BIOSIMILAR MULTIDISCIPLINARY EVALUATION AND REVIEW

Application Type	BLA
Application Number	761364
Received Date	October 10, 2023
BsUFA Goal Date	October 10, 2024
Division/Office	Division of Dermatology and Dentistry (DDD)/Office of Immunology and Inflammation (OII)
Review Completion Date	See DARRTS stamped date
Product Code Name	DMB-3115
Proposed Nonproprietary Name[1]	Ustekinumab-srlf
Proposed Proprietary Name[1]	Imuldosa
Pharmacologic Class	Interleukin-12 and -23 antagonist
Applicant	Accord BioPharma, Inc.
Applicant Proposed Indication(s)	• Moderate to severe plaque psoriasis (Ps) in adult patients and pediatric patients 6 years of age and older, who are candidates for phototherapy or systemic therapy • Active psoriatic arthritis in adult patients and pediatric patients 6 years of age and older • Moderately to severely active Crohn's disease in adults • Moderately to severely active ulcerative colitis in adults
Recommendation on Regulatory Action	Approval

[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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OPQAIII = Office of Pharmaceutical Quality Assessment III
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
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
U.S.-Stelara	U.S.-licensed Stelara

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1. Executive Summary

1.1. Product Introduction

Accord BioPharma Inc (also referred to as “Applicant” in this review) has submitted a biologics license application (BLA) under section 351(k) of the Public Health Service Act (PHS Act) for DMB-3115 (non-proprietary name: ustekinumab-srlf; proprietary name: Imuldosa) as a proposed biosimilar to US-licensed Stelara (US-Stelara, ustekinumab).

DMB-3115 is a recombinant human immunoglobulin isotype class G subclass 1 kappa monoclonal antibody (mAb) that binds to the p40 protein subunit of the IL-23 and IL-12 cytokines to neutralize IL-23 and IL-12 mediated signaling. Interleukin-12 stimulates natural killer cells and drives the differentiation of cluster of differentiation 4-positive T cells toward the T helper 1 phenotype; IL-23 induces the T helper 17 pathway. The primary structure of DMB-3115 and STELARA are identical. The active substance for both products is ustekinumab produced in a murine myeloma mammalian cell line transformed by recombinant DNA technology.

The applicant is seeking licensure for DMB-3115 injection, 45 mg/0.5 mL and 90mg/mL pre-filled syringe (PFS) for subcutaneous use and 130 mg/26 mL single-dose vial for intravenous (IV) use. The strengths, dosage form, and routes of administration of DMB-3115 are the same as those approved for US-Stelara. In this submission, the Applicant is not seeking licensure of DMB-3115 in a 45 mg/0.5 mL single-dose vial for subcutaneous use. US-Stelara is available in a 45 mg/0.5 mL single-dose vial for subcutaneous use for weight-based dosing of pediatric patients with a body weight of less than 60 kg. Section 2 of the labeling for DMB-3115 will note that there is no dosage form of the product that allows weight-based dosing for pediatric patients below 60 kg.

(b) (4)

Accord BioPharma Inc is seeking licensure of DMB-3115 for the following indications for which US-licensed Stelara is approved.

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

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 their respective indications was obtained from the Division of Gastroenterology (DG) and the Division of Rheumatology and Transplant Medicine (DRTM) 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

DMB-3115 is a recombinant human immunoglobulin isotype class G subclass 1 kappa monoclonal antibody (mAb) that belongs to the pharmacologic class of Interleukin -23 (IL-23) and Interleukin-12 (IL-12) antagonists. It is expressed in a murine cell line, Sp2/0-Ag14, and binds to the p40 protein subunit of the IL-23 and IL-12 cytokines to neutralize IL-23 and IL-12 mediated signaling. Interleukin-23 and IL-12 are naturally occurring cytokines that are involved in inflammatory and immune responses in inflammatory conditions such as plaque psoriasis and psoriatic arthritis (among others). Interleukin-12 stimulates natural killer cells and drives the differentiation of CD4+ T cells toward the T helper 1 phenotype, while IL-23 induces and maintains the IL-17 pathway. DMB-3115 has the same mechanism(s) of action as that of US-licensed Stelara.

DMB-3115 is a sterile, preservative-free, colorless to slightly yellow and clear to slightly opalescent (b) (4) liquid solution (b) (4) available in single-dose vial and prefilled syringe presentations. DMB-3115 injection is proposed as below:

For subcutaneous injection:
- 45 mg/0.5 mL in a PFS
- 90 mg/mL in a PFS

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

Each strength of DMB-3115 in each presentation is the same as that of US-licensed Stelara. DMB-3115 also has the same dosage form and routes of administration as that of US-licensed Stelara. In this submission, the Applicant is not seeking licensure of DMB-3115 in a 45 mg/0.5 mL single-dose vial for subcutaneous use. US-Stelara is available in a 45 mg/0.5 mL single-dose vial for subcutaneous use for weight-based dosing of pediatric patients with a body weight of less than 60 kg. Additionally, the condition(s) of use for which the applicant is seeking licensure have been previously approved for US-licensed Stelara. The 45mg/0.5mL concentration of DMB-3115 supports the dosing regimens for the proposed indications of adult and pediatric patients ≥ 6 years of age with moderate to severe plaque psoriasis and psoriatic arthritis and a body weight (BW) of 60 kg to ≤100kg. The 90mg/mL concentration of DMB-3115 supports the dosing regimens for the proposed indications of adult and pediatric patients ≥ 6 years of age with moderate to severe plaque psoriasis and psoriatic arthritis and Body Weight (BW)>100kg and the maintenance dosing for the indications of Crohn's

disease and ulcerative colitis. The single dose vial containing 130 mg/26 mL (5 mg/mL) for IV use supports the dosing regimen for the indications of Crohn's disease and ulcerative colitis.

1.4. Inspection of Manufacturing Facilities

The Agency's Office of Pharmaceutical Manufacturing Assessment (OPMA) conducted a pre-licensing inspection (PLI) of the DMB-3115 drug substance and drug product manufacturer of the prefilled syringe, (b) (4) for this BLA. The inspection resulted in observations that were listed in a Form FDA 483. The firm responded to the observations, and they were found satisfactory. The firm was recommended for approval by OPMA.

An inspection waiver was granted to the drug product manufacturer of the vial presentation, (b) (4) based on previous inspection history.

All other testing facilities were found acceptable and are in a current state of compliance.

The Office of Pharmaceutical Quality (OPQ), CDER, has completed assessment of BLA 761364 for DMB-3115 (45 mg/0.5 mL, 90 mg/mL, 130 mg/26mL) manufactured by (b) (4) The data submitted in this application are adequate to support a conclusion that the manufacture of DMB-3115 is well-controlled and will lead to a product that is pure and potent for the duration of the shelf-life. OPQ recommends approval of the proposed DMB-3115 (45 mg/0.5 mL, 90 mg/mL) prefilled syringe presentation and the single dose vial containing 130 mg/26 mL (5 mg/mL) presentation. Refer to the integrated quality assessment and related primary reviews for detailed information. The OPQ team determined that the data submitted for these proposed presentations in this application is adequate.

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 DMB-3115-2, which used EU-Stelara as the comparator, for 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 DMB-3115, US-licensed Stelara, and EU-approved

Stelara was established.

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

1.6. Biosimilarity Assessment

Table 1: Summary and Assessment of Biosimilarity

Comparative Analytical Studies[2]	
Summary of Evidence	• DMB-3115 is highly similar to US-Stelara notwithstanding minor differences in clinically inactive components. • The strengths, dosage form and routes of administration of DMB-3115 are the same as those of US-Stelara. • The analytical component of the scientific bridge between DMB-3115, 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.
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	

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

Summary of Evidence	• PK similarity between DMB-3115, US-Stelara, and EU-Stelara was evaluated in healthy adult subjects (Study DMB-3115-1) and supports a demonstration of no clinically meaningful differences between DMB-3115 and US-Stelara. • PK similarity between DMB-3115, US-Stelara, and EU-Stelara provides the PK component of the scientific bridge to support the relevance of comparative data generated using EU-Stelara in Study DMB-3115-2 to the assessment of biosimilarity. • In Studies DMB-3115-1 and DMB-3115-2, the numerical difference in ADA and NAb incidences between DMB-3115 and the comparator product (s) are not considered to be clinically significant and does not preclude the conclusion of no clinically meaningful differences between DMB-3115 and US-Stelara, as the systemic exposure between the three treatment groups are comparable among ADA positive and ADA negative subjects.
Assessment of Residual Uncertainties	• There are no residual uncertainties from a clinical pharmacology perspective
Additional Clinical Studies	
Summary of Evidence	• In Study DMB-3115-1, there were no meaningful differences in terms of efficacy between DMB-3115 and EU-Stelara. The frequency of treatment emergent adverse events, serious events, and events leading to discontinuation of study drug had no meaningful differences between the treatment arms. • Given the scientific bridge was established (based on the analytical and PK comparisons) between DMB-3115, 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 DMB-3115-2 supports a demonstration of no clinically meaningful differences between DMB-3115 and US-Stelara in the studied indication (plaque psoriasis, PsO).

Assessment of Residual Uncertainties	• There are no residual uncertainties from the clinical or statistical 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 DMB-3115 as a biosimilar, under section 351(k) of the PHS Act, for the following indications for which US-licensed Stelara has been previously approved: o Moderate to severe plaque psoriasis in adult patients and pediatric patients 6 years of age and older who are candidates for phototherapy or systemic therapy o Active psoriatic arthritis in adult patients and pediatric patients 6 years of age and older o Moderately to severely active Crohn's disease in adults o Moderately to severely active ulcerative colitis in adults
Assessment of Residual Uncertainties	• There are no residual uncertainties regarding the extrapolation of data and information to support licensure of DMB-3115 as a 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 DMB-3115 is highly similar to US-licensed Stelara, notwithstanding minor differences in clinically inactive components, and that there are no clinically meaningful differences between DMB-3115 and US-licensed Stelara in terms of the safety, purity, and potency of the product. The information submitted by the Applicant, including adequate justification for extrapolation of data and information, demonstrates that DMB-3115 is biosimilar to US-licensed Stelara for each of the following indications for which US-licensed Stelara has been previously approved and for which the Applicant is seeking licensure of DMB-3115:

- Moderate to severe plaque psoriasis in adult patients and pediatric patients 6 years

and older, who are candidates for phototherapy or systemic therapy.
- Active psoriatic arthritis in 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

Therefore, the FDA review team recommended an Approval action for DMB-3115 injection:

For subcutaneous use:
- 45 mg/0.5 mL, in a pre-filled syringe (PFS)
- 90 mg/mL, in a pre-filled syringe

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

The Applicant is not seeking licensure of DMB-3115 in a 45 mg/0.5 mL single-dose vial for subcutaneous use. US-Stelara is available in a 45 mg/0.5 mL single-dose vial for subcutaneous use for weight-based dosing of pediatric patients with a body weight of less than 60 kg. Section 2 of the labeling for DMB-3115 will note that there is no dosage form of the product that allows weight-based dosing for pediatric patients below 60 kg (132 pounds). Please see Section 10 below for more information.

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

Author:
Snezana Trajkovic, MD
Cross-Discipline Team Leader (CDTL)

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 DMB-3115. Key discussions are detailed below:

An Initial Advisory Biosimilar Meeting was held via teleconference on February 27, 2019, which focused on the overall development plan for DMB-3115 and analytical data needed to support the development of DMB-3115, a proposed biosimilar to US-licensed Stelara.

A Bisomilar Product Development (BPD) Type 2 meeting with written responses only (WRO) was held on July 13, 2020. Comments from CMC, clinical and biostatistics were conveyed.

A BPD Type 2 meeting with written responses only (WRO) was held on October 29, 2020. Comments from CMC, clinical and biostatistics were conveyed.

A BPD Type 2 meeting with written responses only (WRO) was held on April 26, 2021. Comments from Office of Pharmaceutical Quality (OPQ) were conveyed.

An initial pediatric study plan (iPSP) for DMB-3115 was submitted on 20 Sept 2021 and an iPSP Agreement letter was sent to the Applicant on 11 April 2022.

A BPD Type 2 meeting with written responses only (WRO) was held on Sept 20, 2022. Comments from CMC were conveyed.

A BPD Type 4 meeting via teleconference was held on May 24, 2023. Comments from regulatory, CMC, clinical, nonclinical, clinical pharmacology, biostatistics and clinical were conveyed. The Agency recommended the Applicant submit a revised initial pediatric study plan for extrapolation as US-licensed Stelara was approved for the treatment of pediatric patients 6 years and older with active psoriatic arthritis (PsA) on 29 July 2022 post-issuance of the agreed PSP letter. The Agency also reached an agreement with the Applicant's proposed approach for the presentation of clinical efficacy and safety data in the BLA submission.

2.2. Studies Submitted by the Applicant

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

Table 2: Table Listing All Relevant Submitted Clinical Studies

Study Identity	Eudra Clinical Trial no.	Study Objective	Study Design	Study Population	Treatment Groups
PK Similarity Study					
DMB-3115-1	2018-004033-33	Primary: To determine PK similarity of DMB-3115, US-Stelara, and EU-Stelara	Double-blind, randomized, parallel-group, active-controlled,	Healthy Subjects	DMB-3115-001: 100 US-Stelara: 100

Study Identity	Eudra Clinical Trial no.	Study Objective	Study Design	Study Population	Treatment Groups
		based on AUCinf and Cmax	three-way pairwise		EU-Stelara: 100
Comparative Clinical Study					
DMB-3115-2	2020-005108-21	Primary: Efficacy of DMB-3115 compared with EU-Stelara	Double-blind, randomized, parallel-group, active-controlled	Moderate- to- severe chronic plaque psoriasis	DMB-3115: 299 EU-Stelara: 299 45 or 90 mg SC beginning at Week 4, then q12 weeks

Authors:

Sangeeta Jain, MD
Clinical Reviewer

Snezana Trajkovic, MD
Clinical Team Leader

3. Summary of Conclusions of Other Review Disciplines

3.1. Office of Pharmaceutical Quality (OPQ)

The Office of Pharmaceutical Quality, CDER, recommends approval of BLA 761364 for Imuldosa. The data submitted in this application are adequate to support the conclusion that the manufacture of Imuldosa is well-controlled and leads to a product that is pure, safe, and potent. The comparative analytical data support a demonstration that Imuldosa is highly similar to US-licensed Stelara, notwithstanding minor differences in clinically inactive components. It is recommended that this product be approved for human use under conditions specified in the package insert.

3.2. Devices

DMB-3115 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 PFS consists of a sterile (b) (4) glass syringe with a fixed half-inch needle with a (b) (4) stopper equipped with a plunger rod with needle guard system.

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

DMEPA evaluated the use-related risk analysis (URRA) and threshold analyses (hereafter, referred to as comparative analyses) submitted under IND 141843 for DMB-3115 Prefilled Syringe (PFS) to determine whether the applicant needs to submit human factors (HF) validation study results to support their marketing application as a biosimilar to US-licensed Stelara. The review of the use-related risk analysis and comparative analyses did not identify any new, differing, or unique risks for the proposed product as compared to Stelara. As such, DMEPA agreed with the applicant's justification for not submitting the results of an HF validation study as part of their marketing application.

The applicant submitted prescribing information, medication guide, instructions for use, container labels and carton labeling to determine if they are acceptable from a medication error perspective. The safety evaluator Amy Bao, PharmD, MPH concluded, "The proposed prescribing information (PI), medication guide (MG), instructions for use (IFU), container labels, and carton labeling may be improved to promote the safe use of this product from a medication error perspective. We provide the identified medication error issues, our rationale for concern, and our proposed recommendations to minimize the risk for medication error in Section 4 for the Division and in Section 5 for Accord BioPharma Inc." Subsequent revisions to labeling have been implemented and DMEPA finds the final versions of the labeling acceptable.

Refer to DMEPA reviews dated March 28, 2024, August 28, 2024, and September 6, 2024.

3.3. Office of Study Integrity and Surveillance (OSIS)

OSIS inspections were requested for both bioanalytical and clinical sites for Study DMB-3115-1.

- OSIS determined that an inspection was not needed for the clinical site in Berlin, Germany because the inspection was conducted in May 2024 under BLA NON-RESPONSIVE and concluded data from the site were reliable.
- OSIS conducted an analytical inspection of study DMB-3115-1 located at (b) (4) . OSIS reviewer observed objectionable conditions and issued Form FDA 483 to the firm, (b) (4). Based on the firm's response dated September 26, 2024, OSIS concluded that there were no concerns regarding the reliability of the data for inspected study DMB-3115-1.

Refer to the OSIS review memo by Dr. Scheibner dated October 7, 2024, for additional information.

3.4. Office of Scientific Investigations (OSI)

The comparative clinical study involves approximately 600 subjects, and the sponsor's oversight of this study led to the exclusion of one site with seven subjects as a result of the clinical investigator's improper manipulation of source data (Site 1616). The exclusion of this site concretely demonstrates the sponsor's oversight of the study, as well as their willingness to exclude and report those sites not adhering to appropriate study standards. Therefore, as 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, it was decided that OSI would not perform clinical inspections for this application.

Author:
Snezana Trajkovic
Cross Discipline Team Leader

4. Nonclinical Pharmacology and Toxicology Evaluation and Recommendations

4.1. Nonclinical Executive Summary and Recommendation

Imuldosa (ustekinumab-srlf, code name: DMB-11335) is a human immunoglobulin G, subclass 1, κ light chain (IgG1κ) monoclonal antibody that specifically binds to the shared p40 protein subunit of the human cytokines interleukin (IL)-12 and IL-23. The binding prevents the IL-12 and IL-23 cytokines from binding to the IL-12Rβ1 receptor protein expressed on the surface of natural killer (NK) or T cells. Imuldosa has been developed as a biosimilar product to US-Stelara.

Animal studies were not required to support biosimilarity of DMB-3115 to US-Stelara. However, the applicant conducted single-dose and 4-week repeat-dose (twice weekly SC administration at 0.9 or 45 mg/kg/dose) nonclinical studies in cynomolgus monkey with DMB-3115 and EU-approved Stelara. The study reports were submitted to the BLA. These studies are reviewed in Section 14.3. The study results showed that the PK/TK and toxicity profiles of DMB-3115 and EU-Stelara are similar. There are no unique or additional concerns for DMB-3115.

This BLA is approvable from a nonclinical 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 composition of the DMB-3115 product (vial or pre-filled syringe) is shown in the tables below.

Table 3. Composition of DMB-3115 drug product (vial)

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Table P.1-1 Qualitative and Quantitative Composition of DMB-3115 Vial Drug Product

Name of Ingredient	Quantity (mg) per 26 mL (vial)	Function	Reference to Quality Standard
Ustekinumab	130	Active pharmaceutical ingredient	In-house
Sucrose	2210	(b) (4)	NF, Ph. Eur., JP
(b) (4) histidine	20		USP, Ph. Eur., JP
L-histidine hydrochloride monohydrate	27		Ph. Eur., JP
Polysorbate 80	10.4		NF, Ph. Eur., JP
(b) (4) Methionine	10.4		USP, Ph. Eur., JP
EDTA disodium (b) (4)	0.52		USP, Ph. Eur., JP.
(b) (4)			USP, Ph. Eur., JP

Table 4. Composition of DMB-3115 drug product (pre-filled syringe

Table 3.2.P.1-1. Qualitative and quantitative composition of DMB-3115 Pre-Filled Syringe Drug Product

Name of Ingredient	Quantity (mg) per 0.5 mL (PFS)	Quantity (mg) per 1.0 mL (PFS)	Function	Reference to Quality Standard
Ustekinumab	45	90	Active pharmaceutical ingredient	In-house
Sucrose	25.9	51.8	(b) (4)	NF/USP
(b) (4) histidine	2.23	4.46		USP

Name of Ingredient	Quantity (mg) per 0.5 mL (PFS)	Quantity (mg) per 1.0 mL (PFS)	Function	Reference to Quality Standard
L-histidine hydrochloride monohydrate	4.14	8.28	(b) (4)	Ph. Eur
Polysorbate 80	0.02	0.04		NF/USP
(b) (4)				USP, Ph. Eur, KP, JP

Comments on Excipients

No novel excipients are present in the DMB-3115 solution for infusion in vial. The excipients used are equivalent to those used in US-Stelara.

