CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

761373Orig1s000
761425Orig1s000

MULTI-DISCIPLINE REVIEW

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

Biosimilar Multidisciplinary Evaluation and Review (BMER) 351(k) BLA 761373 and 761425, SB17, a proposed (b) (4) biosimilar to U.S.-Stelara

BIOSIMILAR MULTIDISCIPLINARY EVALUATION AND REVIEW

Application Type	351 (k) BLA
Application Number	BLA 761373 and BLA 761425
Received Date	March 30, 2023
BsUFA Goal Date	June 30, 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	SB17
Proposed Nonproprietary Name[1]	ustekinumab-ttwe

[1]Section 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.

Proposed Proprietary Name[1]	PYZCHIVA
Pharmacologic Class	Human interleukin-12 and -23 antagonist
Applicant	Samsung Bioepis Co., Ltd.
Applicant Proposed Indication(s)	Adult patients with: • moderate to severe plaque psoriasis (Ps) who are candidates for phototherapy or systemic therapy. • active psoriatic arthritis (PsA). • moderately to severely active Crohn's disease (CD). • moderately to severely active ulcerative colitis (UC). Pediatric patients 6 years and older with: • moderate to severe plaque psoriasis, who are candidates for phototherapy or systemic therapy. • active psoriatic arthritis (PsA).
Recommendation on Regulatory Action	Approval of SB17 as biosimilar to U.S.-Stelara. [redacted]

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Reviewers of Biosimilar Multidisciplinary Evaluation and Review

Regulatory Project Manager	Strother D. Dixon
Nonclinical Pharmacology/Toxicology Reviewer(s)	Jianyong Wang
Nonclinical Pharmacology/Toxicology Supervisor	Barbara Hill
Clinical Pharmacology Reviewer(s)	Liping (Cindy) Pan
Clinical Pharmacology Team Leader(s)	Chinmay Shukla
Clinical Reviewer(s)	Shera Schreiber (DDD) Sandhya Apparuju (DG) Susie Anderson (DRTM)
Clinical Team Leader(s)	David Kettl (DDD) Suna Seo (DG) Nadia Habal (DRTM)
Clinical Statistics Reviewer(s)	Junghi Kim
Clinical Statistics Team Leader(s)	Jessica Kim

Cross-Discipline Team Leader(s) (CDTL(s))	David Kettl (DDD)
Designated Signatory Authority	Tatiana Oussova

Additional Reviewers of Application

OPQAIII	Gunther Boekhoudt, CMC Primary assessor Diana Pei, Labeling assessor Samuel Mindaye, Application Technical Lead Jennifer Swisher, Tertiary Assessor Kristine Leahy, Regulatory Business Process Manager (OPRO)
OPMA	Esther C. Broner, Ekaterina Allen, Zhong Li, Maxwell Van Tassell
OPDP	Montherson SaintJuste
PLT	Laurie Buonaccorsi
OSE/DEPI	Joel Weissfeld, and Benjamin Booth
OSE/DMEPA	Madhuri Patel, Florence Mwangi, and Yevgeniya Kogan
OSE/DPV	Zachary Pedretti, Melissa Reyes, Jamie Klucken, and Vicky Chan
DPMH	Mona Khurana

OTBB	Juwaria Waheed, Sarah Schrieber, Ruby Wu, Christine Corser, Wendy Streight

OPQA = Office of Product Quality Assessment

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

DPV = Division of Pharmacovigilance

PLT = Patient Labeling Team

OTBB = Office of Therapeutic Biologics and Biosimilars

Glossary

AC	Advisory Committee
ADA	Anti-drug Antibodies
AE	Adverse Event
BLA	Biologics License Application
BMER	Biosimilar Multidisciplinary Evaluation and Review
BMI	Body Mass Index
BPD	Biosimilar Biological Product Development
BsUFA	Biosimilar User Fee Agreements
CDER	Center for Drug Evaluation and Research
CDRH	Center for Devices and Radiological Health
CDTL	Cross-Discipline Team Leader
CFR	Code of Federal Regulations
CI	Confidence Interval

CMC	Chemistry, Manufacturing, and Controls
CRF	Case Report Form
CRO	Contract Research Organization
CRP	C-reactive Protein
CSC	Computational Science Center
CTD	Common Technical Document
CV	Coefficient of Variation
DEPI	Division of Epidemiology
DIA	Division of Inspectional Assessment
DMC	Data Monitoring Committee
DMA	Division of Microbiology Assessment
DMEPA	Division of Medication Error Prevention and Analysis
DPMH	Division of Pediatric and Maternal Health
DRISK	Division of Risk Management

eCTD	Electronic Common Technical Document
EU-Stelara	EU-approved Stelara
FDA	Food and Drug Administration
FISH	Fluorescence In Situ Hybridization
GCP	Good Clinical Practice
GMR	Geometric Mean Ratio
ICH	International Conference on Harmonization
IND	Investigational New Drug
ITT	Intention to Treat
LLOQ	Lower Limit of Quantitation
MAPP	Manual of Policy and Procedure
mITT	Modified Intention to Treat
MOA	Mechanism of Action
NAb	Neutralizing Antibody

NCI-CTCAE	National Cancer Institute – Common Terminology Criteria for Adverse Events
NCT	National Clinical Trial
OBP	Office of Biotechnology Products
OCP	Office of Clinical Pharmacology
OPDP	Office of Prescription Drug Promotion
OSE	Office of Surveillance and Epidemiology
OSI	Office of Scientific Investigations
OSIS	Office of Study Integrity and Surveillance
PD	Pharmacodynamics
PeRC	Pediatric Review Committee
PK	Pharmacokinetics
PMC	Postmarketing Commitments
PMR	Postmarketing Requirements
PREA	Pediatric Research Equity Act

PHS	Public Health Service
PLR	Physician Labeling Rule
PLLR	Pregnancy and Lactation Labeling Rule
REMS	Risk Evaluation and Mitigation Strategies
ROA	Route of Administration
SAE	Serious Adverse Event
SAP	Statistical Analysis Plan
SOC	System Organ Class
SOP	Standard Operating Procedures
TEAE	Treatment-Emergent Adverse Events
ULOQ	Upper Limit of Quantitation
US-Stelara	U.S.-licensed Stelara

Signatures

Discipline and Title or Role	Reviewer Name	Office/Division	Sections Authored/Approved
Nonclinical Reviewer	Jianyong Wang, PhD	OII/DPT-II	4
	Signature: Jianyong Wang -S Digitally signed by Jianyong Wang -S Date: 2024.06.28 10:32:00 -04'00'		
Nonclinical Supervisor	Barbara Hill, PhD	OII/DPT-II	4
	Signature: Barbara A. Hill -S Digitally signed by Barbara A. Hill -S Date: 2024.06.28 10:38:25 -04'00'		

Clinical Pharmacology Reviewer	Cindy (Liping) Pan, M.D., Ph.D.	OCP/DIIP	6, 14.2
	Signature: Liping Pan -S Digitally signed by Liping Pan -S Date: 2024.06.28 10:52:09 -04'00'		
Clinical Pharmacology Team Leader	Chinmay Shukla, Ph.D.	OCP/DIIP	6, 14.2
	Signature: Chinmay Shukla -S Digitally signed by Chinmay Shukla -S Date: 2024.06.28 11:07:08 -04'00'		
Clinical Reviewer	Shera Schreiber, MD	OII/DDD	1, 2, 3, 6.3, 6.4, 6.5, 6.6, 7, 8, 9, 10, 11, 12, 14.1
	Signature: Shera C. Schreiber -S Digitally signed by Shera C. Schreiber -S Date: 2024.06.28 12:08:13 -04'00'		

Clinical Team Leader	David Kettl, MD	OII/DDD	1, 2, 3, 6, 7, 8, 10, 11
	Signature: David L. Kettl -S Digitally signed by David L. Kettl -S Date: 2024.06.28 12:13:34 -04'00'		
Clinical Reviewer (DG, Collaborative Review Division)	Sandhya Apparaju, PhD	OII/DG	6.6
	Signature: Sandhya K. Apparaju -S Digitally signed by Sandhya K. Apparaju -S Date: 2024.06.28 13:05:11 -04'00'		
Clinical Team Leader (DG, Collaborative Review Division)	Suna Seo, MD, MSc	OII/DG	6.6
	Signature: Suna Seo -S Digitally signed by Suna Seo -S Date: 2024.06.28 16:11:18 -04'00'		

Deputy Division Directory, DG Signatory	Juli Tomaino, MD, MS	OII/DG	6.6
	Signature: Juli A. Tomaino -S Digitally signed by Juli A. Tomaino -S Date: 2024.06.28 16:15:23 -04'00'		
Clinical Reviewer (DRTM, Collaborative Review Division)	Susanne C. Anderson, MD	OII/DRTM	6.6.2
	Signature: Susanne C. Anderson -S Digitally signed by Susanne C. Anderson -S Date: 2024.06.28 14:28:24 -04'00'		
Clinical Team Leader (DRTM, Collaborative Review Division)	Nadia Habal, MD	OII/DRTM	6.6.2
	Signature: Nadia Habal -S Digitally signed by Nadia Habal -S Date: 2024.06.28 14:32:28 -04'00'		

Acting Deputy Director (DRTM, Signatory)	Raj Nair, MD	OII/DRTM	6.6
	Signature: Raj G. Nair -S Digitally signed by Raj G. Nair -S Date: 2024.06.28 15:35:12 -04'00'		
Clinical Statistics Reviewer	Junghi Kim, PhD	OB/DBVIII	6.2
	Signature: Junghi Kim -S Digitally signed by Junghi Kim -S Date: 2024.06.28 15:12:27 -04'00'		
Supervisory Mathematical Statistician	Jessica Kim, PhD	OB/DBVIII	6.2
	Signature: Jeongsook L. Kim -S Digitally signed by Jeongsook L. Kim -S Date: 2024.06.28 15:21:08 -04'00'		

Cross-Discipline Team Leader	David Kettl, MD	OII/DDD	1, 2, 3, 7, 8, 10, 11
	Signature: David L. Kettl -S Digitally signed by David L. Kettl -S Date: 2024.06.28 12:15:55 -04'00'		
Designated Signatory Authority	Tatiana Oussova, MD, MPH	OII/DDD Deputy Director for Safety	All
	Signature: Tatiana Oussova -S Digitally signed by Tatiana Oussova -S Date: 2024.06.28 16:52:32 -04'00'		

1. Executive Summary

1.1. Product Introduction

Samsung Bioepis Co., Ltd. (Samsung; also referred as "the Applicant" in this review) has submitted a biologic license application (BLA) under section 351(k) of the Public Health Service Act (PHS Act) for SB17, a proposed [redacted] (b) (4) biosimilar to US-licensed Stelara.

Samsung is seeking licensure of SB17 for the same indications approved for US-Stelara:

Adult patients with:

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

Pediatric patients 6 years and older with:

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

The applicant is seeking licensure for SB17 injection as follows:

- SB17, 45 mg/0.5 mL prefilled syringe (PFS) for subcutaneous use (b) (4)
- SB17, 90 mg/mL PFS for subcutaneous use (b) (4)
- SB17, 130 mg/26 mL single-dose vial for intravenous (IV) use (b) (4)

The strengths, dosage form and routes of administration of SB17 will be the same as those approved for Stelara.. The Applicant is not seeking licensure of SB17 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 SB17 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 (b) (4)

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

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

Not applicable.

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

SB17 is a recombinant, fully human immunoglobulin G, subclass 1, κ light chain (IgG1κ) monoclonal antibody (mAb) that that belongs to the pharmacologic class of Interleukin -23 (IL-23) and Interleukin-12 (IL-12) antagonists. It binds to the p40 subunit of interleukin IL-12 and IL-23. Binding of the antigen binding fragment (Fab) domain to the p40 protein subunit of both IL-12 and IL-23 inhibits the cytokines from binding to IL-12 and IL-23 receptor complexes on the surface of natural killer (NK) cells or T cells, thereby preventing initiation of downstream immune-response signaling pathways. IL-12 and IL-23 are heterodimeric cytokines secreted by activated antigen presenting cells, such as macrophages and dendritic cells, and both cytokines are involved in inflammatory and immune responses. Among other biological activities, IL-12 activates NK cells to produce and release the interferon gamma (IFN-γ) cytokine and drives CD4+ T cell differentiation toward the T helper 1 (Th1) phenotype; IL-23 induces the T helper 17 (Th17) pathway which are both central to the pathology of certain immune mediated diseases. SB17 has the same mechanism(s) of action as that of US-Stelara.

SB17 product is a sterile liquid solution available in a sterile, single dose, preservative-free solution. SB17 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

SB17, 45 mg/0.5 mL prefilled syringe (PFS) for subcutaneous use has the same strength, dosage form, and route of administration as US-Stelara, 45mg/0.5 mL PFS for subcutaneous use. SB17, 90 mg/mL PFS for subcutaneous use has the same strength, dosage form, and route of administration as US-Stelara 90 mg/mL PFS for subcutaneous use. SB17, 130 mg/26 mL single-dose vial for intravenous (IV) use has the same strength, dosage form, and route of administration as US-Stelara 130 mg/26 mL single-dose vial for IV use.The SB17 45 mg/0.5 mL and 90 mg/mL PFS support the dosing regimens for the proposed indications of adults with PsO and PsA, and the dosing regimens for the pediatric indications of children 6 years and older with PsO and PsA for patients with body weight (BW) ≥60 kg, and the indications of Crohn's disease and ulcerative colitis for maintenance dosing. The single dose vial containing 130 mg/26 mL (5 mg/mL) supports the indications of Crohn's disease and ulcerative colitis for IV induction.

