt-analyt-met\vca36138-04\vca36138-04-report-body.pdf)	Yes
Parallelism	Not applicable	

Carry over	Not applicable	
Method Performance in Study BM12H-NHV-01-G-01 (Document No. ACA35750-01)		
Assay passing rate	343 runs were analyzed for final data evaluation with 16 rejected runs reported int the study due to inacceptable QC performance. 227 runs met all applicable acceptance criteria.	Yes
Standard curve performance	Cumulative bias range: -5.3 to 4.6% Cumulative precision: 2.3 to 5.6%	Yes
QC performance	Cumulative bias range: -0.8 to 6.0% Cumulative precision: 5.9 to 12.0% TE: ≤ 18.1%	Yes
Method reproducibility (Incurred sample reanalysis)	Incurred sample reanalysis was performed in 442 study samples (10.3% of total sample size) and 93.5% of samples met the pre-specified criteria (±30.0%)	Yes
Study sample analysis/ stability	Samples were stored for a maximum of 371 days between first sample collection (10-May-2022) and last sample analysis (16-May-2023), which is within the established long-term stability window of 398 days.	
Method Performance in Study BM12H-PSO-03-G-02 (Document No. ACA36451-01)		
Assay passing rate	255 runs were analyzed for final data evaluation with 13 rejected runs reported int the study due to inacceptable Cal and QC performance. 242 runs met all applicable acceptance criteria.	Yes
Standard curve performance	Cumulative bias range: -5.4 to 5.5% Cumulative precision: 2.4 to 6.1%	Yes
QC performance	Cumulative bias range: -4.9 to 14.0% Cumulative precision: 5.4 to 9.1% TE: ≤ 18.1%	Yes
Method reproducibility (Incurred sample reanalysis)	Incurred sample reanalysis was performed in 245 study samples samples and 97.9% of samples met the pre-specified criteria (±30.0%)	Yes
Study sample analysis/stability	Samples were stored for a maximum of 343 days between first sample collection (01-Sep-2022) and last sample analysis (10-Aug-2023), which is within the established long-term stability window of 398 days.	Yes

13.3.2. Other Clinical Pharmacology Information

Not Applicable.

13.4. Clinical Appendices

13.4.1. CLINICAL SUBSECTION

Not Applicable.

This is a representation of an electronic record that was signed electronically. Following this are manifestations of any and all electronic signatures for this electronic record.

/s/

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