No novel excipients are present in the DMB-3115 solution for injection in pre-filled syringe. All excipients used in Imuldosa are same as used in US-Stelara.

Comments on Impurities of Concern

There are no concerns for impurities contained in DMB-3115.

Authors:
Xinguang (Cindy) Li, PhD
Pharmacologist

Barbara Hill, PhD
Supervisory Pharmacologist

5. Clinical Pharmacology Evaluation and Recommendations

5.1. Clinical Pharmacology Executive Summary and Recommendation

Table 5: Clinical Pharmacology Major Review Issues and Recommendations

Review Issue	Recommendations and Comments
Pharmacokinetics	• Pharmacokinetic (PK) similarity between DMB-3115 and US-Stelara was demonstrated in healthy subjects (Study DMB-3115-1) and supports a demonstration of no clinically meaningful differences between DMB-3115 and US-Stelara. • PK similarity between DMB-3115, EU-Stelara, and US-Stelara in Study DMB-3115-1 provides the PK component of the scientific bridge to support the relevance of using EU-Stelara in the comparative clinical study (Study DMB-3115-2)
Pharmacodynamic	• Not applicable
Immunogenicity	• In healthy subjects, the incidence of anti-drug antibodies (ADA) was numerically lower in DMB-3115 (28.3%) compared to US-Stelara (62.2%) and EU-Stelara (59.6%). However, the incidence of neutralizing antibody (NAb) formation in subjects who developed ADA was similar between DMB-3115 (57.1%), US-Stelara (55.7%), and

	EU-Stelara (61.0%) in the PK similarity study (Study DMB-3115-1). • In patients with plaque psoriasis, the incidence of ADA was numerically lower in DMB-3115 compared to that of EU-Stelara (32.1% vs. 63.2%) but NAb formation was similar in two groups (86.5% vs. 83.6%) in the comparative clinical study (Study DMB-3115-2)[a]. • The numerical difference in ADA and NAb incidences are not considered to be clinically significant and does not preclude the conclusion of no clinically meaningful differences between DMB-3115 and US-Stelara, as the systemic exposure between the three treatment groups are comparable among ADA positive and ADA negative subjects.

[a]Over the initial treatment (Period 1) before re-randomization at week 28

The clinical development for DMB-3115 included two clinical studies:

1) PK similarity Study DMB-3115-1: A single-center, single-dose, randomized, double-blind, 3-arm parallel-group study to compare the PK profiles of DMB-3115 (also referred to as DMB-3115 (Formulation A) by the Applicant), EU-Stelara, and US-Stelara in healthy subjects.
2) Comparative Clinical Study DMB-3115-2: A randomized, double-blind, multi-center, 2-period, parallel group, active-controlled comparative clinical study comparing efficacy, safety, and immunogenicity of DMB-3115 and EU-Stelara in patients with moderate to severe chronic plaque psoriasis.

The clinical pharmacology review for this BLA primarily focused on the PK similarity study (Study DMB-3115-1) and additional PK and immunogenicity data from the comparative clinical study (Study DMB-3115-2).

In the PK similarity study, the 90% confidence intervals (CIs) for the geometric mean ratios (GMRs) of DMB-3115 to US-Stelara, DMB-3115 to EU-Stelara, and EU-Stelara to US-Stelara were contained within the prespecified margin of 80%to 125% for the area under the time versus concentration curve (AUC) from time 0 to infinity ($AUC_{0\text{-}inf}$), maximal observed concentration (C_{max}), and AUC from time 0 to last time point (AUC_{last}) (Table 4). The results of the PK similarity study demonstrated that PK similarity was established between DMB-3115, US-Stelara, and EU-Stelara. The PK similarity study also supported the relevance of use of EU-Stelara in the comparative clinical study to establish the PK component of the scientific bridge.

Table 6: Summary of Statistical Analyses for Assessment of PK Similarity (Study DMB-3115-1)

	Geometric Mean	Geometric Mean Ratio[a] (90% CI)

PK Metrics	DMB-3115 (n=98)	US-STELARA (n=99)	EU-STELARA (n=98)	DMB-3115 vs US-STELARA	DMB-3115 vs EU-STELARA	EU-STELARA vs US-STELARA
$AUC_{0\text{-}inf}$ (h·ng/mL)	2333417	2455857	2333417	96.9 (89.7, 104.7)	102.0 (94.4, 110.2)	95.0 (88.0, 102.6)
AUC_{last} (h·ng/mL)	2251072	2363282	2251072	97.9 (90.9, 105.5)	102.8 (95.4, 110.7)	95.3 (88.4, 102.6)
C_{max} (ng/mL)	3319	3493	3395	95.0 (88.5, 102.0)	97.8 (91.1, 105.0)	97.2 (90.5, 104.4)

Source: Reviewer's analysis

[a]Presented as percent.

Abbreviations: CI=confidence interval, $AUC_{0\text{-}inf}$=area under the time versus concentration curve (AUC) from time 0 to infinity, AUC_{last}=AUC from time 0 to last time point, C_{max}=maximal observed concentration

The incidence of ADA and NAb formation in subjects treated with DMB-3115 was numerically lower compared to those treated with US-Stelara or EU-Stelara. However, the numerical differences in the incidence of ADA and NAb between DMB-3115 and US-Stelara and EU-Stelara, while similarly affecting the PK parameters of each product to a small extent (i.e., reduced systemic exposure), do not appear to have clinically meaningful impact on efficacy or safety, and does not preclude the conclusion of no clinical meaningful differences between DMB-3115 and US-Stelara.

Overall, the submitted clinical pharmacology information supports a demonstration that there are of no clinically meaningful differences between DMB-3115 and US-Stelara.

5.1.1. Clinical Pharmacology Residual Uncertainties Assessment

There are no residual uncertainties from a clinical pharmacology standpoint.

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

In the PK similarity study in healthy subjects, Study DMB-3115-1, following a single 45 mg SC injection of DMB-3115, EU-Stelara, or US-Stelara, the 90% CIs for the GMRs of DMB-3115 to US-Stelara, DMB-3115 to EU-Stelara, and EU-Stelara to US-Stelara for the tested PK metrics (i.e., $AUC_{0\text{-}inf}$, C_{max}, and AUC_{last}) were all within the prespecified margin of PK similarity of 80-125%. These pairwise comparisons met the pre-specified criteria for PK similarity between DMB-3115, 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 DMB-3115-2).

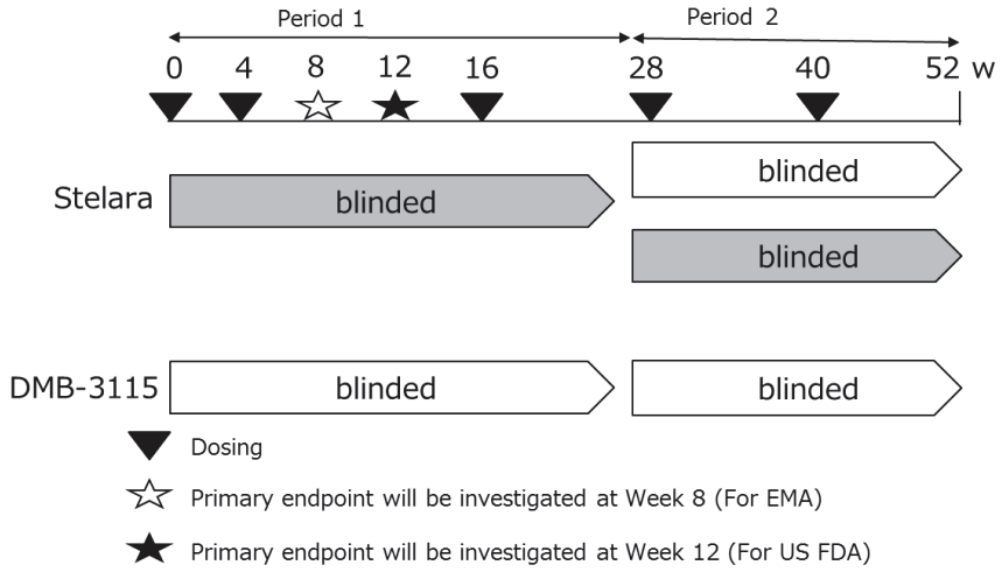
5.3. Human Pharmacokinetic and Pharmacodynamic Studies

Clinical Pharmacology Study Design Features

Two clinical studies provided PK data.

- Study DMB-3115-1 was a single-dose, 3-arm, parallel-group PK similarity study designed to compare the PK, immunogenicity, and safety of DMB-3115-1, US-Stelara, and EU-Stelara in healthy subjects.
- Study DMB-3115-2 was an active-controlled comparative clinical study designed to compare the efficacy, safety, and immunogenicity of subcutaneous DMB-3115 and EU-Stelara in patients with moderate to severe chronic plaque psoriasis. This study also included PK sampling to evaluate C_{max}, time to reach C_{max} (T_{max}), and AUC from week 0 to week 4 (AUC_{w0-w4}) after the first dose of both study drugs in patients receiving DMB-3115 or EU-Stelara. The study design schema is shown in Figure 1.

Figure 1: Treatment Design Schematic for Study DMB-3115-2



Source: Figure 1 in Clinical Study Report of Study DMB-3115-2

Clinical Pharmacology Study Endpoints

Study DMB-3115-1

In this PK similarity study, the primary endpoints were the PK metrics AUC_{inf}, AUC_{tlast} and C_{max}. The secondary endpoints included T_{max}. These endpoints are aligned with the FDA guidance for industry - Clinical Pharmacology Data to Support a Demonstration of Biosimilarity to a Reference Product (2016).

Study DMB-3115-2

In this comparative clinical study, PK and immunogenicity study endpoints included

incidence of ADAs, NAbs, and PK metrics (i.e., C_{max}, T_{max}, and AUC_{w0-w4}).

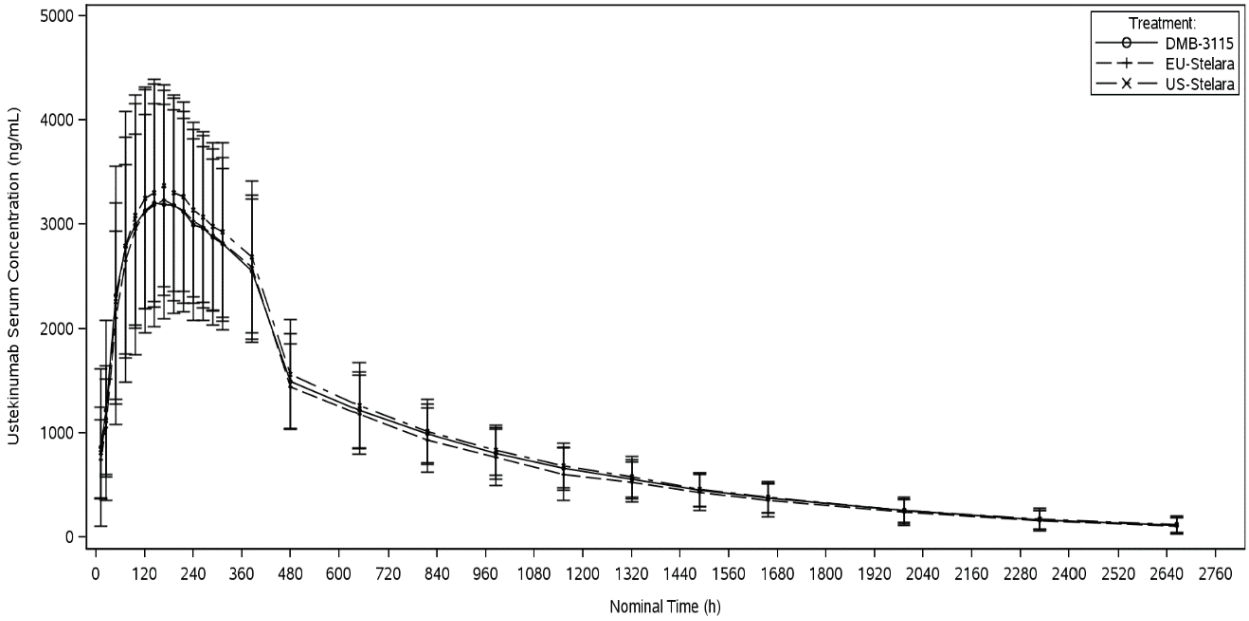
Bioanalytical PK Method and Performance

A validated electrochemiluminescence (ECL)-based assay SG029/2018 was used to quantify serum concentrations of DMB-3115, US-Stelara, and EU-Stelara in PK samples obtained from Studies DMB-3115-1 and DMB-3115-2. The assay was adequately validated with sufficient precision and sensitivity. The in-study performance of the assay for sample analyses from Study DMB-3115-1 and DMB-3115-2 was acceptable. Refer to section 14.4.1 for detailed information about the assay validation and bioanalysis performance.

Study DMB-3115-1 - PK Similarity Assessment

PK similarity between DMB-3115, US-Stelara, and EU-Stelara has been demonstrated in a 3-arm, parallel PK similarity study in healthy subjects (Study DMB-3115-1). PK samples were collected on Day 1 at pre-dose and 12 hours post-dose as well as Days 2, 3, 4, 5, 6, 7, 8, 9, 10, 11, 12, 13, 14, 17, 21, 28, 35, 42, 49, 56, 63, 70, 84, 98, and 112. The point estimates and 90% CIs of the GMRs of PK metrics (AUC_{0-inf}, C_{max} and AUC_{last}) were all within the pre-defined criteria of 0.8 to 1.25 (Table 6). The mean serum concentration-time profiles were similar between the DMB-3115, US-Stelara and EU-Stelara treatment groups (Figure 2). The PK metrics following a single dose of DMB-3115, US-Stelara, and EU-Stelara are summarized in Table 7. In general, PK metrics and inter-subject variability were comparable across the three treatment groups.

Figure 2: Arithmetic Mean (±Standard Deviation) for Study Drug Serum Concentrations Time Data - Linear Scale (Study DMB-3115-1)



Source: Figure 11-1 Clinical Study Report of Study DMB-3115-1

Table 7: Summary of PK Metrics (Study DMB-3115-1)

PK Metrics	Geometric Mean (Geometric CV%)		
	DMB-3115 (n=98)	US-STELARA (n=99)	EU-STELARA (n=99)
$AUC_{0\text{-}inf}$ (h·ng/mL)	2333417 (64.4%)	2455857 (64.8%)	2333417 (63.2%)
AUC_{last} (h·ng/mL)	2251072 (64.0%)	2363282 (64.5%)	2251072 (62.9%)
C_{max} (ng/mL)	3319 (64.0%)	3493 (63.3%)	3395 (62.9%)
T_{max}[a] (hours)	8 (3,17)	8 (5, 17)	9 (5, 17)

[a]Presented as median (minimum, maximum)
Source: Reviewer's analysis
Abbreviations: CV=coefficient of variation in percentage, $AUC_{0\text{-}inf}$= AUC from time 0 to infinity, AUC_{last}=AUC from time 0 to last time point, C_{max}=maximal observed concentration, T_{max}=time to reach C_{max}

Inspection of PK Similarity Study

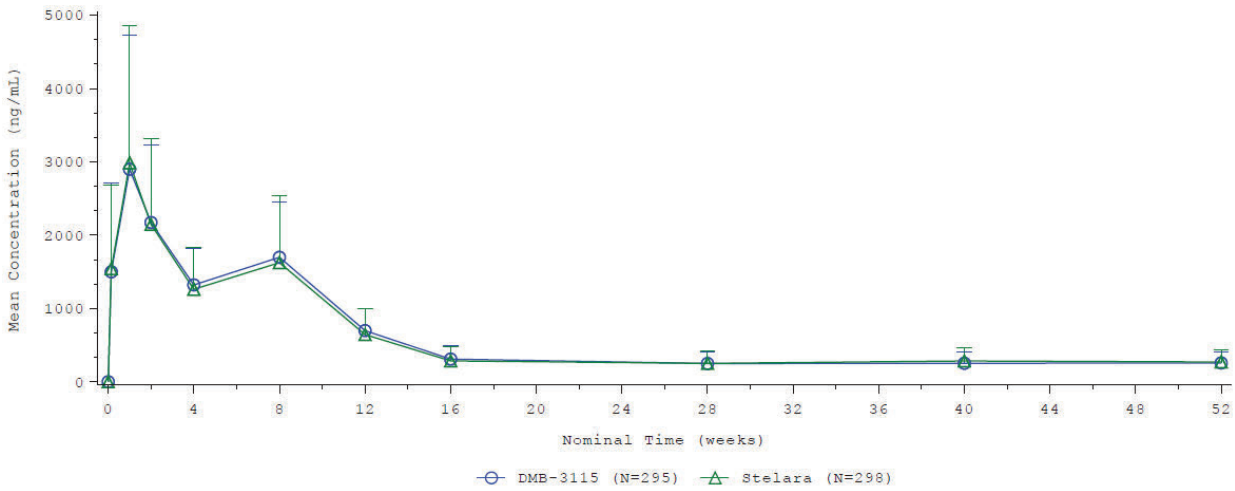
The PK similarity study involved two study sites (1 clinical site and 1 analytical site). OSIS declined to inspect the clinical site in Berlin, Germany as it was recently inspected in May 2024, and they concluded that the data from the site are considered reliable. OSIS conducted an analytical inspection of study DMB-3115-1 located at (b) (4) and observed some objectionable conditions. Form FDA 483 was issued to the site. Upon the review of the firm's response, there were no concerns regarding the reliability of the data for inspected study DMB-3115-1. Refer to Section 3.3 for details.

Study DMB-3115-2 - PK of DMB-3115 and EU-Stelara in Patients with Plaque Psoriasis

In Study DMB-3115-2, PK samples were collected at Weeks 0 (Pre-dose and 24 hours post-dose), 1, 2, 4, 8, 12, 16, 28, 40, and 52 to evaluate serum drug concentrations in patients with moderate to severe chronic plaque psoriasis. Per protocol, patients whose pre-dose concentration > 5% of C_{max} (n=2; one in DMB-3115 group and one in single transition group (also referred to as switch group) were excluded in the PK population.