With respect to SB17, 45 mg/0.5 mL PFS for subcutaneous use, the applicant is seeking licensure as (b) (4) biosimilar for conditions of use that have been previously approved for US-Stelara, 45 mg/0.5 mL PFS for subcutaneous use. With respect to SB17, 90 mg/mL PFS for subcutaneous use, the applicant is seeking licensure as (b) (4) biosimilar for conditions of use that have been previously approved for US-Stelara 90 mg/mL PFS for subcutaneous use. With respect to SB17, 130 mg/26 mL single-dose vial for IV use, the applicant is seeking licensure as (b) (4) biosimilar for conditions of use that have been previously approved for US-Stelara 130 mg/26 mL single-dose vial for IV use.

1.4. Inspection of Manufacturing Facilities

Adequate descriptions of the facilities, equipment, environmental controls, cleaning, and contamination control strategy were provided for (b) (4) (b) (4) and (b) (4) proposed for drug substance and drug product manufacture, respectively. OPQA and OPMA conducted a review of the drug substance manufacturing site records, in lieu of pre-license inspection (PLI), under section 704(a)(4) of the Federal Food, Drug, and Cosmetic Act and found satisfactory. The drug product manufacturing facility at (b) (4) was waived from the PLI inspection. The facility was determined to have sufficient inspection history. All proposed manufacturing and testing facilities are acceptable based on their current CGMP compliance status and recent relevant inspectional coverage.

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

The Applicant provided adequate data to establish the scientific bridge to justify the relevance of data generated from the comparative clinical study SB17-3001, which used EU-Stelara as the comparator, for the assessment of biosimilarity:

- OPQA has determined, that based on the data provided by the Applicant, the analytical component of the scientific bridge between SB17, US-Stelara, and EU-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 (b) (4) Assessment

Table 1. Summary and Assessment of Biosimilarity (b) (4)

Comparative Analytical Studies[2]

[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	• SB17 is highly similar to US-Stelara notwithstanding minor differences in clinically inactive components. • SB17 prefilled syringe for SC injection and single-dose vial for IV infusion have the same strength as that of US-Stelara. • The strengths, dosage form, and route of administration are the same as those of US-Stelara. • The analytical component of the scientific bridge between SB17, 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	

Summary of Evidence	• PK similarity between SB17, US-Stelara, and EU-Stelara was evaluated in healthy subjects (Study SB17-1001) and supports a demonstration of no clinically meaningful differences in PK between SB17 and US-Stelara. • PK similarity between SB17, EU-Stelara, and US-Stelara provides the PK component of the scientific bridge to support the relevance of the data generated using EU-Stelara in the comparative clinical Study SB17-3001 to the assessment of biosimilarity. • In Study SB17-1001 (healthy subjects), the incidence of post-dose anti-drug antibodies (ADA) formation between the SB17 and US/EU-Stelara treatment groups were comparable. • In Study SB17-3001 (subjects with plaque psoriasis, PsO), the incidence of overall ADA positive results was lower in the SB17 treatment group compared to the EU Stelara treatment group. • In both studies, the incidence of neutralizing antibody (Nab) formation per visit were relatively lower in the SB17 than the Stelara treatment groups. This difference is possibly attributable to the differences in the cell lines between SB17 and Stelara, but the clinical impact of the immunogenicity (i.e., lower ADA formation) of SB17 compared to Stelara is not considered to be clinically significant. • The numerical differences in ADA and NAb incidences do not preclude the conclusion of no clinically meaningful differences between SB17 and US-Stelara.

Assessment of Residual Uncertainties	• There are no residual uncertainties from a clinical pharmacology perspective based on the available clinical PK and immunogenicity data.
Additional Clinical Studies	
Summary of Evidence	• In Study SB17-3001, there were no meaningful differences in terms of efficacy between SB17 and EU-Stelara. The frequency of treatment-emergent adverse events, serious events, and events leading to discontinuation of the study drug had no meaningful differences between the treatment arms. • Given that the scientific bridge was established (based on the analytical and PK comparisons) between SB17, 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 SB17-3001, supports a demonstration of no clinically meaningful differences between SB17 and US-Stelara in the studied indication (plaque psoriasis).
Assessment of Residual Uncertainties	• There are no residual uncertainties from the clinical or statistical perspective.
	(b) (4)

(b) (4)

Any Given Patient Evaluation	
Summary of Evidence	• The analytical data and clinical data support a demonstration that SB17 can be expected to produce the same clinical result as that of US-Stelara in any given patient. The Applicant has provided adequate data and information to support a demonstration that SB17 can be expected to produce the same clinical result as that of US-Stelara in any given patient.
Assessment of Residual Uncertainties	• There are no residual uncertainties from the clinical perspective.
Extrapolation	

Summary of Evidence	• DDD, DG, and DRTM teams have determined that the Applicant has provided adequate scientific justification (based on mechanism of action, PK, immunogenicity, and toxicity) to support extrapolation of data and information, including clinical data from the studied population (PsO), to support licensure of SB17 as (b) (4) biosimilar, under section 351(k) of the PHS Act, for the following indications for which US-licensed Stelara has previously been approved: Adult patients with: • moderate to severe plaque psoriasis (Ps) who are candidates for phototherapy or systemic therapy. • active psoriatic arthritis (PsA). • moderately to severely active Crohn's disease (CD). • moderately to severely active ulcerative colitis. Pediatric patients 6 years and older with: • moderate to severe plaque psoriasis, who are candidates for phototherapy or systemic therapy. • active psoriatic arthritis (PsA).
Assessment of Residual Uncertainties	• There are no residual uncertainties regarding the extrapolation of data and information to support licensure of SB17 as an (b) (4) 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 SB17 is highly similar to US-licensed Stelara, notwithstanding minor differences in clinically inactive components, and that there are no clinically meaningful differences between SB17 and US-licensed Stelara in terms of the safety, purity, and potency of the product. The data and information provided by the Applicant are sufficient to demonstrate that SB17 can be expected to produce the same clinical results as US-licensed Stelara in any given patient (b) (4) The information submitted by the Applicant, including adequate justification for extrapolation of data and information, demonstrates that SB17 is biosimilar to US-Stelara, (b) (4) as follows:

- SB17, 45 mg/0.5 mL PFS for subcutaneous use is (b) (4) biosimilar with US-Stelara 45 mg/0.5 mL PFS for subcutaneous use,
- SB17, 90 mg/mL PFS for subcutaneous use is (b) (4) biosimilar with US-Stelara 90 mg/mL PFS for subcutaneous use, and
- SB17, 130 mg/26 mL single-dose vial for intravenous (IV) use is (b) (4) biosimilar with US-Stelara 130 mg/26 mL single-dose vial for IV use,

for the following indications for which US-Stelara has previously been approved and for which the Applicant is seeking licensure:

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

The Applicant is not seeking licensure of SB17 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 SB17 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 (b) (4)

(b) (4)

(b) (4)

Author:

David Kettl, MD

Clinical 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 SB17. Key discussions are detailed below:

A Biosimilar Biological Product Development (BPD) Type 2 meeting was held on April 3, 2019, to discuss the development program for SB17 as a biosimilar to US-licensed Stelara. During this meeting, the applicant sought the Agency's advice regarding the following:

- The proposed quality assessment and analytical similarity strategies
- The proposed stability studies

- The proposed PK study in healthy subjects to demonstrate silimarity in PK profiles between SB17, US-Stelara and EU-Stelara
- The proposed clinical study to evaluate the efficacy, safety, and immunogenicity between SB17 and EU-Stelara in subjects with moderate to severe plaque psoriasis
- The proposal to use EU-Stelara as a sole comparator in the clinical studies

The Agency issued a general advice letter regarding the Applicant's proposed Human Factors (HF) Use-Related Risk Analysis (URRA) on October 13, 2021. Based on the Agency's review of the Applicant's URRA, comparative analyses, and justification, the Agency determined that the Applicant did not need to submit HF validation study data with the 351(k) BLA for the SB17 45 mg/0.5 mL and 90 mg/mL prefilled syringe as a proposed biosimilar to US-licensed Stelara.

The pre-BLA (BPD Type 4) meeting took place on January 17, 2023. The following issues were addressed during this meeting:

- The structure and content of the BLA submission
- The drug substance manufacturing schedule
- The Applicant stated that they intended to seek only the adult indications for psoriasis and psoriatic arthritis at the time of initial BLA (b) (4) The Agency advised the Applicant that PREA requirements would still need to be addresse (b) (4)

The Agency issued BPD Type 2a written responses on July 28, 2023, which addressed additional Chemistry, Manufacturing and Controls (CMC) information.

On March 30, 2023, the Applicant submitted BLA 761373 seeking licensure of the following products:

- SB17 injection, 45 mg/0.5 mL in a pre-filled syringe (PFS) for subcutaneous use
- SB17 injection, 90 mg/mL in a pre-filled syringe for subcutaneous use
- SB17 injection, 130 mg/26 mL (5 mg/mL) in a single-dose vial for intravenous use.

The application was sufficiently complete to permit a substantive review. FDA filed the BLA and commenced review.

(b) (4)

A midcycle meeting with the Applicant was held on September 14, 2023, and a late cycle meeting with the Applicant was held on December 12, 2023.

On January 29, 2024, the Applicant submitted BLA 761425 seeking licensure of SB17 injection, 130 mg/26 mL (5 mg/mL) in a single-dose vial for intravenous use. The cover letter to the BLA stated that the Applicant was "submitting a separate submission package for the 130 mg/26 mL IV vial product with the purpose of separating the BLA in the format similar to that of Stelara (BLA#125261 for the SC injection, and BLA#761044 for the IV vial). As the products are developed from the common drug substance, cross-reference to the BLA#761373 package is made [ ]."

On March 15, 2024, the Applicant amended BLA 761373 to withdraw the SB17 injection, 130 mg/26 mL (5 mg/mL) single-dose vial product. A correspondence within the amendment explained, "With this action, Samsung Bioepis seeks to have separate BLAs for the SC injection and IV infusion, ultimately. Of note, Samsung Bioepis confirms that the SC injection does not rely on the information from the IV infusion, and thus even if the IV infusion information is withdrawn from BLA no. 761373, all information to support the licensure of the SC injection would be complete." This amendment was a major amendment which extended the BsUFA goal date for BLA 761373 by three months.

When BLA 761425 was submitted and BLA 761373 was amended, most of the FDA discipline reviews were completed and finalized. The data and information contained in BLA 761425 in support of licensure of SB 17 130 mg/26 mL (5 mg/mL) was initially all previously included in BLA 761373 and reviewed by the FDA review team. In the interest of administrative efficiency, the discipline reviews for BLA 761373 and 761425 will remain as finalized in BLA 761373, and FDA is taking action on BLAs 761373 and 761425 simultaneously.

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. Listing of All Relevant Submitted Clinical Studies

Study Identity	National Clinical Trial (NCT) no.	Study Objective	Study Design	Study Population	Treatment Groups
PK Similarity Study					
SB17-1001	EudraCT No. 2020-004447-88	Pharmacokinetic similarity and safety of SB17, U.S.-Stelara, and EU-Stelara	Randomized, double-blind, parallel-group, active-controlled, three-arm, single-dose	Healthy Subjects	SB17: 67 U.S.-Stelara: 67 EU-Stelara: 67
Comparative Clinical Study					
SB17-3001	EudraCT No. 2020-006115-19	Comparative efficacy, safety, and immunogenicity of SB17 vs EU-Stelara	Randomized, double-blind, parallel-arm, multiple-dose, active comparator	Patients with moderate to severe plaque psoriasis	Main Period: SB17: 249 EU-Stelara: 254 Transition Period: SB17: 237 EU-Stelara/SB17:

Study Identity	National Clinical Trial (NCT) no.	Study Objective	Study Design	Study Population	Treatment Groups
					122 EU-Stelara/EU-Stelara: 122

Source: Reviewer

Authors:

Shera Schreiber, MD — Clinical Reviewer

David Kettl, 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 761373 and BLA 761425 for SB17 manufactured by Samsung Bioepis Co., Ltd. The data submitted in this application are adequate to support the conclusion that the manufacture of SB17 is well-controlled and leads to a product that is safe, pure, and potent. The comparative analytical data support a demonstration that SB17 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 with the post market commitment to improve detection of potential impurities (i.e. endotoxin).

3.2. Devices

SB17 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 SB17 PFS container closure system consists of a 1 mL Type I glass syringe with a staked-in-place stainless steel needle, assembled with an elastomeric needle shield, a rubber plungerstopper, and a passive safety device.

3.2.1. Center for Devices and Radiological Health (CDRH)

CDRH concluded that the device constituent of the combination product is approvable for the proposed indications, and there are no outstanding unresolved information requests. Based on assessment of device constituent parts of the combination product, CDRH recommends approval. There is no PMC/PMR from CDRH.

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

DMEPA1 reviewed the Applicant's use-related risk analysis (URRA), comparative analyses (CA) and justification for not submitting Comparative Use Human Factors (CUHF) study results, to support their marketing application for SB17 45 mg/0.5 mL and 90 mg/mL PFS, as a proposed (b) (4) biosimilar to US-licensed Stelara. Based on the aforementioned information, DMEPA1 concluded that the Applicant does not need to submit human factors validation study results with their marketing application for SB17 45 mg/0.5 mL and 90 mg/mL, PFS, a proposed biosimilar to US-Stelara. (b) (4)

3.3. Office of Study Integrity and Surveillance (OSIS)

The Division requested that the Office of Study Integrity and Surveillance (OSIS) conduct a routine inspection of the bioanalytical site where the PK and immunogenicity (ADA and neutralizing ADA) samples were analyzed for the pivotal PK similarity study (SB17-1001). OSIS determined that an on-site inspection was not needed because a Remote Regulatory Assessment (RRA) had been conducted for the analytical site in

(b) (4) (refer to Final OSIS Report for RRA conducted under NDA (b) (4) in (b) (4)).

3.4. Office of Scientific Investigations (OSI)

An OSI audit was not requested for Study SB17-3001.

Author:

David Kettl, MD

Cross-Discipline Team Leader (CDTL)

4. Nonclinical Pharmacology and Toxicology Evaluation and Recommendations

4.1. Nonclinical Executive Summary and Recommendation

No nonclinical animal studies with SB17 were requested or submitted. The results of the in vitro studies support a demonstration of biosimilarity between SB17 and U.S.-Stelara. Refer to the OBP/CMC section for detailed documentation (Section 3.1). In the absence of specific pharmacokinetic, physicochemical, or other identifiable concerns, in vivo assays are not anticipated to provide additional meaningful information to inform the evaluation of toxicity. Animal studies with SB17 were not required to support this 351(k) application and the results of the in vitro studies support a demonstration of biosimilarity.

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

4.1.1. Nonclinical Residual Uncertainties Assessment

There are no nonclinical residual uncertainties.

4.2. Product Information

Product Formulation

The composition of the SB17 product [pre-filled syringe (PFS) and vial] is shown in the two tables below.

Composition of the SB17 PFS product:

Component	Nominal Quantity[a]/PFS		Function	Quality Standard[b]
	0.5 mL	1.0 mL		
Ustekinumab	45 mg	90 mg	Active substance	In-house[c]
Histidine	0.095 mg	0.190 mg	(b) (4)	Ph. Eur., USP
Histidine hydrochloride monohydrate	0.405 mg	0.810 mg		Ph. Eur.
Polysorbate 80	0.02 mg	0.04 mg		Ph. Eur., NF
Sucrose	42.5 mg	85.0 mg		Ph. Eur., NF
Water for injections	*q.s.*	*q.s.*		Ph. Eur., USP

[a] Although the nominal quantity per syringe for each component may be adjusted when deemed necessary, the proportion of the components remains constant.
[b] Since the quality standards of the compendial components are described as USP or Ph. Eur. as representative pharmacopoeia, each component may also comply with pharmacopoeia of other regions than those specified.
[c] Specification of SB17 drug substance (ustekinumab) is provided in CTD Section 3.2.S.4.1.

Composition of the SB17 vial product:

Component	Nominal Quantity[a]/Vial	Function	Quality Standard[b]
Ustekinumab	130 mg	Active substance	In-house[c]
Histidine	20 (b) (4) mg	(b) (4)	Ph. Eur., USP
Histidine hydrochloride monohydrate	27 mg		Ph. Eur.
Methionine	10.4 mg		Ph. Eur., USP
Disodium edetate	0.52 mg		Ph. Eur., USP
Polysorbate 80	10.4 mg		Ph. Eur., NF
Sucrose	2,210 mg		Ph. Eur., NF
Water for injections	*q.s.*		Ph. Eur., USP

[a] Although the nominal quantity per vial for each component may be adjusted when deemed necessary, the proportion of the components remains constant.
[b] Since the quality standards of the compendial components are described as USP or Ph. Eur. as representative pharmacopoeia, each component may also comply with pharmacopoeia of other regions than those specified.
[c] Specification of SB17 drug substance (ustekinumab) is provided in CTD Section 3.2.S.4.1.

Comments on Excipients

The excipients in the SB17 SPF product are (b) (4) For the vial presentation, methionine and disodium edetate are added (b) (4). There are no concerns for the excipients at the proposed levels.

Comments on Impurities of Concern

There are no concerns for potential impurities contained in SB17.

Authors:

Jianyong Wang
Master Toxicologist

Barbara Hill
Supervisory Pharmacologist

5. Clinical Pharmacology Evaluation and Recommendations

5.1. Clinical Pharmacology Executive Summary and Recommendation

SB17 is a proposed (b) (4) biosimilar product (hereafter referred to as "biosimilar") to the US-licensed Stelara (hereafter referred to as "US-Stelara") which was approved in 2009.

In support of a Biologics License Application (BLA) under section 351(k) of the Public Health Service Act, the Applicant conducted a pharmacokinetic (PK) similarity study (SB17-1001) in healthy subjects to demonstrate PK similarity between SB17 and US-Stelara, SB17 and EU-approved Stelara (hereafter referred to as EU-Stelara), and between US-Stelara and EU-Stelara. The Applicant also conducted a comparative clinical study between SB17 and EU-Stelara in subjects with psoriasis (SB17-3001). The key review findings with specific recommendations and comments are summarized in Table 3.

Table 3. Clinical Pharmacology Major Review Issues and Recommendations

Review Issue	Recommendations and Comments
Pharmacokinetics	• PK similarity between SB17 and US-Stelara was demonstrated in healthy subjects (Study SB17-1001) and supports a demonstration of no clinically meaningful differences between SB17 and US-Stelara. • PK similarity between SB17 and US-Stelara, SB17 and EU-Stelara, and between US-Stelara and EU-Stelara in Study SB17-1001 provides the PK component of the scientific bridge to support the relevance of using EU-Stelara in the comparative clinical study (SB17-3001).
Pharmacodynamics	• Not applicable
Immunogenicity	Healthy subjects (Study SB17-1001) • The incidence of post-dose anti-drug antibodies (ADAs) was generally comparable across the treatment groups

	(SB17: 26.9%; US-Stelara: 34.3%; and EU-Stelara: 34.3%). • The incidence of neutralizing antibodies (NAbs) at Day 99 was generally lower in the SB17 treatment group (35.7%) compared to that in the US-Stelara (57.9%) or EU-Stelara (63.2%) treatment groups. • The PK parameters in the ADA^+ subgroup were generally lower than that in the ADA^- subgroup. However, systemic exposure (AUC_{inf}, C_{max}) to study drug were comparable across treatment groups within the subgroup. • The numerical differences in NAb incidences do not preclude the conclusion of no clinically meaningful differences between SB17 and US-Stelara. <u>Subjects with psoriasis (Study SB17-3001)</u> • In the Main Treatment Period (up to Week 28), the incidence of ADA in the SB17 treatment group was lower than that in the EU-Stelara treatment group by visits and overall status (i.e., Week 28 overall, SB17: 13.3% and EU-Stelara: 39.4%). • The incidence of NAb in the SB17 treatment group was numerically lower than that in the EU-Stelara treatment group by visits. However, the incidence of NAb at Week 28 were 75% in both treatment groups. • In the Transition Period (Week 28 to Week 52), the incidence of ADA was comparable among treatment groups, 5.6% for SB17+SB17, 5.1% for EU-Stelara+SB17, and 6.7% for EU-Stelara+EU-Stelara. • Overall, the impact of immunogenicity on efficacy, and/or safety between SB17 and EU-Stelara was deemed generally comparable. • The numerical differences in ADA and NAb incidences do not preclude the conclusion of no clinically meaningful differences between SB17 and US-Stelara,

The results of the three pair-wise comparisons in the PK study (SB17-1001) demonstrated that the PK similarity was established between SB17 and US-Stelara, SB17 and EU-Stelara, and between EU-Stelara and US-Stelara. The 90% confidence intervals (CIs) for the geometric least-square mean ratios (GMRs) of the primary PK

parameters ($AUC_{0\text{-}inf}$ and C_{max}) between the proposed biosimilar product SB17 and EU- or US-Stelara were within the prespecified margin of 0.80 to 1.25 (Table 4). The PK similarity study also supported the relevance of use of EU-Stelara in the comparative clinical study to establish the PK component of scientific bridge.

Table 4. Summary of Statistical Analyses for Assessment of PK Similarity (Study SB17-1001)

Parameter	Geometric LSMean			Geometric LSMean Ratio (90% CI)		
	SB17 (n=67)	US-Stelara (n=67)	EU-Stelara (n=67)	SB17 *vs.* US-Stelara	SB17 *vs.* EU-Stelara	EU-Stelara *vs.* US-Stelara
Primary						
$AUC_{0\text{-}inf}$ (ng·h/mL)	4958100	4900400	5020000	1.01 [0.93, 1.10]	0.99 [0.90, 1.08]	1.02 [0.93, 1.12]
C_{max} (ng/mL)	4882	5169	5433	0.94 [0.86, 1.04]	0.90 [0.82, 0.98]	1.05 [0.96, 1.15]

$AUC_{0\text{-}inf}$ = area under the concentration-time curve from time zero to infinity, C_{max} = maximum serum concentration, CI=confidence interval, LSMean = least-square mean
Source: Clinical Study Report SB17-1001, Table 11-4, Table 11-5, and Table 11-6

5.1.1. Clinical Pharmacology Residual Uncertainties Assessment

Overall, based on the available clinical PK and immunogencity data, there are no residual uncertainties and the submitted clinical pharmacology information supports a demonstration that there are no clinically meaningful differences between SB17 and US-Stelara.

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

A non-US-licensed comparator, EU-Stelara, was also evaluated and compared to SB17 as well as US-Stelara in the PK similarity Study SB17-1001. The results demonstrated that the PK similarity was established between SB17 and US-Stelara, SB17 and EU-Stelara, and between US-Stelara and EU-Stelara (Table 4), therefore, the PK portion of the scientific bridge was established to support the relevance of the data generated using EU-Stelara in the comparative clinical study (SB17-3001).

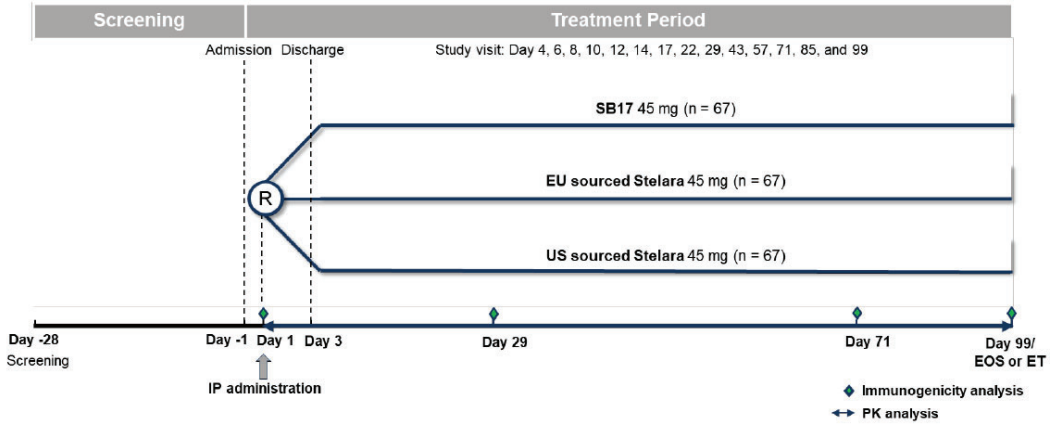
5.3. Human Pharmacokinetic and Pharmacodynamic Studies

5.3.1. Study SB17-1001

Study Design

Study SB17-1001 was a randomized, double-blind, three-arm, parallel group, single-dose study to compare the PK, safety, tolerability, and immunogenicity of SB17, US-Stelara, and EU-Stelara in healthy subjects. A total of 201 healthy subjects aged 18 to 55 years with a body weight (BW) between 60 to 90 kg and a body mass index (BMI) between 19.0 to 29.9 kg/m^2 were randomized in a 1:1:1 ratio to receive a single dose of 45 mg SB17 (n=67), US-Stelara (n=67), or EU-Stelara (n=67) (Figure 1). All investigational products (IPs) were administered subcutaneously in the abdomen.

Figure 1 Design of Clinical Study SB17-1001



EOS=end of study, ET=early termination, IP=investigational product, PK=pharmacokinetic, R=randomisation
Source: Clinical Study Report SB17-1001, Figure 9-1

Study Primary Objectives

- To demonstrate the PK similarity between SB17 and EU-Stelara (for EMA submission)
- To demonstrate the PK similarity between SB17 and US-Stelara (for FDA submission)
- To demonstrate the PK comparability between EU-Stelara and US-Stelara

Primary PK endpoints:

- Area under the concentration-time curve from time zero to infinity ($AUC_{0\text{-}inf}$)
- Maximum serum concentration (C_{max})

Secondary PK endpoints:

AUC from time 0 to the last quantifiable concentration (AUC_{last}), AUC from time zero to 264 hours ($AUC_{0\text{-}264h}$), time to reach C_{max} (T_{max}), apparent volume of distribution during the terminal phase (V_z/F), terminal rate constant (λ_z), terminal half-life ($t_{1/2}$), apparent clearance (CL/F), percentage of AUC_{inf} due to extrapolation from time of last measurable concentration (T_{last}) to infinity ($\%AUC_{extrap}$).

Bioanalytical Assay for Determination of Ustekinumab in Human Serum

Intensive serial blood samples for PK analysis were collected at pre-dose, 12, 24, 48, 72, 120, 168, 216, 264, 312, 384, 504, 672, 1008, 1344, 1680, 2016, and 2352 hours post-dose. A validated enzyme-linked immunosorbent assay (ELISA) was applied to determine concentrations of SB17, US-Stelara and EU-Stelara in human serum samples obtained from the PK similarity study. The method is applicable for the quantitation of ustekinumab within a nominal range of 150 to 1500 ng/mL, with lower limit of quantitation (LLOQ) of 150 ng/mL. Refer to Clinical Pharmacology Appendices Section 14.3.1 for details on method development, validation, and performance.