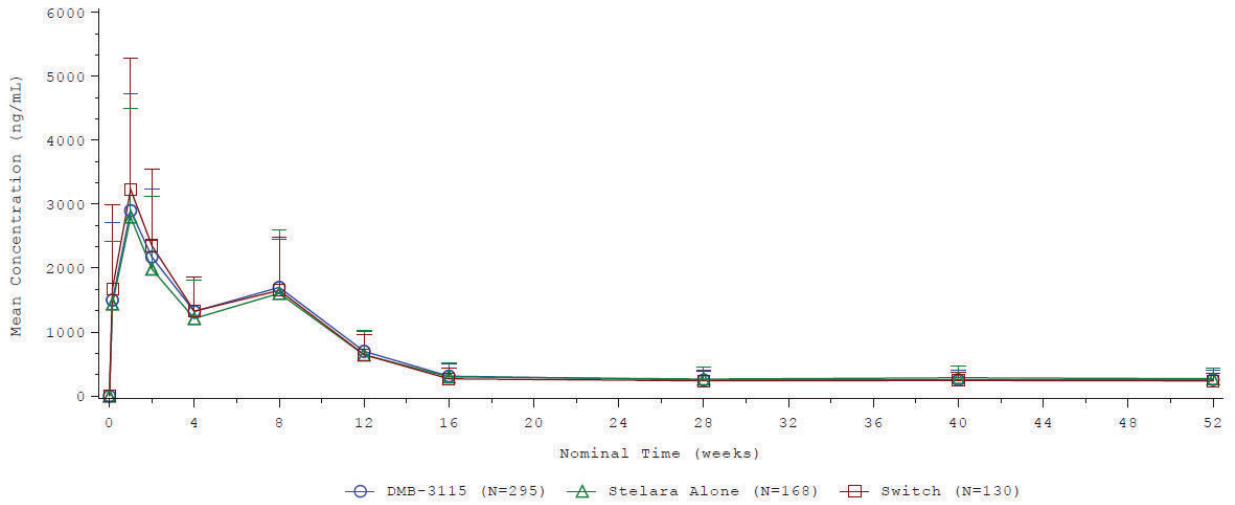
Mean study drug concentration-time profiles for each treatment are shown over the 52-week treatment period in Figure 3 (patients who switched treatment from EU-Stelara to DMB-3115 at Week 28 are excluded after Week 28) and Figure 4 (patients who switched treatment from EU-Stelara to DMB-3115 at Week 28 are shown as a separate Switch treatment group). There was a second peak observed in the PK profiles. This peak is explained by the dose given at week 4 with its long elimination halflife after SC administration (ranged 14.9 – 45.6 days in patients with plaque psoriasis) per Stelara USPI. The mean serum concentration-time profiles were overlapping between the DMB-3115 and EU-Stelara treatments, indicating no clinically significant difference in PK exposure between treatments.

Figure 3: Mean (+Standard Deviation) Study Drug Serum Concentration-time Profiles for Each Treatment from Week 0 to Week 52 on Linear Scale (Concentrations after Week 28 Switch Excluded)



Source: Figure 3 in Clinical Study Report of Study DMB-3115-2
Patients who received DMB-3115 over the entire treatment period are included in the DMB-3115 group.
Patients who received EU-Stelara over the entire treatment period as well as patients who switched from EU-Stelara to DMB-3115 at Week 28 are included in the EU-Stelara group up to Week 28. After Week 28, only patients who received EU-Stelara over the entire treatment period are included.

Figure 4: Mean (+Standard Deviation) Study Drug Serum Concentration-time Profiles for Each Treatment from Week 0 to Week 52 on Linear Scale (Concentrations after Week 28 Switch included)



Source: Figure 4 in Clinical Study Report of Study DMB-3115-2
Patients who received DMB-3115 over the entire treatment period are included in the DMB-3115 group.
Patients who received EU-Stelara over the entire treatment period are included in the Stelara Alone group.
Patients who switched from EU-Stelara to DMB-3115 at Week 28 are included in the Switch group.

Week 0 serum PK metrics following the first dose for DMB-3115 and EU-Stelara treatments are summarized in Table 8. Median T_{max} was similar for both treatments (approximately 7 day (167 hours)). Geometric mean serum C_{max} and AUC_{w0-w4} were comparable between treatments (<3% difference in geometric means between treatments), and variability was similar between treatments. The comparable concentrations across treatment groups in the psoriasis patient population, together with the results of the PK similarity study (Study DMB-3115-1) supports the establishment of PK similarity between DMB-3115 and US-Stelara.

Table 8: Study DMB-3115-2 Summary of Serum Study Drug Pharmacokinetic Metrics Following the First Dose (Week 0) by Treatment

PK Metrics	DMB-3115		EU-STELARA	
	n	Geometric Mean (CV%)	n	Geometric Mean (CV%)
Body Weight ≤100 kg / Dose 45 mg				
		N=214		N=215
C_{max} (ng/mL)	214	2341 (68.1%)	215	2306 (67.7%)
AUC_{w0-w4} (h·ng/mL)	214	1117995 (66.2%)	213	1080537 (66.6%)
T_{max}[a] (hours)	214	166.5 (17.5, 668.2)	215	167.2 (16.6, 671.7)
Body Weight > 100 kg / Dose 90 mg				
		N=81		N=83
C_{max} (ng/mL)	79	3425 (72.0%)	83	3740 (72.8%)
AUC_{w0-w4} (h·ng/mL)	81	1476198 (67.0%)	83	1509194 (68.9%)
T_{max}[a] (hours)	81	167.1 (20.23, 403.5)	83	166.7 (22.3, 337.5)

Source: Reviewer's analysis
[a]median (minimum, maximum)
Patients who received DMB-3115 over the entire treatment period are included in the DMB-3115 group.
Patients who received EU-Stelara over the entire treatment period as well as patients who switched from EU-Stelara to DMB-3115 at Week 28 are included in the EU-Stelara group.
Abbreviations: CV=coefficient of variation in percentage, C_{max}=maximal observed concentration, AUC_{w0-w4}= AUC from week 0 to week 4, T_{max}=time to reach C_{max}

Bioanalytical PK Method and Performance

A validated ECL-based PK sandwich assay method (ECL-based assay SG029/2018) was used to quantify serum concentrations of DMB-3115, US-Stelara, and EU-Stelara in PK samples obtained from Studies DMB-3115-1 and DMB-3115-2. The assay was adequately validated with sufficient precision and sensitivity. The in-study performance of the assay for sample analyses from Studies DMB-3115-1 and DMB-3115-2 was acceptable. Refer to Section 14.4.1. for detailed information about the assay validation and bioanalysis performance.

PD Similarity Assessment

Not applicable.

5.4. Clinical Immunogenicity Studies

Design Features of the Clinical Immunogenicity Assessment

Immunogenicity was assessed in healthy subjects following a single 45 mg SC dose of DMB-3115, US-Stelara, or EU-Stelara in Study DMB-3115-1, and in patients with moderate to severe chronic plaque psoriasis following multiple doses of DMB-3115 and EU-Stelara in Study DMB-3115-2.

Immunogenicity Endpoints

Blood samples collected for immunogenicity assessment were first tested for ADA. Samples that tested positive for ADA were further tested for NAb.

Immunogenicity Assay's Capability of Detecting the ADA and NAb in the Presence of DMB-3115, US-Stelara, and EU-Stelara in the Study Samples

Applicant developed binding and neutralizing antibody assays that are suitable for detecting ADA and NAb in the presence of expected levels of DMB-3115, US-Stelara and EU-Stelara. Refer to the OPQA-III Immunogenicity review for more details on assay validation.

Adequacy of the Sampling Plan to Capture Baseline, Early Onset, and Dynamic Profile of ADA/NAb Formation

The sampling plans were adequate to capture baseline, early onset, and dynamic profile (transient or persistent) of ADA/NAb formation.

- Study DMB-3115-1: Samples for immunogenicity assessment were collected predose on Days 1, 6, 14, 28, 56, and 112 (end of study).
- Study DMB-3115-2: Samples for immunogenicity assessment were collected predose at Weeks 0 (pre-dose and 24 hours post-dose), 2, 4, 8, 12, 16, 28, 40, and 52.

Incidence of ADA and NAb

In Healthy Subjects Following a Single Dose

In Study DMB-3115-1, the incidence of pre-existing antibodies at baseline against ustekinumab was similar among DMB-3115 (6.1%), US-Stelara (10.2%), and EU-Stelara (8.1%). The treatment-induced immunogenicity of DMB-3115 was numerically lower compared to those of US-Stelara and EU-Stelara in healthy adult subjects following a single 45 mg SC dose. The incidence of ADA and NAb by treatment group in Study DMB-3115-1 is summarized in Table 9. The differences were not considered to be clinically significant.

Table 9: Immunogenicity Results for Anti-Drug antibody (ADA) and Neutralizing Antibody (NAb) in Study DMB-3115-1

Treatment	Anti-Drug Antibody Positive, n/N (%)		NAb, n/N (%)
	Baseline	Treatment-Induced	
DMB-3115	6/99 (6.1%)	28/99 (28.3%)	16/28 (57.1%)
US-Stelara	10/98 (10.2%)	61/98 (62.2%)	34/61 (55.7%)
EU-Stelara	8/99 (8.1%)	59/99 (59.6%)	36/59 (61.0%)

Source: Reviewer's analysis
Abbreviations: n=number of subjects with positive results, N=total number of subjects

In Patients with Plaque Psoriasis Following Multiple Doses

In Study DMB-3115-2, there was a similar incidence of pre-existing ADA against ustekinumab at baseline in DMB-3115 (6.4%) and EU-Stelara (6.0%). During the Period 1 throughout Week 28, the ADA incidence became numerically higher in patietns who were treated with EU-Stelara (63.2%) than in those treated with DMB-3115 (32.1%). After re-randomization at Week 28, the ADA incidence was similar between patients who underwent a single transition (68.7%) and patients who continued being treated with EU-Stelara (74.3%). However, the ADA incidence was numerically lower in patients who received DMB-3115 continuously (37.4%) than other two treatment groups. Immunogenicity results are summarized by treatment group through Week 28 (Period 1) and post Week 28 (Period 2) for re-randomized subjects in Table 8. The differences in ADA and NAb incidence in Study DMB-3115-2 were not considered to be clinically significant, and this is consistent with the findings from Study DMB-3115-1.

Table 10: Immunogenicity Results for Binding Anti-Drug Antibody (ADA) and Neutralizing Antibody (NAb) in Study DMB-3115-2

Treatment		ADA Positive, n/N (%)			NAb, n/N (%)	
Period 1	Period 2	Baseline	Period 1	Period 2	Period 1	Period 2
DMB-3115		19/299 (6.4%)	96/299 (32.1%)	99/265 (37.4%)	83/96 (86.5%)	84/99 (84.8%)
EU-Stelara	EU-Stelara	18/299 (6.0%)	189/299 (63.2%)	101/136 (74.3%)	158/189 (83.6%)	82/101 (81.2%)
	DMB-3115			90/131 (68.7%)		78/90 (86.7%)

Source: Reviewer's analysis
Abbreviations: n=number of subjects with positive results, N=total number of subjects

Incidence of NAb

In Study DMB-3115-1, the overall incidence of neutralizing antibodies (NAb) formation in healthy subjects following single dose was similar as 57.1%, 55.7% and 61.0%, for DMB-3115, US-Stelara, and EU-Stelara, respectively (Table 7).

In Study DMB-3115-2, the incidence of NAb formation was similar between DMB-3115, and EU-Stelara (86.5% and 83.6%, respectively) during the Period 1. In the Period 2, the incidence of NAb formation was 84.8% in patients who continued with DMB-3115,

81.2% in patients who continued with EU-Stelara, and 86.7% in patients who switched from EU-Stelara to DMB-3115 (Table 10).

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 DMB-3115 and EU-Stelara, and do not preclude a conclusion of no clinically meaningful differences between DMB-3115 and US-Stelara.

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

In Study DMB-3115-1, following a single dose of 45 mg ustekinumab SC injection, the development of ADAs resulted in a slight decrease in systemic exposure in each treatment group (Table 11). A lower exposure was noted in ADA positive patients compared to ADA negative patients in all three treatment groups. The magnitude of AUC difference with respect to different ADA status was similar between DMB-3115 and US-Stelara, while a slightly lesser difference was noted with EU-Stelara. Overall, the exposure in ADA positive subjects were similar to that in ADA negative subjects and the impact of ADA on PK of the study drug is not considered as significant in all three treatment groups.

Table 11: Summary of PK Metrics (Geometric mean (geometric CV%)) by Treatment and Anti-Drug Antibody (ADA) Status (Study DMB-3115-1)

PK Metrics	DMB-3115 (N=99)		US-Stelara (N=98)		EU-Stelara (N=99)	
	ADA + (n=28)	ADA- (n=71)	ADA + (n=61)	ADA- (n=37)	ADA + (n=59)	ADA- (n=40)
$AUC_{0\text{-}inf}$ (h·ng/mL)	84759 (64.9%)	105600[a] (63.3%)	94308 (63.5%)	117064 (62.5%)	92385 (65.1%)	104832 (63.6%)
AUC_{last} (h·ng/mL)	82605 (64.7%)	102472 (63.3%)	91664 (64.9%)	110813 (63.2%)	89554 (63.2%)	100419 (62.4%)
C_{max} (ng/mL)	2935 (65.5%)	3484 (63.7%)	3389 (63.0%)	3672 (63.7%)	3375 (62.8%)	3425 (63.0%)
T_{max}[b] (hours)	9 (4, 17)	7 (3, 14)	8 (5, 17)	8 (5, 17)	8 (5, 17)	9 (5, 17)

Source: reviewer's analysis based on adpc.xpt and adis.xpt for Study DMB-3115-1.
[a]n=70; [b] median and range were reported.
Abbreviations: CV%=coefficient of variation in percentage, $AUC_{0\text{-}inf}$= AUC from time 0 to infinity, AUC_{last}=AUC from time 0 to last time point, C_{max}=maximal observed concentration, T_{max}=time to reach C_{max}

In Study DMB-3115-1, the exposure (both AUC and C_{max}) of study drug in patients with NAb positive patients was also similar among three treatment groups. The magnitude of AUC difference was similar across three treatment groups (Table 12).

Table 12: Summary of PK Metrics (Geometric mean (geometric CV%)) by Treatment and Neutralizing Antibody (NAb) Status (Study DMB-3115-1)

PK Metrics	DMB-3115 (N=28)		US-Stelara (N=61)		EU-Stelara (N=59)	
	NAb+ (n=16)	NAb- (n=12)	NAb+ (n=34)	NAb- (n=27)	NAb+ (n=36)	NAb- (n=23)
$AUC_{0\text{-}inf}$ (h·ng/mL)	83547 (65.6%)	86401 (64.5%)	89239 (66.7%)	101103 (63.0%)	88362 (63.7%)	99053 (63.1%)
AUC_{last} (h·ng/mL)	81214 (65.2%)	84497 (64.4%)	87455 (66.5%)	97253 (62.9%)	86136 (63.4%)	95179 (62.8%)
C_{max} (ng/mL)	3042 (64.7%)	2798 (66.9%)	3544 (62.9%)	3203 (63.1%)	3413 (62.6%)	3317 (63.3%)
T_{max}[a] (hours)	9 (4, 17)	8 (3, 14)	7.5 (5, 12)	8 (5, 17)	8.5 (5, 13)	9 (5, 17)

Source: reviewer's analysis based on adpc.xpt and adis.xpt of Study DMB-3115-1.
[a] median and range were reported.
Abbreviations: CV%=coefficient of variation in percentage, $AUC_{0\text{-}inf}$= AUC from time 0 to infinity, AUC_{last}=AUC from time 0 to last time point, C_{max}=maximal observed concentration, T_{max}=time to reach C_{max}

In the multiple dose study in patients with severe chronic plaque psoriasis (Study DMB-3115-2), the development of ADAs seems not associated with the exposure in each dosing group of DMB-3115 and EU-Stelara (Table 13).

Table 13: Summary of PK Metrics (Geometric mean (geometric CV%)) by Treatment and Anti-Drug Antibody (ADA) Status (Study DMB-3115-2)

Dose	PK Metrics	DMB-3115 (N=295)		EU-Stelara (N=298)	
		ADA +	ADA-	ADA +	ADA-
45 mg (Body Weight ≤100 kg)	N	51	163	128	87
	C_{max} (ng/mL)	2396 (67.7%)	2324 (68.3%)	2274 (68.2%)	2355 (67.0%)
	$AUC_{w0\text{-}w4}$ (h·ng/mL)	1138638 (66.0%)	1111613 (66.2%)	1042094 (67.4%)	1141119 (65.5%)
	T_{max}[a] (hours)	166.5 (20.9, 361.9)	166.6 (17.5, 668.2)	167.1 (16.6, 670.1)	167.3 (21.9, 671.7)
90 mg (Body Weight > 100 kg)	N	33	48	47	36
	C_{max} (ng/mL)	3335 (73.7%)	3488 (71.2%)	3916 (69.3%)	3522 (77.8%)
	$AUC_{w0\text{-}w4}$ (h·ng/mL)	1422681 (67.5%)	1513782 (66.7%)	1523110 (66.2%)	1491216 (72.8%)
	T_{max}[a] (hours)	166.7 (117.5, 360.7)	177.7 (20.3, 403.5)	166.6 (22.3, 337.5)	167.0 (118.2, 335.9)

Source: Reviewer's analysis based on adpc.xpt and adis.xpt for Study DMB-3115-2.
Note: ADA status was based on the ADA results at week 4 when the PK metric was collected.
[a] median and range were reported.
Abbreviations: CV%=coefficient of variation in percentage, C_{max}=maximal observed concentration, $AUC_{w0\text{-}w4}$= AUC from week 0 to week 4, T_{max}=time to reach C_{max}

In Study DMB-3115-2, the exposure of study drug in patients NAb positive was similar between DMB-3115 and EU-Stelara groups. Lower exposures were noted in NAb positive patients compare to NAb negative patients (Table 14).

Table 14: Summary of PK Metrics (Geometric mean (geometric CV%)) by Treatment and Neutralizing Antibody (NAb) Status in Patients with Anti-Drug Antibody Positive (Study DMB-3115-2)

Dose	PK Metrics	DMB-3115 (N=295)		EU-Stelara (N=298)	
		NAb +	NAb -	NAb +	NAb -
45 mg (Body Weight ≤100 kg)	N	36	15	94	34
	C_{max} (ng/mL)	2226 (65.6%)	2860 (72.1%)	2262 (68.5%)	2308 (67.5%)
	AUC_{w0-w4} (h·ng/mL)	1064221 (64.6%)	1339165 (68.7%)	1036887 (67.7%)	1056627 (66.8%)
	T_{max}[a] (hours)	166.8 (20.9, 358.4)	166.5 (17.5, 668.2)	167.0 (16.6, 670.1)	167.2 (21.9, 671.7)
90 mg (Body Weight > 100 kg)	N	27	6	37	10
	C_{max} (ng/mL)	3060 (73.1%)	4914 (71.6%)	3912 (69.7%)	3932 (68.9%)
	AUC_{w0-w4} (h·ng/mL)	1394546 (67.8%)	1584716 (67.0%)	1487587 (66.9%)	1662081 (64.1%)
	T_{max}[a] (hours)	166.8 (141.6, 360.7)	167.3 (20.3, 403.5)	166.15 (22.3, 335.3)	167.0 (118.2, 337.5)

Source: reviewer's analysis based on adpc.xpt and adis.xpt for Study DMB-3115-2.
Note: ADA status was based on the ADA results at week 4 when the PK metric was collected.
[a] median and range were reported.
Abbreviations: CV%=coefficient of variation in percentage, C_{max}=maximal observed concentration, AUC_{w0-w4}= AUC from week 0 to week 4, T_{max}=time to reach C_{max}

Impact of ADA on Safety

In Study DMB-3115-1, the overall number of participants who experienced injection site reaction, any treatment-emergent adverse event (TEAE), TEAE related to investigational product, or infection and infestation was similar across the 3 treatment groups regardless the ADA and NAb status.

In Study DMB-3115-2, no apparent impact of ADA status on the TEAE profile of DMB-3115, or EU-Stelara was observed. Incidence of TEAEs, serious TEAEs, treatment-related TEAEs, Grade 3+ TEAEs, and treatment discontinuation due to TEAEs was comparable to the overall population regardless of ADA status. The most common TEAE was nasopharyngitis, and the incidence of that event was higher in the ADA positive subgroups (13.7%, 12.9%, and 14.1% for DMB-3115, EU-Stelara, and EU-Stelara switched to DMB-3115, respectively) compared with the ADA negative subgroups (7.1%, 6.0%, and 12.8% for DMB-3115, EU-Stelara, and EU-Stelara switched to DMB-3115, respectively). There was no evidence of an impact of NAb status on the TEAE profile for any of the treatment arms either. Incidence of TEAEs, serious TEAEs, treatment-related TEAEs, Grade 3+ TEAEs, and treatment discontinuation due to TEAEs was comparable to the overall population regardless of NAb status. For further discussion on safety Refer to Section 6.3.

Impact of ADA on Efficacy

In Study DMB-3115-2, the primary efficacy endpoint was percent change in Psoriasis Area and Severity Index (PASI) score from baseline to Week 12. For each of the 4 subgroups determined by ADA or NAb status at Week 12, there were no statistically significant treatment differences in least square (LS) mean percent change in PASI scores from baseline to Week 12 (Table 15). Comparable PASI percent improvement was observed between ADA positive and ADA negative subgroups for both DMB-3115 and EU-Stelara in Study DMB-3115-2.

Table 15: Percent of Change in PASI from Baseline to Week 12 By Anti-Drug Antibody (ADA) and Neutralizing Antibody (NAb) Status (Study DMB-3115-2)

	ADA Positive		**ADA Negative**	
	DMB-3115	EU-Stelara	DMB-3115	EU-Stelara
LS mean change in PASI	82.9% (n=35)	83.3 (n=80)	88.2% (n=264)	89.1% (n=219)
LS mean difference (90% CI)	−0.39 % (-5.8, 5.0)		-0.9% (-3.2, 1.4)	
	NAb Positive		**NAb Negative**	
	DMB-3115	EU-Stelara	DMB-3115	EU-Stelara
LS mean change in PASI	73.9% (n=16)	77.0% (n=40)	88.7% (n=283)	89.1% (n=259)
LS mean difference (90% CI)	-3.1% (-10.7, 4.4)		-0.3% (-2.5, 1.8)	

Source: Tabulated based on the Applicant's IR response dated July 16, 2024.
Abbreviation: LS=least square, CI=confidence interval

In summary, the numerical differences in the incidence of ADA and NAb between DMB-3115 and US-Stelara and EU-Stelara, while similarly affecting the PK parameters of each product to a small extent (i.e., reduced systemic exposure), do not appear to have clinically meaningful impact on efficacy or safety. Clinical Pharmacology review concludes that PK similarity between DMB-3115 and US-Stelara was established and the use of EU-Stelara in the comparative clinical study is supported by the results of the PK similarity study.

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6. Statistical and Clinical Evaluation and Recommendations

6.1. Statistical and Clinical Executive Summary and Recommendation

The statistical review evaluated DMB-3115 as a proposed biosimilar to US-Stelara based on a comparative clinical study, DMB-3115-2. Study DMB-3115-2 was a

randomized, double-blind, multi-center, parallel-group, and active-controlled study in 598 subjects with moderate to severe chronic plaque psoriasis, comparing DMB-3115 and EU-Stelara. The Applicant provided adequate data to establish analytical and PK components of the scientific bridge (refer to Section 5) to justify the relevance of data generated from Study DMB-3115-2, which used EU-Stelara as the comparator, for the assessment of biosimilarity.

In Study DMB-3115-2, the primary endpoint was percent change in the Psoriasis Area and Severity Index (PASI) score from baseline to Week 12. The primary analysis results of the primary endpoint in ITT (refer to Table 20) showed that there were no clinically meaningful differences between DMB-3115 and EU-Stelara with an estimated difference (DMB-3115 minus EU-Stelara) of -0.2% and 90% confidence interval of (-2.1%, 1.7%), which was contained within the Agency-recommended similarity margin of ± 10%. The results of sensitivity/supplementary analyses of the primary endpoint were consistent with those of the primary analysis. Percent change in PASI from baseline, percentage of subjects with a PASI 50/75/90/100 response, and percentage of subjects with a Physician's Global Assessment (PGA) score of Cleared or Minimal throughout the study were also evaluated and appeared to be comparable between the treatment groups.

The collective evidence from Study DMB-3115-2 supports a demonstration of no clinically meaningful differences between DMB-3115 and EU-Stelara.

6.1.1. Statistical and Clinical Residual Uncertainties Assessment

There are no residual uncertainties based on the statistical analyses.

6.2. Review of Comparative Clinical Studies with Statistical Endpoints

6.2.1. STUDY DMB-3115-2

Study DMB-3115-2, a comparative clinical study in subjects with moderate to severe chronic plaque psoriasis, evaluated whether there were any clinically meaningful differences between DMB-3115 and EU-Stelara.

Data and Analysis Quality

There are no concerns regarding data quality and integrity.

Study Design and Endpoints

Study DMB-3115-2 was a randomized, double-blind, multi-center, parallel-group, and active-controlled study comparing the efficacy, safety, and immunogenicity of subcutaneous DMB-3115 and EU-Stelara in subjects with moderate to severe chronic plaque psoriasis. The study was conducted at 79 sites across 9 countries (Poland,

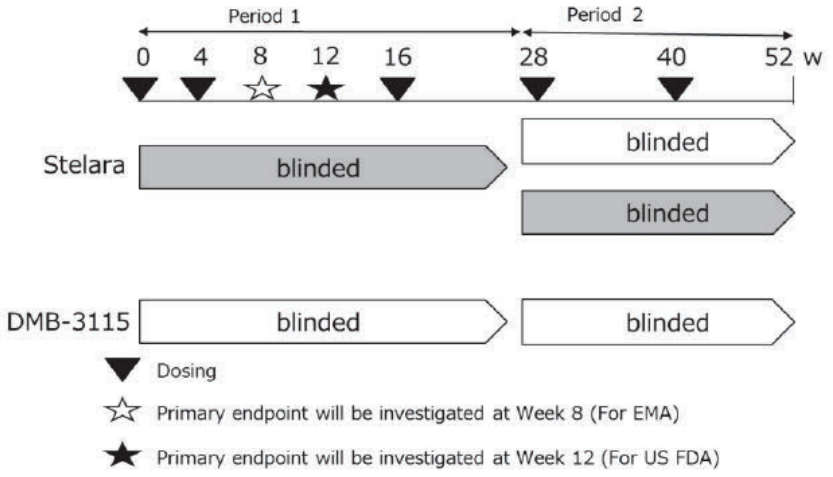
Bulgaria, Czech Republic, Hungary, Ukraine, Estonia, United States, Latvia, and Georgia).

After a screening period of up to 4 weeks, the eligible subjects were randomly assigned in a 1:1 ratio to receive treatment with either DMB-3115 or EU-Stelara. Randomization was stratified according to body weight at baseline (≤ 100 kg or > 100 kg), geographic region (EU, US, or Rest of the World [ROW]), and the number of previous systemic therapies for psoriasis (< 3 or ≥ 3).

The study consisted of two periods after screening period: Period 1 (28 weeks) and Period 2 (24 weeks). In Period 1 (Week 0 to Week 28), subjects received the assigned treatment, either DMB-3115 or EU-Stelara, at Weeks 0, 4, and 16. Subjects who did not achieve at least PASI50 response by Week 12 were discontinued from further treatment with ustekinumab. Only those subjects who achieved at least PASI75 response at Week 28 were eligible to be included in Period 2 (transition period).

In Period 2 (Week 28 to Week 52), subjects who were randomized to receive EU-Stelara at the beginning of the study were re-randomized and re-stratified based on the body weight at Week 28 (≤ 100 kg or > 100 kg) in a 1:1 ratio to either continue on EU-Stelara or be transitioned to receive DMB-3115 every 12 weeks up to Week 40. The doses at re-randomization were re-assigned based on the body weight at Week 28 (≤ 100 kg or > 100 kg). Subjects who were randomized to receive DMB-3115 at the beginning of the study continued to receive the same treatment up to Week 40 but they were re-randomized to maintain blinding. See Figure 5.

Figure 5 Schematic Study Design of DMB-3115-2



* Abbreviation: EMA = European Medicines Agency; US FDA = United States Food and Drug Administration; w = weeks.

Source: Figure 1 of Applicant's Clinical Study Report DMB-3115-2 (pg. 23 of 3399)

The study enrolled subjects with 18 to 75 years of age, body weight ≤ 140 kg, a diagnosis of plaque-type psoriasis for at least 6 months prior to IP initiation, and moderate to severe psoriasis defined by PASI score of 12 or greater, PGA score of 3 or greater, body surface area (BSA) affected by plaque-type psoriasis of 10% or greater.

The primary efficacy endpoint was percent change in the Psoriasis Area and Severity Index (PASI) score from baseline to Week 12.

The secondary efficacy endpoints included the following:

- Percentage of subjects with a PASI 50 (a 50% reduction in the PASI score) response at Weeks 4, 8, 12, 16, 28, 40, and 52
- Percentage of subjects with a PASI 75 (a 75% reduction in the PASI score) response at Weeks 4, 8, 12, 16, 28, 40, and 52
- Percentage of subjects with a PASI 90 (a 90% reduction in the PASI score) response at Weeks 4, 8, 12, 16, 28, 40, and 52
- Percentage of subjects with a PASI 100 (a 100% reduction in the PASI score) response at Weeks 4, 8, 12, 16, 28, 40, and 52
- Percent change in PASI from baseline at Weeks 4, 8, 12, 16, 28, 40, and 52
- Percentage of subjects with a Physician's Global Assessment (PGA) score of Cleared or Minimal at Weeks 4, 8, 12, 16, 28, 40, and 52

Statistical Methodologies

Analysis Sets

The Applicant defined these analysis sets for the analysis of efficacy.

1) Screened (SCR) set included all subjects who provided informed consent for the study.
2) Intent-to-Treat (ITT) set included all subjects who have been randomized. The ITT set was used for the primary efficacy analysis.
3) Per protocol set (PPS) included subjects who completed the study up to Week 12 and had no critical/major protocol deviations which might have a significant impact on primary endpoint analysis. All decisions to exclude subjects from the per protocol set were made prior to the unblinding of the study.

Similarity Margin and Sample Size Calculation

The similarity margin of ± 10% for the primary efficacy endpoint of the percent change in PASI from baseline to Week 12 was recommended by the FDA in the FDA's written response to the Sponsor's Biosimilar Biological Product Development (BPD) Type 2 Meeting Request submitted on 3/27/2020 under Pre-Investigational New Drug (PIND) 141843. In the BPD Type 2 Meeting Information Package, the Sponsor proposed to use either the primary endpoint of the percent change in PASI from baseline to Week 12 with the similarity margin of ± (b) (4) or the primary endpoint of PASI75 at Week 12 with the similarity margin of ± (b) (4). In the written response, the FDA stated that "we

acknowledge the Agency has previously accepted different margins and different endpoints from the ±10% for the primary efficacy endpoint of percent change in PASI. However, in addition to ensuring that the margin maintains a sufficient proportion of the treatment effect, the margin should ensure that it is adequate for demonstrating no clinically meaningful differences. Thus, for the recommended primary efficacy endpoint of percent change in PASI, the recommended equivalence margin is ±10%."

The Applicant calculations showed that the sample size of 490 subjects in total (245 subjects per treatment group) at baseline can achieve 392 evaluable subjects based on the assumptions of similarity margin of ± 10%, 90% power, 90% confidence interval (significance level of 5%), expected mean difference of 0, common standard deviation (σ) of 0.3 (The SD assumption was derived from the observed SD in studies PHOENIX 1 and PHOENIX 2), and 20% dropout rate. Furthermore, in order to meet the EMA's minimum requirement for safety analysis (at least 100 subjects per treatment group for long-term data), the Applicant planned to randomize 590 subjects at baseline, assuming a dropout rate of 20% in Period 1, a dropout rate of 15% in Period 2, and considering the 1:1 re-randomization rate for Stelara arm in Period 2.

Analysis of Primary Efficacy Endpoint

The primary efficacy endpoint of the percent change in PASI from baseline to Week 12 was analyzed with an analysis of covariance (ANCOVA) model with the baseline PASI score as a covariate and treatment and the three stratification factors (subject's body weight at baseline (≤ 100 kg or > 100 kg), geographic region (EU, US, or Rest of the World [ROW]), and the number of previous systemic therapies for psoriasis (< 3 or ≥ 3)) as factors. The primary analysis population was the ITT set, and the PPS was used for supplementary analysis. The estimates and the 2-sided 90% confidence interval (CI) for the mean difference in the percent change in PASI from baseline to Week 12 between DMB-3115 and Stelara were reported. The 90% CI should be within the similarity margin of ± 10% to conclude that there were no clinically meaningful differences between DMB-3115 and Stelara.

Handling of Missing Values

For the primary efficacy analysis, the Applicant imputed the missing values for the primary endpoint using the following multiple imputation (MI) procedure.

- Step 1: Creation of monotone missing data structure
  Monotone missing data structure was created to ensure that the results do not suffer from a relative efficiency loss. Intermediate (non-monotone) missing data were imputed using the Markov Chain Monte Carlo (MCMC) method including treatment arm, PASI_Baseline, PASI_Week4, PASI_Week8, and PASI_Week12, and assuming that the joint distribution of these variables is multivariate normal and the pattern for missing data is arbitrary. A total of 50 sets of imputations were performed.

- Step 2: Further imputations
  The datasets created in Step 1, with monotone missing data structure, were imputed further, in a stepwise manner to impute each week's PASI from Week 4 to Week 12 using the regression method assuming missing at random. The model for each week included terms for all the previous weeks.

Sensitivity/Supplementary Analyses

The Applicant conducted **(i)** a sensitivity analysis using a mixed linear model with treatment group, baseline body weight (≤ 100 kg or > 100 kg), geographic region (EU, US, or ROW), the number of previous systemic therapies for psoriasis (< 3 or ≥ 3), visit (Week 4 to Week 28), and the treatment-by-visit interaction as fixed effects and baseline PASI score as a covariate, based on the ITT. For the mixed linear model, unstructured variance-covariance matrix was used to model the correlation within each subject. If the model with unstructured variance-covariance matrix failed to converge, a simpler covariance structure was to be used selected by the AIC criterion.

The reviewer conducted the following additional sensitivity analyses to assess the robustness of the primary efficacy analysis results with respect to the handling of missing data and intercurrent events.

(ii) Analysis using the same ANCOVA model as in the primary efficacy analysis, based on the ITT, using available data (no imputation)

(iii) Analysis using the same ANCOVA model as in the primary efficacy analysis, based on the ITT, imputing the 16 subjects with missing PASI at Week 12, with a conservative approach (0 percent change in PASI for DMB-3115 group and 100 percent change in PASI for Stelara group)

The reviewer also conducted:

(iv) a supplementary analysis using the same ANCOVA model as in the primary efficacy analysis based on the PPS.

Additionally, Site 1616 was found to have "site non-compliance with GCP principles of source document handling" from audit at the site after unblinding. As a result, the Applicant excluded all data from Site 1616 from analysis. The Applicant conducted **(v)** a sensitivity analysis including the data from Site 1616.

Reviewer's comments: The assumptions for the FDA's conservative approach in (iii) were based on the distribution of the individual subjects' percent change from baseline in PASI at Week 12, as the minimum and the maximum values of the percent change from baseline were 0% and 100%, respectively.

Analysis of Secondary Efficacy Endpoints

The analyses of the secondary efficacy endpoints were performed using the ITT. The secondary efficacy endpoints were analyzed and summarized differently for Period 1 and Period 2 as follows.

For Period 1, the secondary endpoints based on proportions (or percentages) were analyzed using a logistic regression with the baseline value, baseline body weight (≤ 100 kg or > 100 kg), geographic region (EU, US, or ROW), and the number of previous systemic therapies for psoriasis (< 3 or ≥ 3) as covariates. The 90% confidence interval for the odds ratio of treatment group comparisons were constructed using Wald's test. The percent change in PASI from baseline were analyzed using ANCOVA with baseline PASI score as a covariate and treatment, body weight (≤ 100 kg or > 100 kg), geographic region (EU, US, or ROW), and the number of previous systemic therapies for psoriasis (< 3 or ≥ 3) as factors. The 90% confidence intervals for the mean difference were calculated using the ANCOVA model.

For Period 2, descriptive statistics were provided for the three treatment groups: DMB-3115, Stelara-Stelara, and Stelara-DMB-3115. Continuous variables were summarized by the number of observations, mean, standard deviation (SD), median, minimum, and maximum. Categorical variables were summarized by frequency counts and percentages for each treatment group.

Subject Disposition

A total of 598 subjects were randomized into two treatment groups: 299 in DMB-3115 and 299 in EU-Stelara. Out of those, 31 subjects (10.4%) in DMB-3115 group and 36 subjects (12.0%) in Stelara group discontinued prematurely during Period 1. The discontinuation rates during Period 1 were comparable (10-12%) between the two treatment groups. The most common reason for discontinuation among all randomized subjects was diagnosis of SARS-CoV-2 infection.

For Period 2, 268 subjects in DMB-3115 group continued on DMB-3115 and a total of 263 subjects in EU-Stelara group were re-randomized at Week 28: 132 in EU-Stelara-EU-Stelara and 131 in EU-Stelara-DMB-3115. Out of those, 8 subjects (3.0%) in DMB-3115, 1 subject (0.8%) in EU-Stelara-EU-Stelara, and 6 subjects (4.6%) in EU-Stelara-DMB-3115 discontinued prematurely during Period 2. See Table 16.

Note that 3 subjects (2 subjects in DMB-3115 and 1 subject in EU-Stelara) discontinued prematurely in Period 1 due to death. The reasons for discontinuation for those three subjects are shown as Other in Table 16, but in the listing of discontinued subjects, the reasons for discontinuation are shown as Other: Death. According to the case report forms for the three subjects, the deaths were related to COVID infection or sudden cardiac event and were not related to the study treatment.