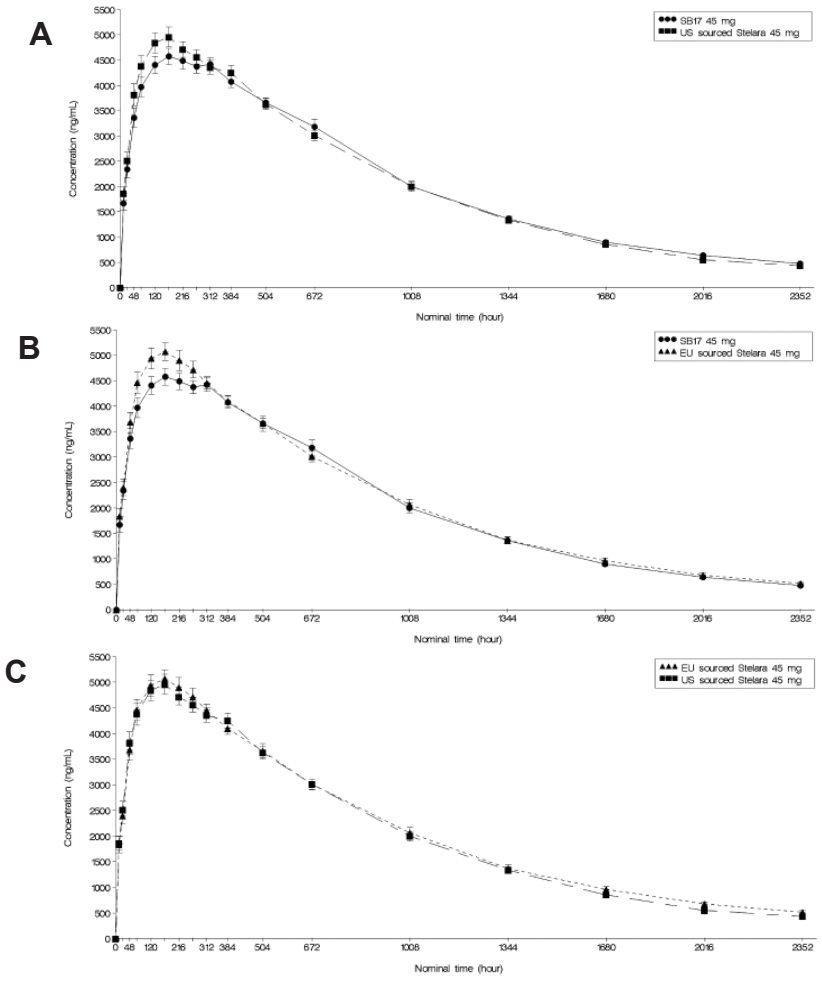
Assessment of PK Similarity

The pairwise comparisons of PK profiles between SB17 and US-Stelara, SB-17 and EU-Stelara, and between EU-Stelara and US-Stelara are presented in Figure 2. The mean serum concentration-time profiles were similar across the three treatment groups after a single SC 45 mg dose of SB17, US-Stelara, or EU-Stelara in healthy subjects.

The median T_{max} value was 168 hours for all 3 treatment groups. The arithmetic mean $t_{1/2}$ values for SB17, US-Stelara, and EU-Stelara were 582.70, 541.07, 563.80 hours, respectively. The arithmetic mean AUC_{last} values for SB17, US-Stelara, and EU-Stelara were comparable (4721000 ng·h/mL, 4769900 ng·h/mL, and 4853500 ng·h/mL, respectively). Refer to Clinical Pharmacology Appendices Section 14.3.2 of this view for details on the primary and secondary endpoints of PK assessment.

In summary, the PK similarity study met the primary objectives as the 90% CIs for the GMRs of $AUC_{0\text{-}inf}$ and C_{max} between SB17 andEU-Stelara and US-Stelara were all within the pre-defined criteria of 0.80 to 1.25 (Table 4).

Figure 2 Pairwise Comparisons of PK Profiles between SB17 and US-Stelara (A), SB17 and EU-Stelara (B), and between EU-Stelara and US-Stelara (C) after A Single SC 45 mg Dose of SB17, US-Stelara or EU-Stelara



Source: Clinical Study Report SB17-1001, Figure 11-1, Figure 11-2, and Figure 11-3

Inspection of PK Similary Study

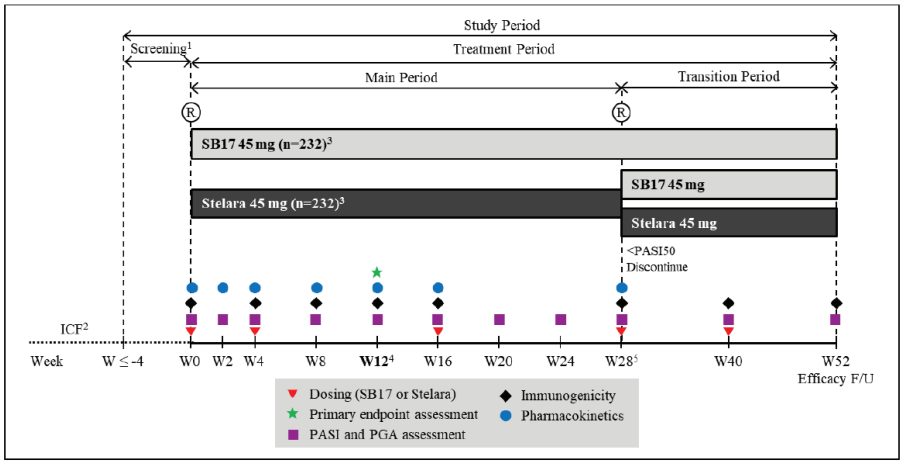
The PK samples were analyzed in one analytical site. The Office of Study Integrity and Surveillance (OSIS) determined than an on-site inspection is not needed as this analytical site was recently inspected for another application and concluded that data from the reviewed studies were reliable. Refer to Section 3.3 for details.

5.3.2. Study SB17-3001

Study Design

Study SB17-3001 was a randomized, double-blind, multicenter clinical study to evaluate the efficacy, safety, tolerability, PK, and immunogenicity of SB17 compared to EU-Stelara in subjects with moderate to severe plaque psoriasis. A total of 503 eligible subjects were randomized in a 1:1 ratio to receive either SB17 or EU-Stelara via SC injection. SB17 or EU-Stelara were administered at Weeks 0, 4 and then every 12 weeks up to Week 40, and the last assessment was done at Week 52 (Figure 3). Subjects with BW ≤100 kg or >100 kg were given 45 mg or 90 mg of SB17/EU-Stelara, respectively. Among 503 subjects, only 24 subjects received 90 mg of SB17 (n=15) or Stelara (n=9) at Weeks 16, 20, 24, or 28. Detailed information about the study design can be find in Section 6.2 of this review.

Figure 3 Design of Clinical Study SB17-3001



Source: Clinical Study Report SB17-3001, Figure 9-1

PK Objective

- To evaluate the PK of SB17 compared to EU-Stelara in subjects participating in PK evaluation

Bioanalytical Assay for Determination of Ustekinumab in Human Serum

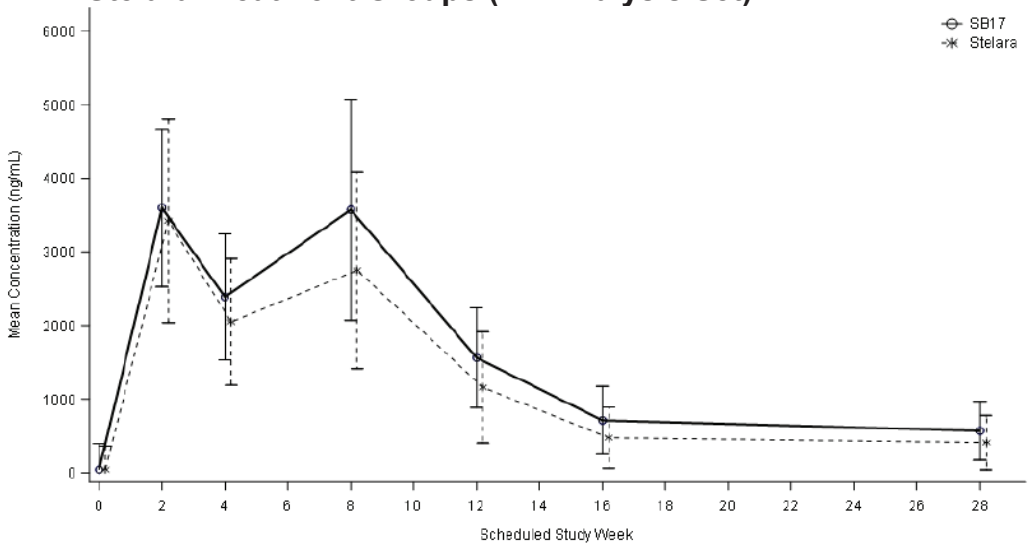
Sparse blood samples for PK analysis were collected at Weeks 2, 8, and 12, and prior to IPs at Weeks 0, 4, 16 and 28. The same bioanalytical method for determination of

study drug concentrations was employed in the clinical studies (i.e., SB17-1001 and SB17-3001). Refer to Sections of 5.3.1 and 14.2.1 of this review for details.

PK Assessment

Serum concentrations of study drug were assessed up to Week 28 in approximately 140 subjects as a PK sub-study in Study SB17-3001 (Figure 3). Mean (± SD) serum concentrations by visit and treatment group are presented in Figure 4 and Table 5. The mean serum concentrations in the SB17 treatment group were up to 50% higher than that in the EU-Stelara treatment group with a coefficient of variation up to 90.1% across the treatment groups (Table 5). The observed higher systemic exposure in the SB17 treatment seems unlikely to be clinically meaningful as the incidence of any adverse events in the Screening and Main Treatment Period (up to Week 28) was comparable between the SB17 (49%) and EU-Stelara (50.4%) treatment groups. Refer to the Section 6 for more information regarding adverse events and/or safety.

Figure 4 Serum Concentrations of Study Drug (Mean±SD) in the SB17 and EU-Stelara Treatment Groups (PK Analysis Set)



Source: Clinical Study Report SB17-3001, Figure 11-2

Table 5 Serum Concentrations of Study Drug in the SB17 and EU-Stelara Treatment Groups (PK Analysis Set)

Week	Mean Concentration (ng/mL) (CV%)		Ratio of mean concentration SB17/EU-Stelara
	SB17 (n=71)	EU-Stelara (n=71)	
0	42.31 (830.7)	41.56 (772.6)	1.01
2	3594.09 (29.8)	3419.94 (40.4)	1.05
4	2385.14 (35.9)	2046.84 (42.0)	1.17
8	3569.38 (42.1)	2749.02 (48.6)	1.30
12	1560.17 (43.5)	1156.77 (65.4)	1.35
16	710.11 (65.1)	473.02 (87.5)	1.50
28	567.22 (70.0)	408.49 (90.1)	1.39

CV=coefficient of variation, n=a total number of subjects
Source: Reviewer's independent analysis based on Clinical Study Report SB17-3001, Table 14.2-4.1

5.4. Clinical Immunogenicity Studies

5.4.1. Design Features of the Clinical Immunogenicity Assessment

Immunogenicity was assessed in healthy subjects (Study SB17-1001) and subjects with moderate to severe plaque psoriasis (Study SB17-3001).

- In Study SB17-1001, healthy male or female subjects aged 18-55 years with BW of 60 to 90 kg and BMI of 19 to 29.9 kg/m^2 at Screening and prior to receiving the IPs were enrolled. Eligible subjects (n=201) were randomized in a 1:1:1 ratio to receive a single SC 45 mg of SB17, US-Stelara, or EU-Stelara. Each IP was presented as 45 mg/0.5 mL in a pre-filled syringe (PFS) for SC injection.
- In Study SB17-3001, subjects aged ≥18 years with moderate to severe plaque psoriasis with BW <95 kg at Screening were enrolled and randomized in a 1:1 ratio to receive a SC dose of 45 mg of IP at Weeks 0, 4, 16, 28 and 40, a total of 5 doses of IP. Each IP was repsented as 45 mg/0.5 mL in a PSF for SC injection.

During the study period, subjects were given a 90 mg of IP when the BW was >100 kg. A 90 mg dose of IP was given by two doses of 45 mg/0.5 mL or two SC injections of 45 mg/0.5 mL in a PFS. Among 503 subjects, 24 subjects received 90 mg of SB17 (n=15) or EU-Stelara (n=9) at Weeks 16, 20, 24, or 28.

Moderate to severe plaque psoriasis was defined as:

- Total affected body surface area ≥10%
- Psoriasis Area and Severity Index (PASI) score of ≥12
- Physician's Global Assessment (PGA) score of ≥3 (moderate)

Overall, the study populations and dose selections in both studies were adequately sensitive to detect immunogenicity events.

5.4.2. Immunogenicity Endpoints

The purpose of immunogenicity testing in the SB17 clinical studies (SB17-1001 and SB17-3001) was to determine the incidences of ADAs and NAbs to study drug by visit and by treatment, and to compare the differences of the incidence between SB17 and US-Stelara and/or EU-Stelara treatment groups. The impact of immunogenicity on PK, efficacy and/or safety was also evaluated and compared in both studies.

5.4.3. Immunogenicity Assay

- Immunogenicity assay for detection of anti-drug antibodies

A bridging ligand-binding assay with electrochemiluminescence (ECL) platform with Meso Scale Discovery (MSD) was developed and validated for assessment of ADAs in the SB17 clinical studies (SB17-1001 and SB17-3001). A three-tiered approach (i.e., screening, confirmation and characterization) for ADA assay was applied. Briefly, the screening assay was performed on human samples to detect the presence of binding antibodies to study drug. Samples with an ECL signal value greater than or equal to the assay cut point were than analyzed to confirm specificity of the ADA^+ confirmed samples by confirmatory assay. In the confirmatory assay format, samples were confirmed as positive for ADA if the % inhibition value was equal to or above the confirmatory cut point. For further characterization, the titration assay and neutralizing assay were also performed in the ADA^+ response samples.

- Immunogenicity assay for detection of neutralizing antibodies

The comparative NAb incidences in response to administration of study drug in the SB17 clinical studies (SB17-1001 and SB17-3001) were evaluated by means of NAb detection in human serum samples using a validated competitive ligand-blinding assay with ECL platform with MSD. NAbs against SB17, US-Stelara, and EU-Stelara in human serum were detected with a single tier ECL.

Briefly, the assays had drug tolerance level of 40 mcg/mL of SB17 or US-Stelara/EU-Stelara in serum for detection of as low as 0.1 mcg/mL ADA, and drug tolerance level of 0.1 to 1 mcg/mL of SB17, or US-Stelara/EU-Stelara in serum for detection of as low as 0.15 mcg/mL NAb. Refer to the Product Quality Review for more information regarding method development, validation, and performance of the immunogenicity assays.

5.4.4. Immunogenicity Results

- Immunogenicity in healthy subjects in the PK similarity study SB17-1001

A total of 201 healthy subjects were randomized in a 1:1:1 ratio to receive a single SC dose of 45 mg of SB17 (n=67), US-Stelara (n=67), and EU-Stelara (n=67). Blood samples were collected at Days 1 (baseline), 29, 71, and 99 or early termination visit for immunogenicity assessment. Given the elimination half-life and drug tolerance of ustekinumab, the immunogenicity sampling scheme was adequate.

The incidences of ADA and NAb by visit and by treatment are summarized in Table 6. The incidence of subjects with post-dose of ADAs across timepoints was numerically generally comparable in the SB17 treatment group compared to that in the US- or EU-Stelara treatment group. The overall incidences of ADA to study drug were 26.9%, 34.3%, and 34.3% in the SB17, US-Stelara, and EU-Stelara, respectively.

The incidence of subjects with NAb at each timepoint was lower in the SB17 treatment group compared to that in the US- or EU-Stelara treatment group, except for that at Day 29. The incidence of NAb at Day 99 was 35.7%, 57.9%, and 63.2% in the SB17, US-Stelara, and EU-Stelara treatment groups, respectively. However, the numerical differences in NAb incidences do not preclude the conclusion of no clinically meaningful differences between SB17 and US-Stelara.

Table 6 Incidences of ADAs and NAbs in Healthy Subjects (Study SB17-1001)

Parameter	Timepoint	Result	SB17 N = 67		EU Stelara N = 67		US Stelara N = 67		Total N = 201	
			n/n′	%	n/n′	%	n/n′	%	n/n′	%
ADA	Day 1 Pre-dose (BL)	Positive	2/67	3.0	4/67	6.0	2/67	3.0	8/201	4.0
		Negative	65/67	97.0	63/67	94.0	65/67	97.0	193/201	96.0
	Day 29	Positive	10/66	15.2	6/65	9.2	6/65	9.2	22/196	11.2
		Negative	56/66	84.8	59/65	90.8	59/65	90.8	174/196	88.8
	Day 71	Positive	9/63	14.3	12/62	19.4	14/62	22.6	35/187	18.7
		Negative	54/63	85.7	50/62	80.6	48/62	77.4	152/187	81.3
	Day 99	Positive	14/62	22.6	19/62	30.6	19/60	31.7	52/184	28.3
		Negative	48/62	77.4	43/62	69.4	41/60	68.3	132/184	71.7
	Post-dose[a]	Positive	18/67	26.9	23/67	34.3	23/67	34.3	64/201	31.8
		Negative	49/67	73.1	44/67	65.7	44/67	65.7	137/201	68.2
NAb[b]	Day 1 Pre-dose (BL)	Positive	0/2	0.0	1/4	25.0	0/2	0.0	1/8	12.5
		Negative	2/2	100.0	3/4	75.0	2/2	100.0	7/8	87.5
	Day 29	Positive	6/10	60.0	2/6	33.3	2/6	33.3	10/22	45.5
		Negative	4/10	40.0	4/6	66.7	4/6	66.7	12/22	54.5
	Day 71	Positive	5/9	55.6	10/12	83.3	11/14	78.6	26/35	74.3
		Negative	4/9	44.4	2/12	16.7	3/14	21.4	9/35	25.7
	Day 99	Positive	5/14	35.7	12/19	63.2	11/19	57.9	28/52	53.8
		Negative	9/14	64.3	7/19	36.8	8/19	42.1	24/52	46.2

BL=baseline; N=number of subjects in the safety set; n=number of subjects within assessment category; n'=number of subjects with available assessment at each timepoint
[a]: Post-dose ADA was definded as "positive" if subjects had at least one ADA positive on post-baseline, and "Negative" if subjects had no ADA positive on post-baseline
[b]: NAb results only for subjects determined as ADA positive were used for the summary
Source: Summary of Clinical Pharmacology Studies, Table 12

- Immunogenicity in subjects with psoriasis in comparative clinical study SB17-3001

Immunogenicity was assessed in Study SB17-3001 which consisted of two treatment periods, Main Treatment Period (Week 0 to Week 28) and Transition Period (Week 28 to Week 52) (Figure 3). A total of 503 subjects with psoriasis were randomized in a 1:1 ratio to receive either SB17 or EU-Stelara SC injection at Weeks 0 and 4, and then every 12 weeks up to Week 40, and last assessment was Week 52. At Week 28, only subjects in the EU-Stelara treatment group who achieved a PASI50 response were randomized again in a 1:1 ratio to either continue on EU-Stelara (Stelara+Stelara) or switch to SB17 (Stelara+SB17) until Week 40. Subjects in the SB17 treatment group continued to receive SB17 until Week 40. Blood samples were collected at Weeks 0, 4, 16, 28 and 40 prior to IP administration and Weeks 8, 12 and 52 or early termination for immunogenicity assessment. The blood sampling scheme was appropriate for immunogenicity assessment in the comparative clinical study.

The incidences of ADA and NAb by visit and by treatment are summarized in Table 7. The incidence of ADA was lower in the SB17 than EU-Stelara (Stelara Overall) treatment group by visit and overall status. The incidences of ADA up to Week 28 (by the end of Main Treatment Period) were 13.3% and 39.4% for the SB17 and Stelara Overall treatment groups, respectively. After Transition or Switch (Week 28 to Week 52), the overall incidence of ADA was comparable among treatment groups, 5.6% for SB17+SB17, 5.1% for EU-Stelara+SB17, and 6.7% for Stelara+Stelara. The incidences of ADA up to Week 52 (Main Treatment Period + Transition Period) were 16.5%, 39.3%, and 43.3% in the SB17, EU-Stelara+SB17, and Stelara+Stelara treatment groups, respectively. Additionally, the majority of ADA titers were low-titer and the titer distribution for ADA was comparable between treatment groups.

The incidences of NAb up to Week 16 tended to be lower in the SB17 than the Stelara Overall treatment group by visit (Table 7). At Week 28, the incidence of NAb was 75% for both treatment groups. The incidences of NAb at Week 52 were 50%, 64.7%, and 74.1% in the SB17, EU-Stelara+SB17, and Stelara+Stelara, respectively.

However, the numerical differences in ADA and NAb incidences do not preclude the conclusion of no clinically meaningful differences between SB17 and US-Stelara.

Table 7 Incidences of ADAs and NAbs by Visits & Treatment Group (Safety Set 1)

Timepoint	Parameter	SB17 N=249 n/n' (%)	Stelara Overall N=254 n/n' (%)	Stelara +SB17[a] N=122 n/n' (%)	Stelara +Stelara[a] N=122 n/n' (%)
Baseline	ADA	8/249 (3.2)	2/254 (0.8)	1/122 (0.8)	1/122 (0.8)
	NAb	4/8 (50.0)	1/2 (50.0)	1/1 (100.0)	0/1 (0.0)
Week 4	ADA	10/249 (4.0)	46/254 (18.1)		
	NAb	4/10 (40.0)	38/ 46 (82.6)		
Week 8	ADA	12/247 (4.9)	58/253 (22.9)		
	NAb	6/12 (50.0)	42/58 (72.4)		
Week 12	ADA	25/246 (10.2)	70/252 (27.8)		
	NAb	15/ 25 (60.0)	65/70 (92.9)		
Week 12 Overall	ADA	19/249 (7.6)	80/254 (31.5)	38/122 (31.1)	38/122 (31.1)
Week 16	ADA	32/241 (13.3)	66/246 (26.8)		
	NAb	26/32 (81.3)	60/66 (90.9)		
Week 28	ADA	32/234 (13.7)	64/242 (26.4)	30/118 (25.4)	33/121 (27.3)
	NAb	24/32 (75.0)	48/64 (75.0)	20/30 (66.7)	27/33 (81.8)
Week 28 Overall	ADA	33/249 (13.3)	100/254 (39.4)	46/122 (37.7)	50/122 (41.0)
Week 40	ADA	30/233 (12.9)	49/237 (20.7)	22/118 (18.6)	27/119 (22.7)
	NAb	16/30 (53.3)	36/49 (73.5)	13/22 (59.1)	23/27 (85.2)
Week 52	ADA	24/230 (10.4)	44/230 (19.1)	17/114 (14.9)	27/116 (23.3)
	NAb	12/24 (50.0)	31/44 (70.5)	11/17 (64.7)	20/27 (74.1)
After transition overall (Week 28 to Week 52)	ADA	13/234 (5.6)	14/237 (5.9)	6/118 (5.1)	8/119 (6.7)
Week 52 Overall	ADA	41/249 (16.5)	105/254 (41.3)	48/122 (39.3)	53/122 (43.4)

N=total number of patients in the Safety Set 1; n=number of patients with available data with each category; n'=number of patients with available assessment results at each visit
[a]: Based on patients in the Safety Set 2, Stelara+SB17 and Stelara+Stelara may not add up to Stelara Overall.
Overall ADA results were defined as "Positive" for a patient with treatment-induced or treatment-boosted ADA, where treatment-induced ADA indicates at least one positive result after first IP administration at Week 0 for patients with negative ADA at baseline, and treatment-boosted ADA indicates at least one positive result with high titer level compared to baseline after first IP administration at Week 0 for patients with positive ADA at baseline
Source: Clinical Study Report SB17-3001, Table 12-11

5.4.5. Impact of Immunogenicity on PK, Efficacy and Safety

- Impact of immunogenicity on PK

The impact of immunogenicity on the PK was assessed in healthy subjects in Study SB17-1001, the PK paramers by post-dose ADA status are summarized in Table 8. Overall, systemic exposure to each study drug in the ADA^+ sub-group was lower than those in the ADA^- sub-group across the treatment groups. Further comparison analysis indicated that systemic exposure (i.e., primary PK endpoints: AUC_{inf} and C_{max}) in either ADA^+ or ADA^- sub-groups were comparable across the treatment groups (Table 9), suggesting that the impact of immunogenicity on the PK of study drug in healthy subjects between SB17 and US-Stelara and EU-Stelara was comparable.

Table 8 Summary of PK by Post-dos ADA Status and Treatment Group (SB17-1001)

		SB17		EU Sourced Stelara		US Sourced Stelara	
PK Parameter	Statistics	Positive N=18	Negative N=49	Positive N=23	Negative N=44	Positive N=23	Negative N=44
AUC_{inf} (ng·h/mL)	n	18	44	22	42	21	39
	Mean	4882600	5250400	4455800	5701000	4477600	5460600
	SD	1797300	1212000	1656000	1492800	1030800	1647100
	Median	4551400	5129900	4091200	5487100	4498200	5438500
	Min	2414000	2723000	2045000	3167000	2559000	2118000
	Max	8884000	8834000	8627000	10280000	6447000	10200000
C_{max} (ng/mL)	n	18	44	22	42	21	39
	Mean	5179	5061	5374	5854	4883	5709
	SD	1782	1386	1383	2086	1317	1766
	Median	4835	5080	5685	5430	4790	5660
	Min	2630	2730	2950	3260	2850	1590
	Max	8730	9030	7290	13700	8070	11100
AUC_{last} (ng·h/mL)	n	18	44	22	42	21	39
	Mean	4583900	4777100	4176500	5208200	4239500	5055500
	SD	1686600	1060500	1480200	1284500	956640	1433100
	Median	4150800	4847900	3857900	5108900	3990900	5133000
	Min	2302000	2610000	1974000	3012000	2434000	1959000
	Max	8526000	7733000	7752000	9786000	6019000	9257000
$AUC_{0\text{-}264h}$ (ng·h/mL)	n	18	44	22	42	21	39
	Mean	1044900	1044700	1141400	1151700	1024700	1167700
	SD	404210	293130	324400	389370	317540	369000
	Median	992540	1060900	1145100	1097400	946320	1190300
	Min	458500	470000	601400	565500	482900	291500
	Max	1780000	1673000	1660000	2820000	1704000	2042000