Table 16 Summary of Subject Disposition and Reasons for Discontinuation

Period 1

	DMB-3115 (N=299)	EU-Stelara (N=299)		Total (N=598)
Randomized[a]	299 (100.0%)	299 (100.0%)		598 (100.0%)
Treated[a]	299 (100.0%)	299 (100.0%)		598 (100.0%)
Completed Period 1[a]	268 (89.6%)	263 (88.0%)		531 (88.8%)
Discontinued prematurely during Period 1[a]	31 (10.4%)	36 (12.0%)		67 (11.2%)
Reasons for discontinuation				
Not achieving PASI50 response by Week 12	4 (1.3%)	4 (1.3%)		8 (1.3%)
Not achieving PASI75 response by Week 28	5 (1.7%)	5 (1.7%)		10 (1.7%)
Investigator decision	1 (0.3%)	2 (0.7%)		3 (0.5%)
Diagnosis of SARS-CoV-2 infection	12 (4.0%)	13 (4.3%)		25 (4.2%)
Subjects own decision	3 (1.0%)	6 (2.0%)		9 (1.5%)
Significant protocol deviation	0 (0.0%)	1 (0.3%)		1 (0.2%)
Other	6 (2.0%)	4 (1.3%)		10 (1.7%)
Diagnosis of SARS-Cov-2 infection; Severe or serious AE	0 (0.0%)	1 (0.3%)		1 (0.2%)
Period 2				
	DMB-3115 (N=268)	**EU-Stelara-EU-Stelara (N=132)**	**EU-Stelara-DMB-3115 (N=131)**	**Total (N=531)**
Re-randomized[b]	268 (100.0%)	132 (100.0%)	131 (100.0%)	531 (100.0%)
Treated[b]	267 (99.6%)	132 (100.0%)	131 (100.0%)	530 (100.0%)
Completed the study[b]	258 (96.3%)	130 (98.5%)	124 (94.7%)	512 (96.4%)
Discontinued prematurely during Period 2[b]	8 (3.0%)	1 (0.8%)	6 (4.6%)	15 (2.8%)
Reasons for discontinuation				
Investigator decision	1 (0.4%)	0 (0.0%)	0 (0.0%)	1 (0.2%)
Diagnosis of SARS-CoV-2 infection	0 (0.0%)	0 (0.0%)	3 (2.3%)	3 (0.6%)
Subjects own decision	1 (0.4%)	0 (0.0%)	2 (1.5%)	3 (0.6%)
Other	5 (1.9%)	1 (0.8%)	1 (0.8%)	7 (1.3%)
Not achieving PASI75 response by Week 28	1 (0.4%)	0 (0.0%)	0 (0.0%)	1 (0.2%)

[a] Percentages are based on the number of randomized subjects at Week 0.
[b] Percentages are based on the number of randomized subjects at Week 28.
Source: Table 6 of Clinical Study Report DMB-3115-2 and reviewer's analysis

A total of 831 subjects were screened. Of the 831 screened subjects, 598 subjects were randomized and included in the ITT set and 514 subjects were included in the PPS. See Table 17.

Table 17 Summary of Analysis Sets

	DMB-3115	EU-Stelara	Total
Screened Set			831
Intent-to-Treat (ITT) set	299 (100.0%)	299 (100.0%)	598 (100.0%)
Per-Protocol Set (PPS)	250 (83.6%)	264 (88.3%)	514 (86.0%)

Source: Table 8 of Clinical Study Report DMB-3115-2

Demographics and Baseline Characteristics

Most subjects in the study were white (99%) and from EU region (91%). More subjects in the study were males (69%) compared to females (31%). The average age of the subjects in the study was about 46 years (range from 18 to 75 years). The mean duration of plaque type psoriasis was about 18 years (range from 1 to 59 years). The mean PASI score at baseline was 21.4 (range from 6.6 to 65.4). See Table 18 and Table 19.

Table 18 Demographics by Treatment Group (ITT)

	DMB-3115 (N=299)	EU-Stelara (N=299)	Total (N=598)
Age (years)			
Mean (SD)	45.4 (13.03)	45.7 (13.46)	45.6 (13.23)
Median	45.0	46.0	45.0
Min, Max	19.0, 73.0	18.0, 75.0	18.0, 75.0
Age Group, n (%)			
< 65	270 (90.3%)	269 (90.0%)	539 (90.1%)
≥ 65	29 (9.7%)	30 (10.0%)	59 (9.9%)
[redacted], n (%)			
Male	202 (67.6%)	212 (70.9%)	414 (69.2%)
Female	97 (32.4%)	87 (29.1%)	184 (30.8%)
Race, n (%)			
White	295 (98.7%)	298 (99.7%)	593 (99.2%)
Asian	3 (1.0%)	0 (0.0%)	3 (0.5%)
Black or African American	1 (0.3%)	0 (0.0%)	1 (0.2%)
Not Reported	0 (0.0%)	1 (0.3%)	1 (0.2%)
Ethnicity, n (%)			
Hispanic or Latino	1 (0.3%)	5 (1.7%)	6 (1.0%)
Not Hispanic or Latino	297 (99.3%)	294 (98.3%)	591 (98.8%)
Unknown	1 (0.3%)	0 (0.0%)	1 (0.2%)
Country, n (%)			
Poland	138 (46.2%)	116 (38.8%)	254 (42.5%)
Bulgaria	62 (20.7%)	63 (21.1%)	125 (20.9%)
Czech Republic	32 (10.7%)	53 (17.7%)	85 (14.2%)
Hungary	20 (6.7%)	17 (5.7%)	37 (6.2%)
Ukraine	13 (4.3%)	16 (5.4%)	29 (4.8%)
Estonia	13 (4.3%)	12 (4.0%)	25 (4.2%)

United States	10 (3.3%)	11 (3.7%)	21 (3.5%)
Latvia	8 (2.7%)	9 (3.0%)	17 (2.8%)
Georgia	3 (1.0%)	2 (0.7%)	5 (0.8%)
Geographic region, n (%)			
EU	273 (91.3%)	270 (90.3%)	543 (90.8%)
US	10 (3.3%)	11 (3.7%)	21 (3.5%)
ROW	16 (5.4%)	18 (6.0%)	34 (5.7%)
Baseline bodyweight, n (%)			
≤ 100 kg	217 (72.6%)	216 (72.2%)	433 (72.4%)
> 100 kg	82 (27.4%)	83 (27.8%)	165 (27.6%)

Source: Table 9 of Clinical Study Report DMB-3115-2 (pg. 67-69 of 3399) and reviewer's analysis

Table 19 Baseline Disease Characteristics by Treatment Group (ITT)

	DMB-3115 (N=299)	EU-Stelara (N=299)	Total (N=598)
Duration of plaque type psoriasis (years)			
Mean (SD)	18.3 (12.71)	17.4 (11.84)	17.9 (12.28)
Median	16.0	15.0	15.5
Min, Max	1.0, 59.0	1.0, 57.0	1.0, 59.0
Number of previous systemic therapies for psoriasis, n (%)			
< 3	276 (92.3%)	277 (92.6%)	553 (92.5%)
≥ 3	23 (7.7%)	22 (7.4%)	45 (7.5%)
PASI score			
Mean (SD)	21.16 (7.576)	21.58 (8.631)	21.37 (8.117)
Median	19.00	18.90	18.90
Min, Max	12.0, 49.5	6.6, 65.4	6.6, 65.4
PGA score, n (%)			
2	1 (0.3%)	1 (0.3%)	2 (0.3%)
3	239 (79.9%)	236 (78.9%)	475 (79.4%)
4	59 (19.7%)	62 (20.7%)	121 (20.2%)

Source: Table 9 of Clinical Study Report DMB-3115-2 (pg. 67-69 of 3399) and reviewer's analysis

Analysis of Primary Clinical Endpoint(s)

The analysis results of the primary efficacy endpoint, percent change in PASI from baseline to Week 12, are summarized in .

DMB-3115 demonstrated no clinically meaningful differences from Stelara with respect to the primary efficacy endpoint. The adjusted mean percent changes in PASI from baseline to Week 12 were comparable for the two treatment groups with 87.6% for DMB-3115 and 87.8% for Stelara. The mean difference (DMB-3115 minus Stelara) was -0.2% with 90% confidence interval of (-2.1%, 1.7%), which was contained within the similarity margin of ± 10%.

Figure 6 shows that the distribution of percent change in PASI from baseline to Week 12 is comparable in the two treatment groups, which supports the conclusion of similarity of DMB-3115 and EU-Stelara regarding the primary efficacy endpoint.

Table 20 Percent Change in PASI from Baseline to Week 12

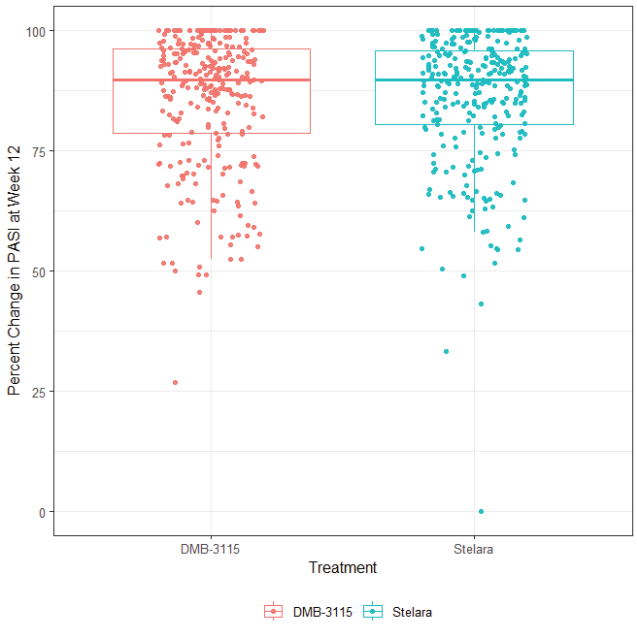
		DMB-3115	EU-Stelara
Primary Analysis[1]			
	LS Mean (SE)	87.62 (1.759)	87.79 (1.758)
	Difference (SE)	-0.17 (1.141)	
	90% CI	**(-2.05, 1.70)**	
Sensitivity/Supplementary Analyses			
(i) Mixed model in ITT	LS Mean (SE)	85.45 (1.375)	85.56 (1.369)
	Difference (SE)	-0.12 (1.128)	
	90% CI	(-1.98, 1.74)	
(ii) Available Data in ITT	LS Mean (SE)	87.76 (1.742)	87.97 (1.742)
	Difference (SE)	-0.21 (1.130)	
	90% CI	(-2.07, 1.65)	
(iii) FDA's conservative approach in ITT[2]	LS Mean (SE)	86.66 (2.157)	89.78 (2.146)
	Difference (SE)	-3.12 (1.394)	
	90% CI	(-5.42, -0.82)	
(iv) PPS	LS Mean (SE)	87.10 (1.946)	87.20 (1.946)
	Difference (SE)	-0.10 (1.231)	
	90% CI	(-2.13, 1.93)	
(v) Including Site 1616 with GCP issues	LS Mean (SE)	87.73 (1.762)	87.65 (1.762)
	Difference (SE)	0.08 (1.133)	
	90% CI	(-1.78, 1.95)	

[1] The primary analysis was based on an ANCOVA model with baseline PASI as a covariate and treatment and the three stratification factors (body weight, geographic region, and number of previous systemic therapies for psoriasis) as factors was used. Missing values were imputed by the multiple imputation procedure described in Statistical Methodologies section.

[2] The FDA's conservative approach was based on the same ANCOVA model as in the primary analysis using the ITT, imputing the 16 subjects with missing PASI at Week 12, with a conservative approach (0 percent change in PASI for DMB-3115 group and 100 percent change in PASI for Stelara group).

Source: Reviewer's analysis

Figure 6 Distribution of Percent Change in PASI from Baseline to Week 12 by Treatment Group (ITT Using Available Data)



Source: Reviewer's analysis

Potential Effects of Missing Data

The numbers of subjects with missing PASI data at Week 12 for the primary efficacy analysis in ITT are summarized in Table 21 .

There were 16 subjects with missing PASI values at Week 12 (9 for DMB-3115 and 7 for EU-Stelara). To assess the robustness of the primary efficacy analysis results with respect to the handling of missing data, the reviewer conducted a sensitivity analysis imputing the 16 missing PASI values with a conservative approach, 0 percent change in PASI for DMB-3115 group and 100 percent change in PASI for Stelara group. The results are shown in (iii) of Table 21. The confidence interval remained within the similarity margin of ± 10%, confirming the robustness of the primary efficacy analysis results.

Table 21 Subjects with Missing PASI Data at Week 12 for Primary Efficacy Analysis (ITT)

	DMB-3115 (N=299)	EU-Stelara (N=299)	Total (N=598)
Subjects with missing PASI at Week 12	**9 (3.0%)**	**7 (2.3%)**	**16 (2.7%)**
Subjects who discontinued treatment	**5 (1.7%)**	**5 (1.7%)**	**10 (1.7%)**
Reasons for discontinuation			

Subject Is Diagnosed with Sars-Cov-2 Infection	2	1	3
Subjects Own Decision to Discontinue the Treatment	1	1	2
Physician Decision	1	1	2
Other (Death)	1	0	1
Covid-19 Infection Subject Is Diagnosed with Sars-Cov-2 Infection; Severe or Serious AE	0	1	1
Protocol Deviation	0	1	1
Subjects who completed but had missing PASI at Week 12	**4 (1.3%)**	**2 (0.7%)**	**6 (1.0%)**
Had Week 12 visit but had missing PASI assessment	4	1	5
Didn't have Week 12 visit	0	1	1

Source: Reviewer's analysis

Analysis of Secondary Clinical Endpoint(s)

The analysis results of the secondary efficacy endpoints:

- percent change in PASI from baseline,
- percentage of subjects with a PASI 50/75/90/100 response, and
- percentage of subjects with a PGA score of Cleared or Minimal

at Weeks 4, 8, 12, 16, 28, 40, and 52 are summarized in Table 22 through Table 27.

Percent Change in PASI from Baseline at All Timepoints

The adjusted mean percent change in PASI from baseline (mean percent change in PASI from baseline for Period 2) was comparable between the treatment groups at Weeks 4, 8, 12, 16, 28, 40, and 52. See Table 22.

Figure 7 presents a graphical display of the adjusted mean percent change from baseline in PASI over time through Week 28 for the DMB-3115 group and the EU-Stelara group. The two treatment groups show consistently similar trends in percent change in PASI over time.

Table 22 Percent Change in PASI from Baseline at Weeks 4, 8, 12, 16, 28, 40, and 52 (ITT using Available Data)

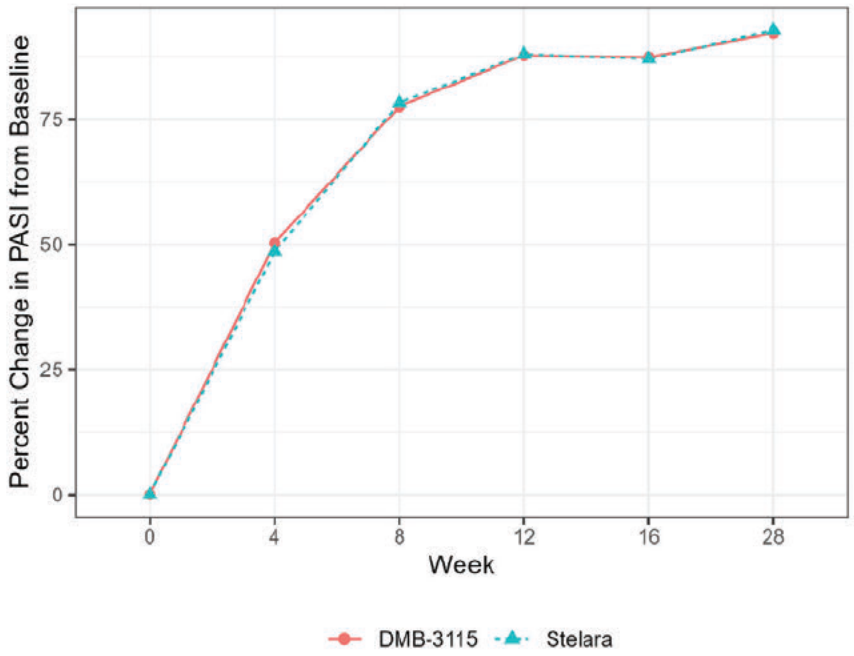
Period 1[a]					
	Treatment	**n**	**LS Mean (SE)**	**Difference (SE)**	**90% CI**
Week 4	DMB-3115 (N=299)	297	50.3 (2.98)	1.73 (1.93)	(-1.45, 4.92)
	EU-Stelara (N=299)	296	48.5 (2.96)		
Week 8	DMB-3115 (N=299)	291	77.5 (2.38)	-0.74 (1.55)	(-3.29, 1.82)
	EU-Stelara	295	78.3 (2.36)		

	(N=299)				
Week 12	DMB-3115 (N=299)	290	87.8 (1.74)	-0.21 (1.13)	(-2.07, 1.65)
	EU-Stelara (N=299)	292	88.0 (1.74)		
Week 16	DMB-3115 (N=299)	283	87.4 (1.55)	0.38 (1.01)	(-1.28, 2.04)
	EU-Stelara (N=299)	285	87.0 (1.54)		
Week 28	DMB-3115 (N=299)	275	92.1 (1.28)	-0.58 (0.829)	(-1.95, 0.79)
	EU-Stelara (N=299)	271	92.7 (1.28)		
Period 2					
	Treatment	**n**	**Mean (SD)**	**Median**	**(Min, Max)**
Week 40	DMB-3115 (N=268)	257	94.1 (8.62)	97.4	(33.8, 100.0)
	EU-Stelara-EU-Stelara (N=132)	131	94.5 (8.27)	97.5	(39.7, 100.0)
	EU-Stelara-DMB3115 (N=131)	125	94.4 (7.92)	98.2	(64.8, 100.0)
Week 52	DMB-3115 (N=268)	256	94.1 (10.14)	98.7	(39.6, 100.0)
	EU-Stelara-EU-Stelara (N=132)	129	94.5 (9.52)	98.9	(48.4, 100.0)
	EU-Stelara-DMB3115 (N=131)	122	94.0 (9.51)	97.9	(32.3, 100.0)

[a] For Period 1, ANCOVA model with baseline PASI as a covariate and treatment and the three stratification factors (body weight, geographic region, and number of previous systemic therapies for psoriasis) as factors was used based on ITT with available data.

Source: Reviewer's analysis

Figure 7 Graphical Display of LS Mean Percent Change from Baseline in PASI Over Time Through Week 28 by Treatment Group (ITT using Available Data)



The LS mean percent changes in PASI from baseline are based on ANCOVA model with baseline PASI as a covariate and treatment and the three stratification factors (body weight, geographic region, and number of previous systemic therapies for psoriasis) as factors in ITT with available data.
Source: Reviewer's analysis

Percentage of Subjects with a PASI 50/75/90/100 Response

The percentage of subjects with a PASI 50/75/90/100 response was comparable between the treatment groups at Weeks 4, 8, 12, 16, 28, 40, and 52. See Table 23, Table 24, Table 25, and Table 26.

Table 23 Percentage of Subjects with a PASI50 Response (ITT Using Available Data)

Period 1[a]					
	DMB-3115 (N=299)		EU-Stelara (N=299)		
	n	Subjects with PASI50, n (%)	n	Subjects with PASI50, n (%)	Odds Ratio (90% CI)
Week 4	297	133 (44.8%)	296	134 (45.3%)	0.99 (0.75, 1.30)
Week 8	291	255 (87.6%)	295	268 (90.8%)	0.73 (0.47, 1.13)
Week 12	290	286 (98.6%)	292	288 (98.6%)	1.02 (0.38,2.74)
Week 16	283	280 (98.9%)	285	282 (98.9%)	1.02 (0.34, 3.07)
Week 28	275	273 (99.3%)	271	268 (98.9%)	1.45 (0.44, 4.78)
Period 2					
	DMB-3115 (N=268)		EU-Stelara-EU-Stelara (N=132)		EU-Stelara-DMB3115 (N=131)

	n	Subjects with PASI50, n (%)	n	Subjects with PASI50, n (%)	n	Subjects with PASI50, n (%)
Week 40	257	256 (99.6%)	131	130 (99.2%)	125	125 (100%)
Week 52	256	254 (99.2%)	129	128 (99.2%)	122	121 (99.2%)

[a] For Period 1, a logistic regression with baseline value, baseline body weight (≤ 100 kg or > 100 kg), geographic region (EU, US, or ROW), and the number of previous systemic therapies for psoriasis (< 3 or ≥ 3) as covariates was used based on ITT with available data. The 90% CI for odds ratio of treatment group comparison was constructed using Wald's test.

Source: Reviewer's analysis

Table 24 Percentage of Subjects with a PASI75 Response (ITT Using Available Data)

Period 1[a]					
	DMB-3115 (N=299)		**EU-Stelara (N=299)**		
	n	**Subjects with PASI75, n (%)**	**n**	**Subjects with PASI75, n (%)**	**Odds Ratio (90% CI)**
Week 4	297	36 (12.1%)	296	32 (10.8%)	1.15 (0.76, 1.75)
Week 8	291	155 (53.3%)	295	170 (57.6%)	0.84 (0.64, 1.11)
Week 12	290	228 (78.6%)	292	239 (81.8%)	0.83 (0.59, 1.17)
Week 16	283	248 (87.6%)	285	247 (86.7%)	1.12 (0.74, 1.69)
Week 28	275	269 (97.8%)	271	266 (98.2%)	0.86 (0.34, 2.15)

Period 2						
	DMB-3115 (N=268)		**EU-Stelara-EU-Stelara (N=132)**		**EU-Stelara-DMB3115 (N=131)**	
	n	**Subjects with PASI75, n (%)**	**n**	**Subjects with PASI75, n (%)**	**n**	**Subjects with PASI75, n (%)**
Week 40	257	250 (97.3%)	131	128 (97.7%)	125	120 (96.0%)
Week 52	256	244 (95.3%)	129	124 (96.1%)	122	117 (95.9%)

[a] For Period 1, a logistic regression with baseline value, baseline body weight (≤ 100 kg or > 100 kg), geographic region (EU, US, or ROW), and the number of previous systemic therapies for psoriasis (< 3 or ≥ 3) as covariates was used based on ITT with available data. The 90% CI for odds ratio of treatment group comparison was constructed using Wald's test.

Source: Reviewer's analysis

Table 25 Percentage of Subjects with a PASI90 Response (ITT Using Available Data)

Period 1[a]					
	DMB-3115 (N=299)		**EU-Stelara (N=299)**		
	n	**Subjects with PASI90, n (%)**	**n**	**Subjects with PASI90, n (%)**	**Odds Ratio (90% CI)**
Week 4	297	6 (2.0%)	296	4 (1.4%)	1.44 (0.57, 3.67)
Week 8	291	69 (23.7%)	295	62 (21.0%)	1.18 (0.85, 1.64)
Week 12	290	144 (49.7%)	292	144 (49.3%)	1.02 (0.78, 1.35)
Week 16	283	178 (62.9%)	285	178 (62.5%)	1.05 (0.78, 1.40)
Week 28	275	205 (74.5%)	271	212 (78.2%)	0.83 (0.60, 1.16)

Period 2						
	DMB-3115 (N=268)		**EU-Stelara-EU-Stelara (N=132)**		**EU-Stelara-DMB3115 (N=131)**	
	n	**Subjects with PASI90, n (%)**	**n**	**Subjects with PASI90, n (%)**	**n**	**Subjects with PASI90, n (%)**
Week 40	257	199 (77.4%)	131	107 (81.7%)	125	103 (82.4%)
Week 52	256	204 (79.7%)	129	103 (79.8%)	122	97 (79.5%)

[a] For Period 1, a logistic regression with baseline value, baseline body weight (≤ 100 kg or > 100 kg), geographic region (EU, US, or ROW), and the number of previous systemic therapies for psoriasis (< 3 or ≥ 3) as covariates was used based on ITT with available data. The 90% CI for odds ratio of treatment group comparison was constructed using Wald's test.
Source: Reviewer's analysis

Table 26 Percentage of Subjects with a PASI100 Response (ITT Using Available Data)

Period 1[a]					
	DMB-3115 (N=299)		EU-Stelara (N=299)		
	n	Subjects with PASI100, n (%)	n	Subjects with PASI100, n (%)	Odds Ratio (90% CI)
Week 4	297	2 (0.7%)	296	1 (0.3%)	2.20 (0.48, 10.21)
Week 8	291	20 (6.9%)	295	12 (4.1%)	1.72 (0.95, 3.12)
Week 12	290	41 (14.1%)	292	37 (12.7%)	1.13 (0.76, 1.68)
Week 16	283	59 (20.8%)	285	45 (15.8%)	1.38 (0.97, 1.98)
Week 28	275	85 (30.9%)	271	84 (31.0%)	0.98 (0.72,1.34)

Period 2						
	DMB-3115 (N=268)		EU-Stelara-EU-Stelara (N=132)		EU-Stelara-DMB3115 (N=131)	
	n	Subjects with PASI100, n (%)	n	Subjects with PASI100, n (%)	n	Subjects with PASI100, n (%)
Week 40	257	95 (37.0%)	131	48 (36.6%)	125	52 (41.6%)
Week 52	256	116 (45.3%)	129	55 (42.6%)	122	52 (42.6%)

[a] For Period 1, a logistic regression with baseline value, baseline body weight (≤ 100 kg or > 100 kg), geographic region (EU, US, or ROW), and the number of previous systemic therapies for psoriasis (< 3 or ≥ 3) as covariates was used based on ITT with available data. The 90% CI for odds ratio of treatment group comparison was constructed using Wald's test.
Source: Reviewer's analysis

Percentage of Subjects with a PGA Score of Cleared or Minimal

The percentage of subjects with a PGA score of Cleared or Minimal was comparable between the treatment groups at Weeks 4, 8, 12, 16, 28, 40, and 52. See Table 25.

Table 27 Percentage of Subjects with PGA of Cleared or Minimal (ITT Using Available Data)

Period 1[a]					
	DMB-3115 (N=299)		EU-Stelara (N=299)		
	n	Subjects with PGA of Cleared or Minimal, n (%)	n	Subjects with PGA of Cleared or Minimal, n (%)	Odds Ratio (90% CI)
Week 4	297	48 (16.3)	296	50 (16.9)	0.95 (0.656,1.363)
Week 8	291	180 (61.2)	295	186 (62.8)	0.93 (0.702,1.233)
Week 12	290	245 (84.2)	292	234 (80.1)	1.34 (0.932,1.917)
Week 16	283	251 (88.1)	285	239 (83.3)	1.51 (1.007,2.253)
Week 28	275	259 (93.8)	271	245 (90.4)	1.67 (0.985,2.841)

Period 2						
	DMB-3115 (N=268)		EU-Stelara-EU-Stelara (N=132)		EU-Stelara-DMB3115 (N=131)	
	n	Subjects with PGA of Cleared or Minimal,	n	Subjects with PGA of Cleared or Minimal,	n	Subjects with PGA of Cleared or Minimal,

		n (%)		n (%)		n (%)
Week 40	257	243 (94.2)	131	117 (89.3)	125	109 (87.2)
Week 52	256	228 (88.7)	129	111 (86.0)	122	106 (86.9)

[a] For Period 1, a logistic regression with baseline value, baseline body weight (≤ 100 kg or > 100 kg), geographic region (EU, US, or ROW), and the number of previous systemic therapies for psoriasis (< 3 or ≥ 3) as covariates was used based on ITT with available data. The 90% CI for odds ratio of treatment group comparison was constructed using Wald's test.

Source: Reviewer's analysis

Authors:

Namhee Choi, PhD
Clinical Statistics Primary Reviewer

Elena Rantou, PhD
Clinical Statistics Secondary Reviewer

6.3. Review of Safety Data

6.3.1. Methods

Clinical Studies Used to Evaluate Safety

To evaluate comparative safety, adverse events, laboratory examination, vital signs, hypersensitivity, and immunogenicity were reviewed. The primary safety evaluation is based on a single comparative clinical study, DMB-3115-2, which enrolled and randomized adult subjects with moderate to severe chronic plaque psoriasis. A subset of subjects initially randomized to EU-Stelara were re-randomized to continue EU-Stelara or switch to DMB-3115 in order to assess for potential safety issues from the single transition. In addition, safety data from the PK comparability study (DMB-3115-1) in healthy volunteers were reviewed as supportive of the primary safety assessment.

The Applicant collected safety data from two clinical studies, as listed in Section 2.3 and summarized below. In both studies, subjects received at least one dose of either DMB-3115, US-Stelara or EU-Stelara SC. The primary safety data was derived from the conduct of Study DMB-3115-2.

Study DMB-3115-1 was a multicenter, randomized, double-blind, single-dose, three-arm parallel group trial in healthy subjects designed to compare the PK of DMB-3115, US-Stelara, and EU-Stelara administered as a single-dose 45mg/0.5 mL SC injection. There were 300 subjects (100 subjects/arm) who received the study drug. Randomization was stratified by body weight and ethnicity.

The primary safety database consists of data from the comparative clinical study, DMB-3115-2, which was a randomized, double-blind, parallel group, active-controlled subject in subjects with moderate to severe chronic plaque-type psoriasis. The safety population included 598 subjects, 299 initially randomized to DMB-3115 and 299 initially randomized to EU-Stelara.

Patients received either EU-Stelara® or DMB-3115 based on the patient's body weight at the time of randomization (patients with body weight ≤100 kg received 45

mg doses of ustekinumab and patients with body weight >100 kg received 90 mg doses of ustekinumab). The doses at re-randomization (Week 28) were also assigned based on the body weight at that time. Subjects with body weight ≤100 kg received a 45 mg loading dose SC injection followed by a 45 mg dose 4 weeks later, and then every 12 weeks thereafter. Subjects with body weight >100 kg received a 90 mg loading dose SC injection followed by a 90mg. At Week 12, subjects who were initially randomized to DMB-3115 continued to receive DMB-3115 (DMB-3115/DMB-3115; N = 193) through week 40. Subjects who were initially randomized to EU-Stelara and had >PASI 50response were re-randomized in a 1:1 ratio to receiving DMB-3115 (EU-Stelara/DMB-3115, N = 131) or continue on EU-Stelara (EU-Stelara/EU-Stelara, N = 132) through Week 40. The transition was used to assess potential risks in safety and immunogenicity as a result of transitioning from EU-Stelara to DMB-3115. Additional details of the study design are described in Section 7.2 above.

For Study DMB-3115-2, an audit at site 1616 revealed site non-compliance with Good Clinical Practice principles of source document handling. As a result of this, it was decided to exclude all data from site 1616 from the analyses sets. After this adjustment, the Safety Sets included 598 subjects as described above.

Extent of Exposure:
In Study DMB-3115-1, 645 subjects were screened, of which 300 subjects were randomized and 296 subjects received a single dose of study drug.

In Study DMB-3115-2, a total of 598 subjects were enrolled and randomized. During Period 1 of Study DMB-3115-2, a total of 299 subjects were exposed to at least 1 dose of DMB-3115 and 299 subjects were exposed to at least 1 dose of EU-Stelara. In Period 2, 398 subjects (267 and 131 subjects in the DMB-3115 and EU-Stelara switched to DMB-3115 groups, respectively) received at least 1 dose of DMB-3115 and 132 subjects received at least 1 dose of EU-Stelara. The extent of exposure is shown in the table below.

Table 28: Number of Subjects Who Received at least 1 Dose of Study Drug (Extent of Exposure) in Study DMB-3115-2

	DMB-3115/DMB-3115 N=299	EU-Stelara/DMB-3115 N=149	EU-Stelara/EU-Stelera N=150
Period 1	299	149	150
Period 2	267	131	132

Source: Adapted from Tables 2.7.4.2 and 2.7.4.3 from the Summary of Clinical Safety

Categorization of Adverse Events

An adverse event (AE) is any untoward medical occurrence in a patient or subject, temporally associated with the use of study treatment, whether or not considered related to the study treatment.

A serious adverse event (SAE) is defined as any untoward medical occurrence that, at any dose:
a) Results in death
b) Is life-threatening
c) Requires inpatient hospitalization or prolongation of existing hospitalization
d) Results in persistent disability/incapacity
e) Is a congenital anomaly/birth defect
f) Other situations: Medical or scientific judgment should be exercised in deciding whether SAE reporting is appropriate in other situations such as important medical events that may not be immediately life-threatening or result in death or hospitalization but may jeopardize the patient or may require medical or surgical intervention to prevent one of the other outcomes listed in the above definition. These events should usually be considered serious.

To assess for severity, all AEs and SAEs observed are graded using Common Terminology Criteria for Adverse Events (CTCAE) v 5.0:

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

To assess the relationship between study treatment and each occurrence of each AE/SAE, the AE is characterized as unrelated, unlikely to be related, possibly related, probably related, or not applicable as defined below:

- “Unrelated” is used if there is not a reasonable possibility that the study treatment caused the AE.
- “Unlikely to be related” suggests that only a remote connection exists between the study treatment and the AE. Other conditions, including chronic illness, progression or expression of the disease state or reaction to concomitant therapy, appear to explain the reported AE.
- “Possibly related” suggests that the association of the AE with the study treatment is unknown; however, the AE is not reasonably supported by other conditions.
- “Probably related” conveys that there are facts, evidence, and/or arguments to suggest a causal relationship, rather than a relationship cannot be ruled out.

- All efforts should be made to classify the AE according to the above categories. The category “not applicable” may be used for SAEs which happen prior to any procedures/dosing.

Adverse events of special interest related to any specific AE that has been identified at the project/compound level as being of particular concern for prospective safety monitoring and safety assessment within this study, e.g., the potential for AEs based on knowledge from other compounds in the same class. The following are considered as AESIs:

- Acquired immunodeficiency syndrome
- Autoimmune disease
- Cerebrovascular accident
- Confirmed myocardial infarction
- Congestive heart failure
- Depression
- Erythrodermic psoriasis
- Facial palsy
- Hematologic events (e.g., pancytopenia, aplastic anemia, or agranulocytosis)
- Hepatic injury
- Hypersensitivity reactions
- Injection Site Reactions
- Malignancies
- Neurologic or demyelinating events
- Opportunistic infections
- Pustular psoriasis
- Transient ischemic attack
- Tuberculosis
- Unexpected reaction to a vaccine (e.g., active infection by live-attenuated vaccine).

Safety Analyses

The safety population includes all subjects randomized and treated with at least 1 dose of study drug except for those from Site 1616 due to non-compliance with Good Clinical Practice principles of source document handling. All remaining subjects were included in the safety analysis set for a total of 568 subjects. The Applicant did not plan and perform any integrated (pooling) analysis of the AE data across the two clinical studies due to inherent differences in the study design.

AEs, treatment-emergent adverse events (TEAE)s, and SAEs were summarized by system organ class (SOC) and preferred term (PT) according to MedDRA terminology with descriptive comparisons between DMB-3115 and EU-Stelara and, where applicable, US-Stelara.

For the comparative clinical study DMB-3115-2, the Applicant pre-specified the following safety endpoints and analyses: incidence of AEs, SAEs, including incidence of injection site reactions, changes in vital signs, and laboratory abnormalities.

6.3.2. Major Safety Results

Relevant Characteristics of the Population Evaluated for Safety

The population demographics of subjects in Study DMB-3115-2 are summarized in the table below. In general, the baseline characteristics of the patients in Study DMB-3115-2 are representative of the chronic plaque psoriasis population with moderate to severely active disease. The baseline characteristics were similar between the DMB-3115-2 and EU-Stelara treatment arms.

Table 29: Summary of Demographics for Study DMB-3115-2

	DMB-3115 (N=299) n%	EU-Stelara (N=299) n%
[redacted]		
F	97 (32.4)	87 (29.1)
M	202 (67.6)	212 (70.9)
Age		
Mean (SD)	45.4 (13.03)	45.7 (13.46)
Median (Min, Max)	45.0 (19, 73)	46.0 (18, 75)
Race		
ASIAN	3 (1.0)	0
BLACK OR AFRICAN AMERICAN	1 (0.3)	0
NOT REPORTED	0	1 (0.3)
WHITE	295 (98.7)	298 (99.7)
BMI		
Mean (SD)	29.3 (6.02)	29.3 (5.79)
Median (Min, Max)	28.7 (18.4, 52.5)	28.7 (16.7, 47.5)
Weight		
<=100 KG	217 (72.6)	216 (72.2)
>100 KG	82 (27.4)	83 (27.8)

Source: Reviewer's analysis

Deaths

There were 3 deaths reported in Trial DMB-3115-2. All deaths occurred in Part 1 of the trial and are summarized below. None were deemed related to study drug by the Investigator.

Table 30: Summary of Deaths in Study DMB 3115-2

Preferred Term	DMB-3115 N = 299 n (%)	EU-Stelara N = 299 n (%)
Any Death	2 (0.6)	1 (0.3)
Covid-19	1 (0.3)	1 (0.3)
Sudden cardiac death	1 (0.3)	0 (0.0)

Source: Reviewer's analysis

The narratives are presented below:

- **Subject** (b) (6) was a 57-year-old white male with past history of right bundle branch block, developed a non-serious adverse event of hypertension (blood pressure: 167/105 mmHg) of CTCAE Grade 2 intensity. The subject received treatment with telmisartan 40 mg which was continued through the trial. On (b) (6) (b) (6), 30 days after the most recent administration of DMB-3115, the subject had sudden cardiac death. The subject did not receive any treatment for the event. An autopsy was performed. The autopsy report includes the following diagnoses: sudden cardiac death, drowning, acute pancreatitis, and influence of the organism by alcohol. The death was deemed not-related to study drug by the Investigator.
- **Subject** (b) (6) was a 68-year-old White male was diagnosed with moderate to severe chronic plaque psoriasis was randomized to receive Stelara (90 mg/1 mL) subcutaneously on (b) (6). On (b) (6), 3 days after the most recent administration of Stelara, the subject was hospitalized due to a serious adverse event of COVID-19. On (b) (6), the subject died due to the event of COVID-19. It was unknown if autopsy was performed. The Investigator considered the primary cause of death as COVID-19. The Investigator and the Sponsor assessed the event of COVID-19 as not related to the Stelara.
- **Subject** (b) (6), a 65-year-old white male was diagnosed with moderate to severe chronic plaque psoriasis and was randomized to receive DMB-3115 (90 mg/1 mL) subcutaneously on (b) (6). On (b) (6), 33 days after the most recent administration of the DMB-3115, the participant was hospitalized and diagnosed with gastric cancer. On (b) (6), 8 days after the most recent administration of the DMB-3115, the subject developed a serious adverse event of COVID-19. On (b) (6), the subject died due to the events of gastric cancer and COVID-19. It was unknown if autopsy was performed. The Investigator considered the primary cause of death as gastric cancer associated with COVID-19 and concluded neither event was associated with DMB-3115. Of note the investigator deemed the event of gastric cancer was not resolved at the time of death.

Reviewer's Comment: This reviewer agrees that the two events of COVID-19 and sudden cardiac death were not related to study drug.

Serious adverse events (SAE)s:

In Part 1 of the study, treatment-emergent serious adverse events (SAEs) were comparable between the treatment groups. All treatment-emergent SAEs were reported by single subject each, with the exception of COVID-19, which was reported by 2 subjects (0.6%) in the EU-Stelara treatment group (versus 1 subject (0.3%) in the DMB-3115 treatment group) . None of the SAEs in the DMB-3115 group were considered by the investigator to be treatment-related.

Table 31: Summary of Serious Adverse Events in Study DMB-3115-2 Period 1 (Up to Week 28)

Preferred Term	DMB-3115 N = 299 n (%)	EU-Stelara N = 299 n (%)
Any SAE	5 (1.7)	3 (1.0)
Acute myocardial infarction	1 (0.3)	0 (0.0)
Atrial fibrillation	1 (0.3)	0 (0.0)
Covid-19[a]	1 (0.3)	2 (0.6)
Gastric cancer	1 (0.3)	0 (0.0)
Humerus fracture	1 (0.3)	0 (0.0)
Vith nerve paralysis	0 (0.0)	1 (0.3)

Source: Reviewer's analysis
a: Covid 19 includes Covid-19 pneumonia

In Part 2 of the study, three SAEs were reported in EU-Stelara/EU-Stelara group. None of the SAEs were considered by the investigator to be treatment-related.