PK Parameter	Statistics	SB17 Positive N=18	SB17 Negative N=49	EU Sourced Stelara Positive N=23	EU Sourced Stelara Negative N=44	US Sourced Stelara Positive N=23	US Sourced Stelara Negative N=44
T_{max}	n	18	44	22	42	21	39
(h)	Median	264.000	168.000	120.000	168.000	168.000	168.000
	Min	72.00	48.00	48.00	12.00	48.00	48.00
	Max	504.00	672.00	264.00	504.00	1008.00	384.00
V_z/F	n	18	44	22	42	21	39
(mL)	Mean	6633.9	7940.3	6898.5	7280.7	7163.6	7282.0
	SD	2964.7	1898.4	2066.5	1560.9	2211.3	2285.2
	Median	6187.3	7623.8	6682.9	7143.7	6932.0	7001.6
	Min	2817	5146	3117	2825	3207	3624
	Max	12910	12420	11560	11290	12520	17980
λ_z	n	18	44	22	42	21	39
(1/h)	Mean	0.0019391	0.0011641	0.0018504	0.0011718	0.0015615	0.0012552
	SD	0.0013913	0.00025457	0.0012854	0.00024946	0.00040252	0.00027122
	Median	0.0013989	0.0011694	0.0015573	0.0011242	0.0014812	0.0012276
	Min	0.0008067	0.0007264	0.0009547	0.0007386	0.0007192	0.0008110
	Max	0.005569	0.001895	0.007060	0.001738	0.002264	0.002108
$t_{1/2}$	n	18	44	22	42	21	39
(h)	Mean	484.82	622.75	459.81	618.27	477.13	575.50
	SD	215.27	132.32	162.75	133.03	147.58	115.46
	Median	495.49	592.78	445.28	616.74	467.96	564.64
	Min	124.5	365.8	98.2	398.7	306.1	328.8
	Max	859.2	954.2	726.0	938.4	963.8	854.7
CL/F	n	18	44	22	42	21	39
(mL/h)	Mean	10.387	9.0397	11.509	8.3858	10.601	9.0725
	SD	3.6284	2.2178	4.3848	2.0669	2.6252	3.1883
	Median	9.8880	8.7722	10.999	8.2012	10.004	8.2744
	Min	5.065	5.094	5.216	4.378	6.980	4.411
	Max	18.64	16.52	22.01	14.21	17.59	21.25
$\%AUC_{extrap}$	n	18	44	22	42	21	39
	Mean	5.94	8.71	5.86	8.20	5.16	6.95
	SD	3.51	5.33	2.74	3.95	3.28	2.98
	Median	4.74	6.88	5.15	7.37	4.10	6.01
	Min	1.4	2.4	1.6	2.9	2.2	2.7
	Max	14.6	30.2	12.8	18.5	13.8	14.9

Source: Clinical Study Report SB17-1001, Table 11-7

Table 9 Comparison of AUC_{inf} and C_{max} by ADA Status between SB17 and EU-Stelara (A), or US-Stelara (B), or Between EU-Stelara and US-Stelara (C) in Healthy Subjects

A

Post-dose ADA Result: Positive						
PK Parameter	Treatment	N	n	Geo-LS Mean	Ratio A/B	90% CI of Ratio
AUC_{inf}	SB17	18	18	4594200		
(ng·h/mL)	EU sourced Stelara	23	22	4176400	1.10	[0.90, 1.34]
C_{max}	SB17	18	18	4890		
(ng/mL)	EU sourced Stelara	23	22	5186	0.94	[0.80, 1.12]
Post-dose ADA Result: Negative						
PK Parameter	Treatment	N	n	Geo-LS Mean	Ratio A/B	90% CI of Ratio
AUC_{inf}	SB17	49	44	5115100		
(ng·h/mL)	EU sourced Stelara	44	42	5527800	0.93	[0.85, 1.01]
C_{max}	SB17	49	44	4879		
(ng/mL)	EU sourced Stelara	44	42	5566	0.88	[0.79, 0.97]

B

Post-dose ADA Result: Positive						
PK Parameter	Treatment	N	n	Geo-LS Mean	Ratio A/B	90% CI of Ratio
AUC_{inf}	SB17	18	18	4594200		
(ng·h/mL)	US sourced Stelara	23	21	4362500	1.05	[0.90, 1.24]
C_{max}	SB17	18	18	4890		
(ng/mL)	US sourced Stelara	23	21	4715	1.04	[0.88, 1.23]
Post-dose ADA Result: Negative						
PK Parameter	Treatment	N	n	Geo-LS Mean	Ratio A/B	90% CI of Ratio
AUC_{inf}	SB17	49	44	5115100		
(ng·h/mL)	US sourced Stelara	44	39	5217000	0.98	[0.89, 1.08]
C_{max}	SB17	49	44	4879		
(ng/mL)	US sourced Stelara	44	39	5431	0.90	[0.80, 1.00]

C

Post-dose ADA Result: Positive						
PK Parameter	Treatment	N	n	Geo-LSMean	Ratio A/B	90% CI of Ratio
AUC_{inf}	EU sourced Stelara	23	22	4176400		
(ng·h/mL)	US sourced Stelara	23	21	4362500	0.96	[0.82, 1.12]
C_{max}	EU sourced Stelara	23	22	5186		
(ng/mL)	US sourced Stelara	23	21	4715	1.10	[0.95, 1.27]
Post-dose ADA Result: Negative						
PK Parameter	Treatment	N	n	Geo-LSMean	Ratio A/B	90% CI of Ratio
AUC_{inf}	EU sourced Stelara	44	42	5527800		
(ng·h/mL)	US sourced Stelara	44	39	5217000	1.06	[0.95, 1.18]
C_{max}	EU sourced Stelara	44	42	5566		
(ng/mL)	US sourced Stelara	44	39	5431	1.02	[0.91, 1.15]

Souce: Clinical Study Report SB17-1001 Table 11-8, Table 11-9, and Table 11-10

The impact of immunogenicity on PK was also characterized up to Week 28 in approximately 140 subjects with psoriasis following multiple dosing SB17 or EU-Stelara as a PK sub-study in Study SB17-3001. The mean serum concentrations of study drug in the SB17 treatment group were up 50% higher than in the EU-Stelara treatment group (Table 10). The observed difference in the mean serum concentrations is possibly due to the differences in ADA status and its corresponding mean serum concentrations between two treatment groups. In the subgroup analysis, for subjects with overall ADA−, the mean concentrations of study drug were comparable between the SB17 and EU-Stelara treatment groups (Table 10). While for subjects with overall ADA+, the mean concentrations in the SB17 treatment group were up to 2-fold higher than that in the EU-Stelara treatment group (Table 10). Further, the patient numbers are small and it is difficult to draw conclusions as to the clinical relevance of this observation. Moreover, the higher systemic exposure is unlikely to result in safety concerns as the incidence of any adverse events in the Screening and Main Treatment Period (up to Week 28) of Study SB17-3001 was comparable between the SB17 (49%) and EU-Stelara (50.4%) treatment groups. Refer to the Clinical Review for more information regarding adverse events and/or safety.

Overall, the impact of immunogenicity on PK between SB17 and EU-Stelara was not considered to be clinically meaningful.

Table 10 Serum Concentrations (ng/mL) of Study Drug by Visit, Treatment, and ADA Status in Study SB17-3001 (PK Analysis Set)

		SB17		Stelara	
Time Point	Statistics	Positive N=8	Negative N=61	Positive N=32	Negative N=39
Week 0	n	8	59	30	37
	Mean	364.93	0.00	0.00	75.26
	SD	1032.164	0.000	0.000	431.774
	CV%	282.8	N/A	N/A	573.7
Week 2	n	8	61	32	39
	Mean	3850.45	3537.89	3228.49	3577.03
	SD	713.566	1106.569	1595.692	1179.680
	CV%	18.5	31.3	49.4	33.0

Week 4	n	8	60	32	39
	Mean	2290.04	2382.46	1768.63	2275.11
	SD	686.952	861.457	905.531	755.751
	CV%	30.0	36.2	51.2	33.2
Week 8	n	7	59	32	37
	Mean	3096.31	3568.13	2303.73	3134.15
	SD	947.999	1540.283	1239.884	1313.322
	CV%	30.6	43.2	53.8	41.9
Week 12	n	8	60	32	38
	Mean	1271.84	1582.96	804.39	1453.52
	SD	477.987	701.275	559.790	779.044
	CV%	37.6	44.3	69.6	53.6
Week 16	n	8	60	32	37
	Mean	485.79	736.46	250.28	665.66
	SD	422.347	469.516	297.247	406.229
	CV%	86.9	63.8	118.8	61.0
Week 28	n	8	59	32	36
	Mean	458.31	584.38	224.44	572.08
	SD	298.128	414.689	275.991	364.902
	CV%	65.0	71.0	123.0	63.8

Souce: Clinical Study Report SB17-3001 Table 11-11

- Impact of immunogenicity on efficacy

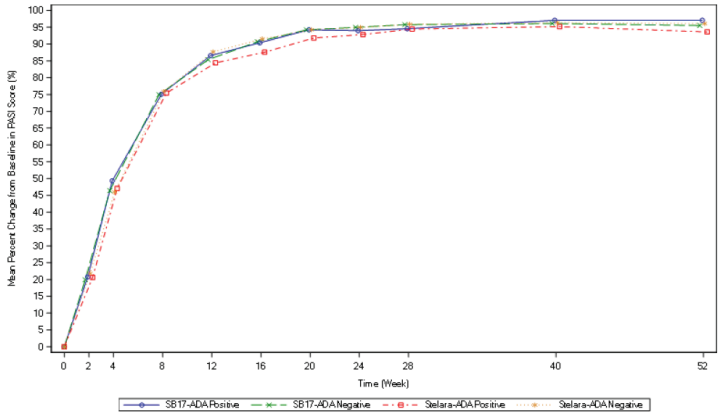
The impact of immunogenicity on efficacy was evaluated in subjects with psoriasis in Study SB17-3001. The comparison of the PASI percent change from baseline at Week 12 (primary efficacy endpoint) and up to Week 52 by overall ADA status and treatment groups are summarized in Table 11 and Figure **5**, respectively. Within each subgroup, the PASI percent change from baseline was similar between the two treatment groups at Week 12 (Table 11). In addition, the percent change from baseline in PASI score by ADA status and/or treatments were comparable up to Week 52 (Figure **5**). These results indicate that the impact of immunogenicity on efficacy between SB17 and EU-Stelara appears to be comparable. See Section 6 for more information.

Table 11 Subgroup Analysis of Percent Change from Baseline in PASI at Week 12 by Overall ADA Statues (Per-protocol Set, Study SB14-3001)

Characteristics	Treatment	n	LSMeans (SE)	Difference (SB17−Stelara)	
				LSMeans (SE)	95% CI
Overall ADA up to Week 52					
Positive	SB17 (N = 40)	40	85.4 (3.99)	2.4 (3.14)	[−3.781, 8.646]
	Stelara (N = 104)	104	83.0 (3.22)		
Negative	SB17 (N = 199)	199	86.4 (3.59)	−2.2 (2.03)	[−6.194, 1.805]
	Stelara (N = 144)	144	88.6 (3.59)		
Inconclusive	SB17 (N = 4)	4	89.0 (0.00)	−19.2 (0.00)	[NE, NE]
	Stelara (N = 1)	1	108.3 (0.00)		

CI=confidence interval, LSMeans=least square mean, N=total number of patients in the Per-protocol Set in each treatment group, n=number of patients with available data at Week 12, NE=not estimable, PASI=psoriasis area and severity index, SE=standard error
Overall ADA positive up to Week 52 was defined positive for a patient with treatment-induced or treatment-boosted ADA, where treatment-induced ADA indicated at least one positive result by Week 52 after first IP administration at Week 0 for patients with negative ADA at baseline, and treatment-boosted ADA indicated at least positive result with higher titer level compared to baseline after first IP administration at Week 0 for patients with positive ADA at baseline.
Overall ADA negative up to Week 52 was defined negative for a patient with negative ADA at baseline and without positive ADA post-baseline by Week 52.
Overall ADA inconclusive up to Week 52 was defined for a patient with positive ADA at baseline and without positive result with higher titer level of observed post-baseline by Week 52
Source: Clinical Study Report, Table 17

Figure 5 Percent Change from Basline in PASI by Overall ADA Status up to Week 52



Source: Clinical Study Report SB17-3001, Figure 9

- Impact of immunogenicity on safety

In Study SB17-1001, the incidences of at least one treatment-emergent adverse event (TEAE) were comparable among three treatment groups (SB17, US-Stelara, and EU-Stelara) by post-dose ADA^+ subgroup (ranging from 56% to 57%) and post-dose ADA^- subgroup (ranging from 59% to 74%).

In Study SB17-3001, a total of 76 (52.1%) patients with overall ADA^+ status had any TEAE. The proportion of patients with any TEAE in the overall ADA^+ subgroup were comparable across the treatment groups (23 [56.1%] in the SB17, 53 [50.5%] in the Stelara Overall, 22 [45.8%] in the EU-Stelara+SB17, 27 [50.9%] in the Stelara+Stelara groups). A total of 189 (53.8%) patients with overall ADA^- status had any TEAE. The proportion of patients with any TEAE in the overall ADA^- subgroup was comparable across the treatment groups (106 [52.2%] in the SB17, 83 [56.1%] in the Stelara Overall, 39 [53.4%] in the EU-Stelara+SB17, and 41 [59.4%] in the Stelara+Stelara treatment groups).

Thus, the impact of immunogenicity on safety between SB17 and EU-Stelara appears to be comparable. Refer to Section 6 of this review for more information.

Authors:

Liping (Cindy) Pan, M.D., Ph.D. — Senior Staff Fellow

Chinmay Chinmay, Ph.D. — Senior Staff Fellow

6. Statistical and Clinical Evaluation and Recommendations

6.1. Statistical and Clinical Executive Summary and Recommendation

The statistical review evaluated SB17 as a potential biosimilar to EU-Stelara by focusing on the single 52-week randomized comparative clinical study, Study SB17-3001. Study SB17-3001 was a double-blind, parallel-group, multicenter study in 503 patients with moderate to severe Plaque Psoriasis, comparing SB17 to EU- Stelara. The Applicant provided adequate data to establish both the analytical and PK components (Refer to Section 5) of the scientific bridge to justify the relevance of data generated from the comparative clinical study SB17-1001, which used EU-Stelara as the comparator, for

the assessment of biosimilarity.

In Study SB17-3001, the primary endpoint was the percent change of baseline in Psoriasis Area and Severity Index (PASI) at Week 12. According to primary targeted estimand using the principal stratum strategy (Table 12), an estimated difference between SB17 and EU-Stelara was -0.69% (90% confidence interval [CI]: -3.33%, 1.95%). The 90% CI is within the similarity margin of ±10% that the Agency recommended. In a supportive analysis using the hypothetical strategy which incorporates missing data imputation, an estimated difference was -0.7% (90% CI: -3.34%, 1.93%), which was within the similarity margin of ±10%. Percent change in PASI other than Week 12, Physician's Global Assessment (PGA) score change, PASI50, PASI75, PASI90, and PASI100 response rate over time, in addition to change from baseline in Dermatology Life Quality Index (DLQL) were also evaluated and appeared to be comparable between the treatment arms.