Table 32: Summary of Serious Adverse Events in Study DMB-3115-2 Period 2

Preferred Term	DMB-3115 N = 267 n (%)	EU-Stelara-DMB 3115 N = 131 n (%)	EU-Stelara/EU Stelara N = 132 n (%)
Any SAE	0 (0.0)	0 (0.0)	2 (1.5)
Back pain	0 (0.0)	0 (0.0)	1 (0.8)
Hypertension	0 (0.0)	0 (0.0)	1 (0.8)
Intervertebral disc disorder	0 (0.0)	0 (0.0)	1 (0.8)

Preferred Term	DMB-3115 N = 267 n (%)	EU-Stelara-DMB 3115 N = 131 n (%)	EU-Stelara/ EU Stelara N = 132 n (%)
Any SAE	0 (0.0)	0 (0.0)	2 (1.5)

Source: Reviewer's analysis

Dropouts and/or Discontinuations

Approximately 14% of subjects (86/598; 14.4%) withdrew and 86% of subjects (512/598; 85.6%) completed Study DMB-3115-2. A summary of causes of withdrawal are presented in the table below.

Table 33 Summary of Discontinuations from Study DMB-3115-2

	DMB-3115 (N=299) n(%)	EU-Stelara (N=299) N(%)
Discontinuation due to:		
Adverse Event	13 (4.3)	19 (6.4)
Withdrawal By Subject	14 (4.7)	12 (4.0)
Other	11 (3.7)	12 (4.0)
Physician Decision	1 (0.3)	3 (1.0)
Study Terminated by Sponsor	1 (0.3)	1 (0.3)

Source: Reviewer's analysis

During Study DMB-3115-2, a total of 32 subjects (32/598; 5.4%) discontinued the study due to TEAEs during Period 1 as shown in the table below. There were no dropouts or discontinuations due to TEAEs in Period 2. In Period 1, a higher proportion of subjects experienced TEAEs that led to study discontinuation in the EU-Stelara arm (19/299 subjects; 6.4%) compared with DMB-3115 arm (13/299 subjects; 4.3%). The most common TEAE that resulted in discontinuation of study intervention in Period 1 was COVID-19. None of the TEAEs leading to discontinuation were deemed related to study drug by the Investigator.

Table 34: Summary of Treatment Emergent Adverse Events Leading to Discontinuation in Study DMB-3115-2

Preferred Term	DMB-3115 N = 299 n (%)	EU-Stelara N = 299 n (%)
Any adverse event	13 (4.3)	19 (6.4)
Covid-19	12 (4.0)	16 (5.4)
Psoriasis	1 (0.3)	0 (0.0)
Asymptomatic covid-19	0 (0.0)	1 (0.3)
Covid-19 pneumonia	0 (0.0)	1 (0.3)
Dermatitis exfoliative generalised	0 (0.0)	1 (0.3)
Guttate psoriasis	0 (0.0)	1 (0.3)

Source: Reviewer's analysis

Treatment Emergent Adverse Events

In Period1 of the study, the DMB-3115 treatment group, there was a higher incidence in TEAEs of hypertension, arthralgia, folliculitis, tonsilitis, and hand fracture as shown in the table below.

In Period 2 of the study, the subjects that switched to DMB-3115 from EU-Stelara there was a higher incidence of oropharyngeal pain. The investigator concluded, 2 events of hypertension (blood pressure increased) and 1 event of nasopharyngitis in the DMB-3115 treatment group were possibly or probably treatment-related. However, with the limitations of, a single study with a relatively small number of subjects and with a switch in treatment, it is difficult to make a definitive conclusion whether meaningful differences between DMB-3115 and EU-Stelara exist.

Table 35: Summary of Treatment Emergent Adverse Events in ≥2 Subjects In Study DMB-3115-2 Period 1

Preferred Term	DMB-3115 N = 299 n (%)	EU-Stelara N = 299 n (%)
Any Adverse Event	41 (13.7)	17 (5.7)
Hypertension[a]	18 (6.0)	14 (4.7)
Arthralgia	5 (1.7)	2 (0.7)
Folliculitis	5 (1.7)	0 (0.0)
Tonsillitis	4 (1.3)	1 (0.3)
Hand fracture	3 (1.0)	0 (0.0)
Haematuria	2 (0.7)	0 (0.0)
Syncope	2 (0.7)	0 (0.0)
Urethritis	2 (0.7)	0 (0.0)

Source: Reviewer's analysis

Preferred Term	DMB-3115 N = 299 n (%)	EU-Stelara N = 299 n (%)
Any Adverse Event	41 (13.7)	17 (5.7)

a: hypertension includes blood pressure increased and white coat hypertension

Table 36: Summary of Treatment Emergent Adverse Events in ≥ 2 Subjects In Study DMB-3115-2 Period 2

Preferred Term	DMB-3115 N = 267 n (%)	EU-Stelara-DMB 3115 N = 131 n (%)	EU-Stelara N = 132 n (%)
Any AE	50 (18.7)	24 (18.3)	28 (21.2)
Nasopharyngitis[a]	12 (4.5)	4 (3.1)	8 (6.1)
Covid-19	4 (1.5)	3 (2.3)	2 (1.5)
Headache	4 (1.5)	2 (1.5)	4 (3.0)
Alanine aminotransferase increased	2 (0.7)	1 (0.8)	2 (1.5)
Rhinitis[b]	2 (0.7)	0 (0.0)	2 (1.5)
Back pain	2 (0.7)	1 (0.8)	1 (0.8)
Oral herpes	2 (0.7)	0 (0.0)	0 (0.0)
Toothache	2 (0.7)	0 (0.0)	0 (0.0)
Abdominal pain[c]	2 (0.7)	0 (0.0)	0 (0.0)
Hypertension	1 (0.4)	3 (2.3)	3 (2.3)
Oropharyngeal pain	1 (0.4)	3 (2.3)	0 (0.0)
Tonsillitis	0 (0.0)	1 (0.8)	2 (1.5)

Source: Reviewer's analysis
a: nasopharyngitis includes pharyngitis, respiratory tract infection, upper respiratory tract infection, and viral upper respiratory tract infection
b: rhinitis includes rhinorrhea
c: abdominal pain includes abdominal pain upper

Adverse Events of Special Interest (AESI):

Overall, there were a small number of AESIs in the study and all occurred during Period 1. The AESIs are presented in the tables below. There was a higher incidence of tuberculosis in the Stelara treatment group than in the DMB-3115 treatment group. Otherwise, there were no clinically meaningful differences between the treatment groups. Of note, of these AESIs, the Applicant considers only the AESIs of injection site reaction to be possibly or probably treatment related.

Table 37: Summary of Adverse Events of Special Interest In Study DMB-3115-2

	DMB-3115 (N=299) n(%)	EU-Stelara (N=299) n(%)
Total AESIs	12 (4.0)	20 (6.7)

Table 37: Summary of Adverse Events of Special Interest In Study DMB-3115-2

	DMB-3115 (N=299) n(%)	EU-Stelara (N=299) n(%)
Tuberculosis	4 (1.3)	14 (4.7)
Injection site reactions	3 (1.0)	4 (1.3)
Confirmed myocardial infarction	1 (0.3)	0
Congestive heart failure	1 (0.3)	0
Hypersensitivity reactions	1 (0.3)	0
Injection site reactions	0	1 (0.3)
Malignancies	1 (0.3)	0
Neurologic or demyelinating events	0	1 (0.3)
Opportunistic infections	1 (0.3)	0

Source: Reviewer's analysis

Adverse Reactions

Overall, there were a small number of adverse reactions in the study (presented in the tables below). There was a higher incidence of hypertension, arthralgia and nasopharyngitis in the DMB-3115 treatment group. Nasopharngitis, including upper respiratory tract infection, and myalgia are included in Section 6 Clinical Trial Experience of labeling for US-Stelara. The investigator concluded that two events of hypertension (blood pressure increased) and one event of nasopharyngitis in the DMB-3115 treatment group were possibly or probably treatment-related. Otherwise, there were no clinically meaningful differences between the treatment groups.

Table 38: Summary of Adverse Reactions in Study DMB-3115-2 Period 1

Preferred Term	DMB-3115 N = 299 n (%)	EU-Stelara N = 299 n (%)
Hypertension[a]	18 (6.0)	14 (4.7)
Arthralgia	5 (1.7)	2 (0.7)

Reviewer's analysis
a: Hypertension includes blood pressure increased and white coat hypertension

Table 39: Summary of Adverse Reactions In Study DMB-3115-2 Period 2

Preferred Term	DMB-3115 N = 267 n (%)	EU-Stelara-DMB 3115 N = 131 n (%)	EU-Stelara N = 132 n (%)
Nasopharyngitis[a]	12 (4.5)	4 (3.1)	8 (6.1)

Reviewer's analysis
a: Nasopharyngitis includes pharyngitis, respiratory tract infection, upper respiratory tract infection, and viral upper respiratory tract infection

6.3.3. Additional Safety Evaluations

- ***Laboratory Findings:*** No clinically meaningful changes or trends in laboratory parameters were noted between treatment groups, from baseline throughout the studies.

- ***Vital Signs:*** No clinically meaningful changes or trends were noted in heart rate between treatment groups, from baseline throughout the studies. Hypertension was noted to be a TEAE and an an adverse reaction as described above.

- ***ECG:*** No clinically meaningful differences were noted in ECG parameters between treatment groups throughout the studies.

- ***QT:*** No significant QT prolongation was detected in the comparative clinical study.

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 40 weeks), and an assessment of the impact of ADA on PK, efficacy and safety. In particular, there were no clinically meaningful differences between the frequency of treatment-emergent AEs in the DMB-3115 group versus the other treatment groups (EU-Stelara/DMB-3115 and EU-Stelara respectively), regardless of nAb status. Therefore, we conclude that DMB-3115 was similar to EU-Stelara in the production of ADA/NAb and their impact on PK, efficacy and safety. Refer to Section 5.4 *Clinical Immunogenicity Studies* for results of the immunogenicity assessments.

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6.5. Extrapolation

The Applicant submitted data and information in support of a demonstration that DMB-3115 is highly similar to U.S.-Stelara notwithstanding minor differences in clinically inactive components and that there are no clinically meaningful differences between DMB-3115 and U.S.-Stelara in terms of safety, purity and potency.

The Applicant is seeking licensure of DMB-3115 for the following indication(s) for which U.S.- Stelara has been previously licensed and for which DMB-3115 has not been directly studied:

- Adult patients with moderately to severely active Crohn's disease.
- Adult patients with moderately to severely active ulcerative colitis.
- Pediatric patients 6-17years with plaque psoriasis
- Active psoriatic arthritis (PsA) in adults and pediatric patients (6 years or older)

The Applicant provided a justification for extrapolating data and information submitted in the application to support licensure of DMB-3115 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 DMB-3115 for each of the following indication(s) for which Accord is seeking licensure of DMB-3115:

- Adult patients with moderately to severely active Crohn's disease.
- Adult patients with moderately to severely active ulcerative colitis.
- Pediatric patients 6-17 years with plaque psoriasis
- Active psoriatic arthritis (PsA) in adults and pediatric patients (6 years or older)

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6.5.1. Division of Gastroenterology (DG)

Executive Summary

Consistent with the principles of the FDA guidance for industry *Scientific Considerations in Demonstrating Biosimilarity to a Reference Product* (April 2015),[3] 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 DMB-3115 as an biosimilar to US licensed Stelara, under section 351(k) of

[3] FDA guidance for industry *Scientific Considerations in Demonstrating Biosimilarity to a Reference Product*.

the PHS Act, for the non-studied indications of moderately to severely active Crohn's disease (CD), and moderately to severely active 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 (Ps; 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 DMB-3115 has the same known and potential mechanisms of action as US-Stelara, which supports extrapolation to indications not directly studied in the DMB-3115 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 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.[4]

The biological activities of DMB-3115 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-23 and IL-12 receptor ligand binding, and inhibition of IL-23 and IL-12 mediated signaling were similar across DMB-3115 vs. US-Stelara. Additionally, similar inhibition of IL-23 and IL-12 induced IFN-γ release, and signal transducer and activator of transcription 3 (STAT3) signaling were demonstrated for DMB-3115 vs. US-Stelara. Overall, these data support the determination that DMB-3115 and US- Stelara are highly similar. Data support the conclusion that DMB-3115 and US- Stelara utilize the same mechanism(s) of action, to the extent such mechanism(s) are known.

Pharmacokinetics (PK)

Study DMB-3115-1 was a randomized, double-blind, 3-arm, parallel group, single dose, PK similarity study conducted in healthy adult subjects. The clinical pharmacology reviewers concluded that the data from study DMB-3115-1 support a demonstration of PK similarity of DMB-3115 to EU-Stelara and US-Stelara in healthy subjects. The 95% CI on the geometric least-squares mean ratios for ustekinumab C_{max}, AUC_{last}, and AUC_{inf} were within the 80% to 125% limits for the comparisons of DMB-3115 to both EU-Stelara and US-Stelara (refer to Section 5 Clinical Pharmacology Evaluation and

[4] Stelara USPI approved 03/06/2023, available on Drugs@FDA.

Recommendations). Available data on US-Stelara do not indicate any major differences in PK based on disease state. Therefore, it is reasonable to conclude that PK for DMB-3115 is expected to be similar between patients with Ps (the studied population) and those with IBD.

Immunogenicity

In the DMB-3115 development program, immunogenicity was evaluated in populations that were considered sensitive for detecting meaningful differences (Ps and healthy subjects). No clinically meaningful differences were identified during the review between DMB-3115 and US-Stelara or EU-Stelara in the PK similarity study (DMB-3115-1) and the comparative clinical study (DMB-3115-2). These results support a demonstration of no clinically meaningful differences between DMB-3115 and US-Stelara.

Study DMB-3115-2 was a phase 3, multicenter, randomized, double-blind, parallel-group study to evaluate the PK of DMB-3115 and EU-Stelara in adult subjects with moderate to severe chronic plaque psoriasis (Ps). In the comparative clinical study (DMB-3115-2), the subjects who received EU-Stelara were rerandomized to either continue EU-Stelara or switch to DMB-3115. There were no meaningful differences in the rates of binding and neutralizing antidrug antibodies in those subjects that underwent a single transition from EU-Stelara to DMB-3115, compared to those that remained on their randomized treatment (EU-Stelara or DMB-3115). Therefore, it is reasonable to conclude that immunogenicity in patients with IBD receiving DMB-3115 would be similar to that observed in patients with IBD receiving US-Stelara.

Safety

The safety of DMB-3115 compared to EU-Stelara was assessed in the comparative clinical study (DMB-3115-2) conducted in subjects with Ps, and supported by a single dose, PK similarity study (DMB-3115-1) conducted in healthy subjects. Safety assessments in the two clinical studies included adverse events (AEs), physical examinations, vital signs, clinical laboratory testing, and immunogenicity assessments. As described in Section 6.3. Review of Safety Data, the data overall support a similar safety profile between the DMB-3115 and EU-Stelara, and there were no meaningful differences in the frequency of TEAEs, SAEs, events of interest and events leading to discontinuation of study drug. 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. Since the safety profile of DMB-3115 has been shown to be similar to that of EU-Stelara in patients with Ps, combined with an adequate PK bridging between US-Stelara and EU-Stelara from the healthy subject study (DMB-3115-1) as well as similar product quality attributes, PK, and immunogenicity, the safety profile in the IBD population is unlikely to be different from that observed in patients with Ps.

Regulatory Recommendations

DG concludes that sufficient scientific justification was provided to support licensure of DMB-3115 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:
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Clinical Reviewer

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Clinical Team Leader

Juli Tomaino, MD, MS
Deputy Division Director

6.5.2. Division of Rheumatology and Transplant Medicine (DRTM)

In addition to the plaque psoriasis indication, the Applicant is seeking licensure of DMB-3115 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 DMB-3115 as a biosimilar for the above indication for which licensure is sought and for which US-Stelara has been previously licensed and DMB-3115 has not been directly studied.

First, as summarized above, the Applicant submitted data and information to demonstrate that DMB-3115 is highly similar to US-Stelara and/or EU-Stelara and that there are no clinically meaningful differences in PK between DMB-3115 and US-Stelara, DMB-3115 and EU-Stelara, and between EU-Stelara and US-Stelara in healthy subjects (DMB-3115-1), and that there are no clinically meaningful differences in terms of efficacy, safety, and immunogenicity between DMB-3115 and EU-Stelara in patients with plaque psoriasis (Ps) (DMB-3115-2).

Further, the additional points considered in the scientific justification for extrapolation of data and information to support licensure of DMB-3115 for the treatment of PsA are described below.

Mechanism of Action (MOA)

In comprehensive in vitro comparative testing, DMB-3115 has been shown to be functionally similar to US-Stelara. These data demonstrate that the biologic activity and

potency of DMB-3115 have a high degree of similarity to US-Stelara 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 adequately addressed each of the known and potential mechanisms of action of Stelara and submitted data to support the conclusion that DMB-3115 and US-Stelara have the same mechanisms for the sought indication of PsA to the extent that the mechanisms of action are known or can reasonably be determined.

Pharmacokinetics (PK)

Similar PK was demonstrated between DMB-3115 and US-Stelara in Study DMB-3115-1, a randomized, double-blind, single-dose PK similarity study in healthy adult subjects, as reviewed in the Clinical Pharmacology section. Importantly, DMB-3115 was demonstrated to be highly similar to 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 DMB-3115 and US-Stelara in the rheumatology indication for licensure (PsA). Thus, a similar PK profile would be expected between DMB-3115 and US-Stelara in patients with PsA.

The Applicant provided adequate justification that a similar PK profile is expected between DMB-3115 and US-Stelara for PsA.

Immunogenicity

Immunogenicity of DMB-3115 was examined in the PK similarity study in healthy subjects (Study DMB-3115-1) and comparative clinical study in subjects with Ps (Study DMB-3115-2). The impact of immunogenicity on PK, efficacy, and safety between DMB-3115 and US/EU-Stelara was generally comparable and there were no meaningful differences in anti-drug antibodies (ADA) in subjects that underwent a single transition from EU-Stelara to DMB-3115.

The Applicant provided adequate justification that there are no clinically significant differences in immunogenicity is expected between DMB-3115 and US-Stelara for PsA.[5]

Toxicity

The Applicant demonstrated that there are no clinically meaningful differences in safety between DMB-3115 and EU-Stelara in patients with Ps and between DMB-3115, EU-Stelara, and US-Stelara following single doses in healthy subjects. Additionally, in controlled clinical studies of US-Stelara submitted to support its approval, as described in the approved labeling, the types of adverse events and their rates were similar across indications. Coupled with the demonstration of analytical and PK similarity between

[5] Stelara USP approved 3/06/2023, available on Drugs@FDA

DMB-3115, US-Stelara, and EU-Stelara, a similar safety profile would be expected between DMB-3115 and US-Stelara in patients with PsA.

The Applicant provided adequate justification that a similar safety profile would be expected between DMB-3115 and US-Stelara for PsA.