There were five subjects who missed the assessment at Week 12 (three [1.2%] subjects in the SB17 arm and two [0.8%] subjects in the EU-Stelara arm). The statistical reviewer included a tipping point analysis to explore the sensitivity of the similarity test results to violations in assumptions about the missing data. Across the possible range of values in the missing subjects, confidence intervals for the differences between SB17 and EU-Stelara ruled out concerning losses in efficacy for the primary endpoint, percent change in PASI at Week 12.

The collective evidence from the comparative clinical study supports a demonstration of no clinically meaningful differences between SB17 and US-Stelara.

6.1.1. Statistical and Clinical Residual Uncertainties Assessment

During this statistical review, a few statistical issues arose. These issues have been adequately addressed through communications between the applicant and the reviewer. There are no residual uncertainties based on the statistical analyses.

The following outlines statistical issues encountered and the corresponding resolutions.

Similarity margin: Under the IND stage, the Agency recommended the use of similarity margin ±10% and 90% confidence level for assessing treatment difference in percent change from baseline in PASI at Week 12. However, in this BLA 761373, the applicant applied the similarity margin ±15% and 95% confidence level for the primary analysis to assess the treatment difference. Despite the lack of agreement on the similarity margin and confidence level, results from the primary analysis of the confirmatory study (90% CI: (-3.33%, 1.95%)), were contained within the ±10% margin that the Agency recommended.

Primary analysis set: The applicant used the per protocol set (PPS) for its primary analysis, which deviated from the applicant's pre-specified primary estimand using the full analysis set (FAS) (Table 12) of their SAP. The Agency informed this discrepancy to the applicant during the review and recommended to align with the intent-to-treat (ITT) principle. Following, the applicant replied that the analysis based on the FAS was included as a supplementary analysis. However, it was noted that the pre-specified estimand strategy using the FAS (e.g., principal strategy) considered drug efficacy in a subgroup where the intercurrent event (IE) did not occur: The defined IEs included early discontinuation from study on or before Week 12 due to reasons including war in Ukraine and missed assessment at Week 12 due to reasons including war in Ukraine. Considering ambiguity of the definition of IEs, the statistical reviewer regarded the data of IEs as missing data and conducted additional sensitivity analyses to assess the potential impact of the missing data. The results from the sensitivity analysis of the primary endpoint were consistent with those of the primary analysis, and supported a demonstration of no clinically meaningful differences between SB17 and EU-Stelara.

6.2. Review of Comparative Clinical Studies with Statistical Endpoints

6.2.1. STUDY SB17-3001

This statistical review evaluated the efficacy of SB17 to EU-Stelara demonstrated in study SB17-3001 in subjects with moderate to severe plaque psoriasis. The statistical reviewer confirmed the applicant's primary and key secondary analyses and performed

additional sensitivity analyses to evaluate the robustness of the results. The results from these supplemental analyses and the applicant's reproducible analyses are presented and described in the tables and figures in subsequent sections.

Data and Analysis Quality

There are no concerns regarding data quality and integrity.

Study Design and Endpoints

Study SB17-3001 was a randomized, double-blind, multicenter comparative clinical study to evaluate the efficacy, safety, tolerability, PK, and immunogenicity of SB17 compared to EU-Stelara in subjects with moderate to severe plaque psoriasis. Subjects were randomized in a 1:1 ratio to receive either SB17 or EU-Stelara via subcutaneous injection. Investigational products (IPs; SB17 or EU-Stelara) were administered at Week 0, 4, and then every 12 weeks up to Week 40, and the last assessment was done at Week 52. At Week 28, subjects who achieved a PASI50 response and were considered eligible entered into the transition period. In the transition period, subjects that received EU-Stelara were randomized again in a 1:1 ratio to either continue on EU-Stelara or transition to SB17 until Week 40. Subjects that received SB17 continued to receive SB17 until Week 40 but they followed the randomization procedure in order to maintain blinding. The Screening period was 4 weeks. IPs (SB17 or EU-Stelara) were administered until Week 40, and the last assessment was done at Week 52. This study was conducted at a total of 45 investigational sites across 8 countries (Czech Republic, Estonia, Hungary, Republic of Korea, Latvia, Lithuania, Poland, and Ukraine).

The primary objective of this study was to demonstrate the equivalence of SB17 to EU-Stelara, in terms of the percent change of baseline in Psoriasis Area and Severity Index (PASI) at Week 12 in subjects with moderate to severe plaque psoriasis.

Other efficacy endpoints included the percent change from baseline of PASI score other than Week 12, PASI50, PASI75, PASI90, and PASI100 response rate at Week 2, 4, 8, 12, 16, 20, 24, 28, 40 and 52, PGA scores at Week 2, 4, 8, 12, 16, 20, 24, 28, 40, and 52, and change from baseline in Dermatology Life Quality (DLQI) at Week 4, 12, 16, 28, 40, and 52. This study did not plan to apply statistical tests for the other efficacy endpoints.

Statistical Methodologies

Analysis Sets

For the primary analysis, the applicant used the per-protocol set (PPS), which deviated from the pre-specified primary estimand based on the full analysis set (FAS) (Table 12) in their SAP. The Agency noted this discrepancy to the applicant during the review and recommended the primary analysis to align with the pre-specified estimand using the FAS. In this review, the primary analysis was conducted using the FAS as pre-specified (Table 12) in the applicant's SAP.

The FAS consisted of all subjects who are randomized. Following the ITT principle, subjects were analyzed according to the treatment group they were assigned to at randomization. We note that the applicant modified the ITT population by excluding subjects who did not have any efficacy assessment result after randomization or did not receive IP during the study period from FAS.

The applicant defined the PPS consisted of all FAS subjects who had weight ≤ 100 kg and received 45 mg IP at Week 0 and Week 4 and had PASI assessment result at baseline and Week 12 without any major protocol deviations (PDs) that had impact on primary efficacy assessment. Major PDs that lead to exclusion from this set was pre-defined prior to unblinding the treatment group assignment for analyses. The major PDs which were applied as reasons for exclusion from the PPS is shown in Table 39 of Section 14.3.1.

Sample Size

The applicant used sample size of 384 patients (192 patients in each treatment group of SB17 and EU-Stelara) for ≥ 80% statistical power to demonstrate similarity of percent change in PASI at Week 12 based on the assumptions of common standard deviation of 31.33, similarity margin of (±10% to ±15%), and a two one-sided 5% significance level. The drop-out rate had been hypothesized at 10% and approximately 100 remainders per treatment group were assumed after transition at Week 28; therefore, approximately 464 patients (232 patients in each treatment group of SB17 and EU-Stelara) were planned to be randomized.

Estimand

The statistical analysis plan (SAP) and protocol included a description of the targeted estimand in this study (Table 12). For the primary estimand, the applicant proposed to handle intercurrent events (IEs) using a principal stratum strategy by taking the population to the principal stratum in which the IEs did not occur. For the supportive analysis, IEs would be handled using a hypothetical strategy with a Missing at Random (MAR) approach in which the missing values were replaced using multiple imputation method.

The applicant *modified* the intent to treat (ITT) population where subjects who did not have any efficacy assessment result after randomization or did not receive IP during the study period were excluded. The definition of IEs was not clear since it did not include how adverse events or death would be handled. Accordingly, the hypothetical situation was also not clearly defined to be used for the hypothetical strategy being employed in their supportive analysis. Considering ambiguity of the definition of IEs, principal stratum, and hypothetical situation, the statistical reviewer regarded the data with IEs as missing data and conducted additional sensitivity analyses to assess the potential impact of the missing data. The evidence from the sensitivity analysis supported a demonstration of no clinically meaningful differences between SB17 and EU-Stelara.

Table 12 Primary Estimand

Population	Randomized subjects who provided informed consent, have at least one efficacy assessment result after randomization and received IP during the study period.
Endpoint	Percent change from baseline in PASI at Week 12
Intercurrent events (IEs)	• Early discontinuation from study on or before Week 12 due to reasons including war in Ukraine • Missed assessment at Week 12 due to reasons including war in Ukraine

Intercurrent event handling strategy	• IEs will be handled using principal stratum strategy, since the target population is taken to the principal stratum in which those IEs would not occur. • For supportive analysis and sensitivity analysis, IEs will also be handled using the hypothetical strategy: Missing outcome at Week 12 will be imputed, using the Multiple imputation at Week 12. If a MAR pattern of missing data is detected, missing values will be replaced using a multiple imputation approach. • A sensitivity analysis would be conducted by excluding any subject which is impacted due to Ukraine war at Week 12 to assess the impact of war on Primary analysis.
Population-level summary measure	(adjusted) LSMeans difference of percent change from baseline in PASI at Week 12
Source: Study Report, p. 58 Abbreviation: IEs=Intercurrent events, IP=Investigational product, LSMeans=Least Squares Means, PASI=Psoriasis Area and Severity Index	

Analysis of the Primary Endpoint and Margin Selection

The primary efficacy analysis aimed to support a demonstration of no clinically meaningful differences between SB17 and EU-Stelara through an evaluation of the difference in percent changes of PASI between SB17 and EU-Stelara at Week 12. The applicant's primary analysis used the PPS and applied analysis of covariance model (ANCOVA) with the baseline value of PASI as a covariate and country and treatment groups as factors. The estimate for the difference in percent change of PASI at Week 12 and the two-sided 95% CI was reported using the pre- specified similarity margin was

15%. The applicant supported this margin choice based on meta-analysis with five[3][4][5][6][7] different studies which showed a treatment effect (Ustekinumab - placebo) of 70.96% with applying the retention rate of approximately 50% of the estimated treatment effect to derive their final margin ±15%.

Based on discussions with the Agency, including the BPD Type 2 Meeting on April 03, 2019, the applicant also calculated a 90% CI of the difference of the percent changes in PASI at Week 12, using both the PPS and FAS, and compared these intervals to a margin of ±10%. This margin 10% was recommended by the Agency based on the regulatory history of the previously approved biosimilar applications (e.g., Amjevita, Erelzi, and Hyrimoz) and recent literature in dermatology that noted some prescribing clinicians may require a more conservative margin than ±15% (e.g., Wan, MT, Strober, BE, Wu, JJ, Shin, DB, Gelfand, JM. How similar are the treatment responses to biosimilars in patients with psoriasis? A systematic review of statistical margins in comparative clinical trials. J Am Acad Dermatol 2017; 77: 569– 572).

The applicant's primary analysis using the PPS deviated from the pre-specified primary estimand (Table 12). The statistical reviewer conducted the primary analysis corresponding to the pre-specified primary estimand (e.g., the principal stratum strategy) under the FAS, using the ANCOVA with baseline value of PASI as a covariate

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[3] Leonardi CL, Kimball AB, Papp KA, et al. Efficacy and safety of ustekinumab, a human interleukin-12/23 monoclonal antibody, in patients with psoriasis: 76-week results from a randomized, double-blind, placebo-controlled trial. Lancet. 2008; 371 (9625): 1665-74.

[4] Papp KA, Langley RG, Lebwohl M, et al. Efficacy and safety of ustekinumab, a human interleukin-12/23 monoclonal antibody, in patients with psoriasis: 52-week results from a randomized, double-blind, placebo-controlled trial. Lancet. 2008; 371 (9625): 1675-84.

[5] Tsai TF, Ho JC, Song M, et al. Efficacy and safety of ustekinumab for the treatment of moderate-to-severe psoriasis: a phase III, randomised, placebo-controlled trial in Taiwanese and Korean patients. J Dermatol Sci. 2011; 63 (3): 154-63.

[6] Zhu X, Zheng M, Song M, et al. Efficacy and safety of ustekinumab in Chinese patients with moderate to severe plaque-type psoriasis: results from a phase 3 clinical trial. J Drugs Dermatol. 2013; 12 (2): 166-74.

[7] Igarashi A, Kato T, Kato M, et al. Efficacy and safety of ustekinumab in Japanese patients with moderate-to severe plaque-type psoriasis: long-term results from a phase 2/3 clinical trial. J Dermatol. 2012; 39 (3):242-52.

and country and treatment groups as factors with applying the 90% CI for the similarity margin ±10%.

Supplemental Analyses of the Primary Endpoint

The applicant performed supportive analyses of the primary endpoint based on the ANCOVA model with the baseline value of PASI as a covariate and country and treatment groups as factors, under the FAS for both available cases (subjects with non-missing primary endpoint) and multiple imputation (for missing values). The applicant reported that the 95% CIs of the difference between the two treatment groups in relation to the percent change from baseline in PASI under FAS were within applicant's pre-specified margin ±15%. Additionally, for sensitivity analyses, the applicant calculated the 90% CIs for the difference in percent change in PASI at Week 12 for the PPS, FAS with available cases, and FAS with multiple imputations and compared these CIs to the narrower margin of ±10%.

Assessing the Impact of Missing Data in the Primary Endpoint

The analyses for the primary endpoint, percent change in PASI at Week 12, used two different approaches for missing data. In the primary estimand analysis, no imputation was performed by the definition of the principal stratum strategy and intercurrent events (IEs). In the analysis for the supportive estimand, missing data due to the IEs were imputed and applied along with all observed data.