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 safety profile) for extrapolation of the data and information to support licensure of DMB-3115 for the rheumatologic indication of psoriatic arthritis for which US-Stelara has been previously licensed and for which the Applicant is seeking licensure.

Authors:

Austin Anderson, D.O.
Clinical Reviewer

Amit Golding, M.D., PhD
Acting Clinical Team Leader

7. Labeling Recommendations

7.1. Nonproprietary Name

The Applicant's proposed nonproprietary name, ustekinumab-srlf, was found to be conditionally accepted by the Agency.

7.2. Proprietary Name

The proposed proprietary name for DMB-3115 is conditionally approved as Imuldosa. This name has been reviewed by DMEPA, who concluded the name was acceptable.

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.

Authors:

Sangeeta Jain, MD

Snezana Trajkovic, MD

Clinical Reviewer | Clinical Team Leader

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. For Study DMB-3115-2, an audit at site 1616 revealed site non-compliance with Good Clinical Practice principles of source document handling. As a result of this, it was decided to exclude all data from site 1616 from the analyses sets. After this adjustment, the study appeared to be in compliance with GCP.

The Applicant has adequately disclosed financial interests and arrangements with the investigators. Form 3454 is noted in Section 13.2 and verifies that no compensation is linked to study outcome. The Principal Investigators (PIs) did not disclose any proprietary interest to the sponsor.

Authors:
Sangeeta Jain, MD
Clinical Reviewer

Snezana Trajkovic, MD
Clinical Team Leader

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.

Author:
Snezana Trajkovic, MD
Cross-Discipline Team Leader

10. Pediatrics

An initial pediatric study plan (iPSP) for DMB-3115 was submitted on 20 Sept 2021 and an iPSP Agreement letter was sent to the Applicant on 11 April 2022. Post issuance of the iPSP agreement letter, US-licensed Stelara was also approved for the treatment of pediatric patients 6 years and older with active psoriatic arthritis (PsA) on 29 July 2022.

As recommended by the Agency in meeting minutes from a BPD type 4 meeting on 24 May 2023, with the application under review.

Currently, there is no dosage form for DMB-3115 that allows for weight-based dosing for patients weighing less than 60 kg.
This Application was discussed at the Pediatric Review Committee (PeRC) meeting on August 27, 2024. PeRC recommended that a post marketing requirement (PMR) be issued for the development of an age-appropriate presentation for weight-based dosing of the product for patients as young as 6 years of age weighing less than 60 kg.

The following PMR has been issued:

- Develop a presentation that can be used to accurately administer Imuldosa (ustekinumab-srlf) to pediatric patients aged 6 and older who weigh less than 60 kg.
  Final Report Submission: April 2025

Authors:

Sangeeta Jain, MD
Clinical Reviewer

Snezana Trajkovic, MD
Clinical Team Leader

11. REMS and Postmarketing Requirements and Commitments

11.1. Recommendations for Risk Evaluation and Mitigation Strategies

None.

11.2. Recommendations for Postmarket Requirements and Commitments

The current DMB-3115 presentation is not designed to allow for accurate administration of doses less than 45 mg, which impacts children who weigh less than 60 kg. For accurate weight- based dosing, an age-appropriate formulation (presentation) is required by PREA. Therefore, a PREA PMR is necessary for the development of a formulation (presentation) that can be used to administer DMB-3115 in patients who

weigh less than 60 kg.

Authors:

Sangeeta Jain, MD
Clinical Reviewer

Snezana Trajkovic, MD
Clinical Team Leader

The applicant agreed to perform real-time shipping studies to support the commercial shipping conditions of the commercial pre-filled syringe drug product from Accord Biopharma Inc., UK to the distribution center(s) in the US and the commercial shipping conditions of the commercial Vial drug product from the [redacted] (b) (4) to the distribution center(s) in the US as post marketing commitments. These shipping studies will cover worst case shipping conditions (i.e., routes and modes of transportation, distance, duration, temperature, packing configuration, and shipping containers employed) on the final packaged drug product in the proposed container closure system to ensure there is no impact to product quality and sterility of the drug product (i.e., comparison of pre-shipment to post-shipment data, assessed against pre-defined acceptance criteria). It is estimated that these studies will be completed by May 2026.

Authors:

Chringma Sherpa, PhD
Product Quality Reviewer

Anshu Rastogi, PhD
Product Quality Team Leader

12. Comments to Applicant

None

13. Appendices

13.1. Financial Disclosure

Covered Clinical Study: DMB-3115-1

Was a list of clinical investigators provided:	Yes ☒	No ☐ (Request list from Applicant)
Total number of investigators identified: 22		
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: _____ Significant payments of other sorts: _____ Proprietary interest in the product tested held by investigator: _____ Significant equity interest held by investigator in S Sponsor of covered study: _____		
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: DMB-3115-2

Was a list of clinical investigators provided:	Yes ☒	No ☐ (Request list from Applicant)
Total number of investigators identified: 260		
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: _____ Significant payments of other sorts: _____ Proprietary interest in the product tested held by investigator: _____ Significant equity interest held by investigator in S Sponsor of covered study: _____		
Is an attachment provided with	Yes ☐	No ☐ (Request details from

details of the disclosable financial interests/arrangements:		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

In Vivo Pharmacology

There were no animal pharmacology studies submitted by the Applicant.

13.2.2. Nonclinical Pharmacokinetics

The pharmacokinetic (PK) profile of DMB-3115 was evaluated in Cynomolgus monkeys and compared to US-Stelara (Study# 8380413, non-GLP).

Single subcutaneous doses of 9 mg/kg of US-Stelara or two different batches of Imuldosa were administered to Cynomolgus monkeys (6 males/group). The PK parameters and the development of antidrug antibodies (ADAs) were evaluated.

Two animals (one in each group corresponding to each batch of Imuldosa) developed a positive ADA response.

US-Stelara and both batches of DMB-3115 were well tolerated by all animals. Each of the batches of DMB-3115 administered exhibited similar pharmacokinetic properties to US-Stelara. The relative bioavailability of both batches of Imuldosa demonstrated that there was no notable difference in exposure of DMB-3115 when compared to US-Stelara.

Following subcutaneous administration of US-Stelara or DMB-3115 to Cynomolgus monkeys at the dose level of 9 mg/kg, measurable concentrations of each test substance were detected at all timepoints from 0.5 to 1008 hours post-dose for all groups. The mean C_{max} was 80.8 ± 5.11, 80.6 ± 4.23 and 91.9 ± 11.5 µg/mL for US-Stelara group, DMB-3115 Batch 1(B165) group and DMB-3115 Batch 2 (171105) group, respectively. The exposure, measured as $AUC_{(0\text{-}inf)}$ was comparable between US-Stelara and both batches of DMB-3115, where the mean values were 40800 ± 6900 hr*µg/mL, 35100 ± 7420 hr*µg/mL, or 39200 ± 4750 hr*µg/mL, for US-Stelara, DMB-3115 Batch 1(B165) and DMB-3115 Batch 2 (171105) groups, respectively.

PK analysis revealed that both US-Stelara and DMB-3115 had a long half-life ranging from 236 to 281 hours, while clearance was low ranging from 0.22 to 0.27 mL/h/kg, and the volume of distribution was between 76.4 and 90.0 mL/kg across all dosing groups. The PK results suggest that DMB-3115 and US-Stelara mainly remain in the circulatory system with low tissue distribution.

13.2.3. General Toxicology

A 4-week repeat-dose toxicity study was conducted in Cynomolgus monkeys with DMB-3115 and US-Stelara (Study# 8379943, GLP). Subcutaneous doses of 0 (vehicle: high histidine formulation buffer), 0.9 and 45 mg/kg of DMB-3115 or US-Stelara were administered to Cynomolgus monkeys (3/sex/group) twice weekly for 4 weeks (on Days 1, 4, 8, 11, 15, 18, 22, and 25) at a volume of 1 mL/kg. The toxicity, immunogenicity and toxicokinetic profile of the test article were compared with US-Stelara.

Study endpoints included clinical signs, body weights, food consumption, body temperature, electrocardiogram (ECG), respiration rate, ophthalmology, clinical pathology (hematology, coagulation, clinical chemistry, and urinalysis), immunphenotyping of circulating lymphocytes including lymphocyte subsets [T lymphocytes (CD3+, CD3+/CD4+ and CD3+/CD8+), B lymphocytes (CD20+), NK cells (CD3-/CD16+) and monocytes (CD14+)], and pathology examinations (organ weight, gross and histopathological examinations in all animals). Toxicokinetic (TK) parameters and ADAs were also evaluated.

There were no significant treatment-related findings. The toxicity profiles of the two products were similar. Evaluation of circulating lymphocytes did not show any noteworthy differences between animals administered DMB-3115 and those administered US-Stelara.

No confirmed ADA was generated for animals administered DMB-3115 or US-Stelara. The TK profiles of the two products at the 45 mg/kg dose showed similar profile. Exposure to DMB-3115 at this dose corresponded to a C_{max} of 1850000 ng/mL and an $AUC_{(0-72)}$ of 121000000 h*ng/mL which was comparable with a C_{max} of 1770000 ng/mL and an $AUC_{(0-72)}$of 119000000 h*ng/mL for US-Stelara at the same dose level.

TK evaluations on Days 1 and 25 post-dose showed linear dose-related systemic exposure to DMB-3115 and US-Stelara over the dose range of 0.9 to 45 mg/kg with no sex-related differences. The similarity of Imuldosa is further evidenced by the relative bioavailability, which ranged from 0.946 to 1.30 (based on C_{max} and $AUC_{(0-72)}$) compared with US-Stelara. The accumulation ratio on Day 25 (Day 25/Day 1) after repeated doses of DMB-3115 and US-Stelara ranged from 4-6 and 5-7, respectively, based on C_{max} and $AUC_{(0-72)}$.

Table 40. Toxicokinetic parameters of DMB-11335 and US-Stelara **in Cynomolgus monkeys**

Text Table 4.6: Summary of the Mean Ustekinumab Toxicokinetic Parameters in Monkey Serum

Day	Dose Group	Dose Level (mg/kg/dose)	Sex	C_{max} (ng/mL)	T_{max} (h)	AUC_{0-72} (h*ng/mL)	AR C_{max}	AR AUC_{0-72}	$F_{(rel)}$ C_{max}	$F_{(rel)}$ AUC_{0-72}
1	2	0.9 (DMB-3115)	M	9230	72.0	471000	NA	NA	0.997	0.922
			F	10500	72.0	578000	NA	NA	1.27	1.28
			MF	9870	72.0	524000	NA	NA	1.13	1.09
	3	45 (DMB-3115)	M	374000	48.0	21800000	NA	NA	0.878	0.891
			F	428000	72.0	24700000	NA	NA	1.07	0.999
			MF	401000	72.0	23300000	NA	NA	0.973	0.946
	4	0.9 (Stelara®)	M	9250	72.0	511000	NA	NA	NA	NA
			F	8280	72.0	450000	NA	NA	NA	NA
			MF	8770	72.0	481000	NA	NA	NA	NA
	5	45 (Stelara®)	M	425000	72.0	24500000	NA	NA	NA	NA
			F	399000	72.0	24700000	NA	NA	NA	NA
			MF	412000	72.0	24600000	NA	NA	NA	NA
25	2	0.9 (DMB-3115)	M	52100	6.00	3330000	5.73	7.39	1.05	1.09
			F	56300	6.00	3280000	5.40	5.97	1.66	1.53
			MF	54200	6.00	3300000	5.56	6.68	1.30	1.27
	3	45 (DMB-3115)	M	2030000	24.0	132000000	5.42	6.09	1.11	1.06
			F	1670000	24.0	111000000	4.01	4.76	0.964	0.991
			MF	1850000	24.0	121000000	4.71	5.43	1.04	1.03
	4	0.9 (Stelara®)	M	49700	1.00	3040000	5.37	5.99	NA	NA
			F	33900	24.0	2140000	4.04	4.62	NA	NA
			MF	41800	3.50	2590000	4.71	5.31	NA	NA
	5	45 (Stelara®)	M	1820000	48.0	126000000	4.28	5.25	NA	NA
			F	1730000	48.0	112000000	4.48	4.74	NA	NA
			MF	1770000	48.0	119000000	4.38	5.00	NA	NA

Notes: Median values are presented for T_{max}. $F_{(rel)}$ values are not mean values, and were calculated as the ratio of group mean values.
Values represented the mean or median of n=3 (males and females) or n=6 (males and females combined).

13.2.4. Other Toxicology Studies

Extractable and leachable studies were conducted by the applicant for the two container closure systems [vial and Pre-Filled Syringe (PFS)]. The chemistry reviewer confirmed that the applicant did identify extractables and leachables in their studies and also provided safety assessment for those identified. Based on toxicity evaluation of the identified extractables and leachables, there are no significant safety concerns for either vial biologic product or PFS product, from a nonclinical perspective.

13.3. 41424344Clinical Pharmacology Appendices

13.3.1. Summary of Bioanalytical Method Validation and Performance

Pharmacokinetics

For the PK similarity study (Study DMB-3115-1), serum DMB-3115, US-Stelara, and EU-Stelara concentrations measured using a validated ECL-based PK sandwich assay method (ECL-based assay SG029/2018) were suitable for assessment of PK similarity. The same bioanalytical method was used for PK samples obtained from the comparative clinical study (Study DMB-3115-2). Both the method validation entitled "Validation Study for the Quantitative Determination of DMB-3115, Stelara® (EU) and Stelara® (US) in Human Serum" and sample analysis for the study were performed at (b) (4). In this method, biotin conjugated anti-ustekinumab antibody (b) (4) coated in 384-well plate was used to capture serum DMB-3115, US-Stelara, and EU-Stelara and SULFO-tag anti-ustekinumab antibody (b) (4) was used to detect the bound analytes. Table 45 shows the summary of ECL-based assay SG029/2018 method performance in quantification of DMB-3115, US-Stelara, and EU-Stelara during the method validation.

Table 45: Summary of the Bioanalytical Method Validation and In-study Performance for Measurement of DMB-3115, US-Stelara, and EU-Stelara

Bioanalytical method validation report title	Validation Study for the Quantitative Determination of DMB-3115, Stelara (EU) and Stelara (US) in Human Serum (Validation Number: SG029/2018)
Materials used for calibration curve & concentration	DMB-3115 Calibration standard: 1500.000, 750.000, 375.000, 187.500, 93.750, 46.875, 23.438, 11.719, 5.859, 2.930 ng/ml
Validated assay range	2.930 to 1500.000 ng/mL
Material used for QCs & concentration	DMB-3115 1500.000 ng/ml (ULOQ), 1200.000 ng/ml (HQC), 600.000 ng/ml (MQC), 6.000 ng/ml (LQC), and 2.930 ng/ml (LLOQ)
Minimum required dilutions (MRDs)	1:1 (50%) dilution with Assay Matrix Dilution using Assay Buffer did not meet acceptance criteria.
Source & lot of reagents (LBA)	Reagent / Manufacturer / Lot DMB-3115 DS* / (b) (4) / 18040001 DMB-3115 / (b) (4) / DMA90302H Stelara® (EU) / Janssen Biotech / ICS2VME Stelara® (US) / Janssen Biotech / ICS2VMF Hu-Anti-Ustekinumab Mab (AbD17829) / (b) (4) Hu-Anti-Ustekinumab Mab (AbD17827_hIgG1) / (b) (4) *Validation was performed using DMB-3115 (lot no. 18040001) as the reference standard.
Regression model & weighting	4-parameter curve fit with weighting of $1/Y^2$

Validation Parameters	Method Validation Summary		Acceptability
Calibration curve performance during accuracy & precision	No of standard calibrators from lower limit of quantitation (LLOQ) to upper limit of quantitation (ULOQ)	10	Yes
	Cumulative accuracy (%bias) from LLOQ to ULOQ DMB-3115	 -2.1 to 5.4%	Yes
	Cumulative precision (%CV) from LLOQ to ULOQ DMB-3115	 2.1 to 8.7%	Yes
QCs performance during accuracy & precision	Cumulative accuracy (%bias) in 3 QCs US-Stelara EU-Stelara DMB-3115	 -5.5 to 4.5% 4.0 to 18.5% -4.7 to 0.6%	Yes
	Inter-batch %CV US-Stelara EU-Stelara DMB-3115	 0.2 to 5.1% 1.6 to 1.7% 5.5 to 15.8%	Yes
	Percent total error (TE) US-Stelara EU-Stelara DMB-3115	 2.1 to 10.6% 5.7 to 10.1% 6.9 to 7.8%	Yes
Selectivity & matrix effect	No matrix effect was observed HQC (1200 ng/ml): Average recovery of 106.0% LQC (6.0 ng/ml): Average recovery of 88.0%		Yes
Interference & specificity	No interference was observed HQC (1200 ng/mL): up to 117.188 ng/mL of IL-12 and IL-23. LQC (6.0 ng/ml): up to 1.850 ng/ml of IL-12 and IL-23		Yes
Hemolysis effect & Lipemic effect	No matrix effect in hemolysed and lipemic serum HQC (1200 ng/ml): Average recovery of 94.7.0% LQC (6.0 ng/ml): Average recovery of 87.2%		Yes
Dilution linearity & hook effect	Dilution factor up to 1024 using Assay Matrix; No high concentration-induced decrease in the signal response up to 12000 ng/ml DMB-3115.		Yes
Bench-top/process stability	Stable at 2-8°C and RT for 24 hrs		Yes
Freeze-Thaw stability	Stable for up to 3 freeze/thaw cycles when stored at -70°C.		Yes

Long-term storage	Stable up to 1218 days (5/30/2019 - 9/29/2022) storage when stored at -70°C	Yes
Lot-to-lot assessment	The lot-to-lot performance of the DMB-3115 lots 18040001, ACA2001, and ACB2001 is acceptable	Yes
Cross-reactivity assessment	Cross-reactivity assessments between the DMB-3115 (lot. 18040001), and EU-Stelara® (lot. KBS2EMH, LBS0SMA, LJS3MMD, KCS12MH, LBS21MA, and LKS1AMA) are acceptable.	Yes
Parallelism	Not applicable	Yes
Carry over	Not applicable	Yes
Method Performance in Study DMB-3115-1		
Assay passing rate	81% (58/72 runs)	Yes
Standard curve performance	Cumulative bias (%RE) range: -1.9 - 3.3% Cumulative precision (%CV): 2.5 - 6.8 %	Yes
QC performance	Cumulative bias (%RE) range: -5.0 - -3.6% Cumulative precision (%CV): 9.2 - 14.3 %	Yes
Method reproducibility	Incurred sample reanalysis was performed in 458 study samples (5.8% of total sample size, n=7919) and 74.7% of samples met the pre-specified criteria	Yes
Study sample analysis/ stability	Samples were stored for a maximum of 502 days between sample collection and analysis, which is within the established long-term stability window of 1218 days.	
Method Performance in Study DMB-3115-2		
Assay passing rate	83% (48/58 runs)	Yes
Standard curve performance	Cumulative bias (%RE) range: -3.0 - 3.8% Cumulative precision (%CV): 1.5 - 15.7%	Yes
QC performance	Cumulative bias (%RE) range: -1.6 - 2.2% Cumulative precision (%CV): 6.5 - 10.0%	Yes
Method reproducibility	Incurred sample reanalysis was performed in 383 study samples (6.0% of total sample size, n=6402) and 98.1% of samples met the pre-specified criteria	Yes
Study sample analysis/ stability	Samples were stored for a maximum of 593 days between sample collection and analysis, which is within the established long-term stability window of 1218 days.	

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/s/

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10/10/2024 01:54:03 PM

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