An approach to consider patients who have IEs (e.g., lack of efficacy, consent withdrawal, lost to follow-up, impact of Ukraine War, etc.), therefore have missing data for the FAS analysis is reasonable, but with such an approach, the primary endpoint is in fact a composite measure of treatment success. For example, the primary PASI percent change endpoint would be a composite measure that includes the following components: (1) remaining in the study through 12 weeks; and (2) achieving an PASI response at Week 12. The use of such a composite outcome combines the effects of treatment on adherence and signs and symptoms, so it is necessary to evaluate the impact of this missing data assumption on the overall treatment effect (e.g., an evaluation of the difference in percent change of PASI at Week 12 in all FAS patients regardless of treatment adherence or remaining in the study) in order to truly target the *de facto* estimand.

The applicant performed additional analysis using the FAS to assess the robustness of the results to the missing data, using multiple imputations with the assumption of monotone missing pattern and regression method for subjects who drop out for the study prior to the primary analysis time point (Week 12). During this review, the Agency expressed concerns with this supportive analysis through an information request letter sent out on July 11, 2023. The Agency indicated that this analysis would not sufficiently explore the potential effect that violations of the assumptions about missing data might have on the reliability of results. To further assess the robustness of the primary analysis results with regards to missing data, the Agency recommended that the applicant conduct additional tipping point sensitivity analyses in the FAS. These analyses should vary assumptions about outcomes among the subsets of patients on the two treatment arms who withdrew from the study early. These varying assumptions should include the possibility that patients with missing data on the SB17 arm had dissimilar outcomes than dropouts on the EU-Stelara arm. The goal of the tipping point analysis is to identify assumptions about the missing data under which the conclusions change, i.e., under which there is no longer evidence of similarity. The plausibility of those assumptions is discussed in Figure 9.

Based on this advice, to further assess the robustness of the primary analysis results in the FAS with regards to missing data, the applicant performed a tipping point analysis by imputing PASI change for the three patients from the SB17 treatment group and two patients from the EU-Stelara who discontinued prior to having an PASI assessment for Week 12 or missed the assessment at Week 12.

The statistical reviewer conducted a separate tipping point analysis and obtained consistent results with the applicant's tipping point analysis. The results from this analysis are presented graphically (Figure 8 and Figure 9) to identify the "tipping point" where a conclusion of similarity is lost based on a comparison of the 90% confidence interval to the ±10% margin. The details for this analysis are provided under subsection 'Potential Effects of Missing Data'.

Analyses of Secondary Endpoints

The secondary efficacy endpoints were percent change from baseline in Psoriasis Area and Severity (PASI), Physician's Global Assessment (PGA) score, PASI50, PASI75, PASI90, and PASI100 response rate, and change from baseline in Dermatology Life Quality Index (DLQL). The applicant provided summary statistics on

the secondary efficacy endpoints by treatment group and visit for the FAS and PPS, which were reproduced by the statistical reviewer.

For the continuous secondary endpoints, the statistical reviewer applied ANCOVA model with treatment group and country as factors and using the corresponding baseline value as a covariate. using the FAS. The binary and categorical secondary endpoints were analyzed using the FAS and Cochran-Mantel-Haenszel chi-squared test.

Subgroup Analyses

To examine the consistency of effect across subgroups for the PASI percent change, the statistical reviewer performed additional analyses by sex, age (<65, ≥ 65 years of age), race (White, Asian), country, use of prior treatment for psoriasis and use of prior biologic treatment. In these analyses, the reviewer calculated within each subgroup, the LSMeans within each treatment arm and the difference in the proportion of responders between treatment arms. These results are summarized in Table 21.

Subject Disposition

This study planned to include 464 total subjects. A total of 658 subjects were screened out of which 503 subjects were randomized (249 subjects to SB5 and 254 to EU-Stelara). Of the 503 subjects randomized, 481 (95.6%) completed Week 28 (SB17: 237 subjects, EU-Stelara: 244 subjects). The completion rate at Week 52 was comparable between the two treatment groups (SB17: 233 subjects, EU-Stelara Overall: 233 subjects).

Figure 6 shows the proportions of patients remaining in this study, indicating similar trends on both arms. The proportions of patients withdrawing early from the study and

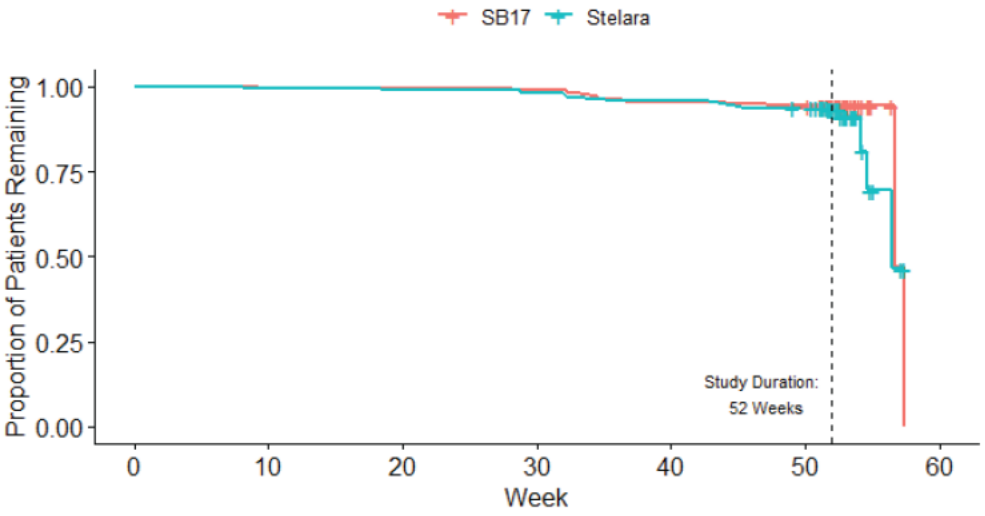
the distributions of reasons for dropout were largely similar between SB17 and EU-Stelara in the study. The most common reason for dropout was “War in Ukraine”, representing 13 subjects from Week 0 to Week 28 and 8 subjects from Week 28 to Week 52. From Week 0 to Week 28, there was not much difference in dropout between SB17 and EU-Stelara overall (SB17: 4.8%, EU-Stelara: 3.9%). From Week 28 to Week 52, there was slightly lower dropout due to impact of Ukraine War on SB17 (1.7%) than EU-Stelara (4.5%).

Table 13 Disposition of Subjects

	SB17 n (%)	**EU-Stelara n (%)**		**Overall n (%)**
Randomized	249	254		503
Completed Week 28	237 (95.2)	244 (96.1)		481 (95.6)
Discontinued from study by Week 28	12 (4.8)	10 (3.9)		22 (4.4)
Consent withdrawal by subjects	2 (0.8)	4 (1.6)		6 (1.2)
Lack of efficacy	1 (0.4)	0 (0)		1 (0.2)
Subject lost to follow-up	0 (0)	1 (0.4)		1 (0.2)
War in Ukraine	8 (3.2)	5 (2)		13 (2.6)
Protocol violation	1 (0.4)	0 (0)		1 (0.2)
	SB17 n (%)	**EU-Stelara+ SB17 n (%)**	**EU-Stelara+ EU-Stelara n (%)**	**Overall n (%)**
Re-randomized at Week 28	237	122	122	481
Completed Week 52[1]	233 (98.3)	117 (95.9)	116 (95.1)	466 (96.9)
Discontinued from study Week 28 to Week 52[1]	4 (1.7)	5 (4.1)	6 (4.9)	15 (3.1)
Adverse event[1]	0 (0)	0 (0)	2 (1.6)	2 (0.4)
Consent withdrawal by subjects[1]	0 (0)	2 (1.6)	0 (0)	2 (0.4)
War in Ukraine[1]	2 (0.8)	2 (1.6)	4 (3.3)	8 (1.6)
Other[1]	1 (0.45)	0 (0)	0 (0)	1 (0.2)
Subject lost to follow-up[1]	1 (0.45)	1 (0.9)	0 (0)	2 (0.4)

Source: Reviewer
Counts (percentages relative to randomized) are presented.
[1]Counts and percentages after week 28, were computed relative to the re-randomized set.

Figure 6 Kaplan-Meier Estimates for Time in Study by Treatment Group



Source: Reviewer
Based on all randomized subjects (treatment assignments are from first randomization). Event at time of study discontinuation, censored at time of study completion.

A summary including number and proportion of subjects with PDs and number of subjects having at least one major PD by analysis set and treatment group is presented in Table 14. Within a randomized set (and a full analysis set), a total of 262 (52.1%) subjects had PDs and 253 (50.3%) subjects had at least one major PD. Eleven subjects had major PDs which led to exclusion from the PPS (related to study procedures in 6 subjects, followed by exclusion criteria in 4 subjects and IP compliance in 1 subject. See detailed information in Table 38. It was noted that within a per-protocol set, a total of 251 (51.0%) subjects had PDs and 242 (49.2%) subjects had at least one major PD. See detailed information about the excluded subject IDs and the major PDs which led to exclusion from the PPS in Section 14.4.1.

Table 14 Protocol Deviations by Treatment Group

	SB17 n (%)	Stelara n (%)	Overall n (%)
Randomized set	249 (100.0)	254 (100.0)	503 (100.0)
At least one PD	126 (50.6)	136 (53.5)	262 (52.1)
At least one major PD	123 (49.4)	130 (51.2)	253 (50.3)
Full Analysis set	249 (100.0)	254 (100)	503 (100.0)
At least one PD	126 (50.6)	136 (53.5)	262 (52.1)
At least one major PD	123 (49.4)	130 (51.2)	253 (50.3)
Per-protocol set	243 (100.0)	249 (100)	492 (100.0)
At least one PD	120 (49.4)	131 (52.6)	251 (51.0)
At least one major PD	117 (48.1)	125 (50.2)	242 (49.2)

Source: Reviewer and Study Report, p. 68
Percentages were based on the number of subjects in each analysis set.

Demographics and Baseline Characteristics

There were no large imbalances in the distributions of baseline demographics (Table 15) across the treatment arms. The population study was very homogeneous, raising some concern of generalizability, with the majority of subjects Gender: male (62%), Race: white (98.8%), and Ethnicity: other (98.6%). The most subjects were studied in Poland (48.3%) and none of the sites were in the United States. The average age (44 years) and body mass index (27 kg/m^2) were also similar across treatment arms.

Similarly, there were no large imbalances in the distributions of baseline disease characteristics (Table 16) across the treatment arms. The average psoriasis disease duration was 15.6 years. The average total psoriasis BSA involvement was 27%; the average percentage of prior psoriasis topical treatment approximately was 93% and the use of prior biologic treatment was approximately 7% in both arms.

The use of prior treatment for psoriasis was slightly lower in the SB17 arm (47% vs. 52%), while the history of psoriatic arthritis slightly higher in the SB17 arm (26% vs. 21%). Otherwise, similar baseline measures for the PASI, distribution of PGA score, and DLQI were observed across the treatment groups.

Table 15 Baseline Demographics of All Randomized Subjects

	SB17	EU-Stelara	Overall
Randomized	249	254	503
Age (years), Mean (SD)	44.0 (13.2)	44.3 (12.4)	44.2 (12.8)
Gender, Male n (%)	150 (60.2)	162 (63.8)	312 (62.0)
Childbearing Potential, n (%)			
Yes	57 (22.9)	59 (23.2)	116 (23.1)
No	42 (16.9)	33 (13.0)	75 (14.9)
Not Applicable (Male)	150 (60.2)	162 (63.8)	312 (62.0)
Race, n (%)			
Asian	2 (0.8)	4 (1.6)	6 (1.2)
White	247 (99.2)	250 (98.4)	497 (98.8)
Country, n (%)			
Czech Republic	26 (10.4)	25 (9.8)	51 (10.1)
Estonia	10 (4.0)	12 (4.7)	22 (4.4)
Hungary	2 (0.8)	3 (1.2)	5 (1.0)
Korea	2 (0.8)	4 (1.6)	6 (1.2)
Lithuania	14 (5.6)	14 (5.5)	28 (5.6)
Latvia	0 (0.0)	2 (0.8)	2 (0.4)
Poland	122 (49.0)	121 (47.6)	243 (48.3)
Ukraine	73 (29.3)	73 (28.7)	146 (29.0)
Ethnicity, n (%)			
Korean	2 (0.8)	4 (1.6)	6 (1.2)
Mixed Ethnicity	0 (0.0)	1 (0.4)	1 (0.2)
Other	247 (99.2)	249 (98.0)	496 (98.6)
Weight (kg), Mean (SD)	80.72 (11.8)	79.91 (12.0)	80.31 (11.9)
BMI (kg/m^2), Mean (SD)	27.24 (3.9)	26.76 (3.7)	27.00 (3.80)

Source: Reviewer
Counts (percentages relative to randomized) or means (standard deviation) are presented.

Table 16 Baseline Disease Characteristics for All Randomized

	SB17	EU-Stelara	Overall
Randomized	249	254	503
Duration of psoriasis (years), Mean (SD)	15.0 (11.4)	16.1(11.9)	15.6 (11.6)
Total psoriasis BSA involvement (%), Mean (SD)	27.3 (13.5)	26.7 (13.8)	27.0 (13.6)
PASI at baseline, Mean (SD)	22.5 (7.8)	22.1 (7.7)	22.2 (7.7)
PGA Score, n (%)			
Score 3	157 (63.1)	160 (63.0)	317 (63.0)
Score 4	68 (27.3)	75 (29.5)	145 (28.8)
Score 5	24 (9.6)	19 (7.5)	43 (8.5)
DLQI at baseline, Mean (SD)	13.4 (7.2)	13.2 (6.96)	13.3 (7.09)
Use of prior psoriasis topical treatment, n (%)			
Yes	232 (93.2)	234 (92.1)	466 (92.6)
No	17 (6.8)	20 (7.9)	37 (7.4)
Use of prior treatment for psoriasis, n (%)			
Yes	117 (47.0)	133 (52.4)	250 (49.7)
No	132 (53.0)	121 (47.6)	253 (50.3)
Use of prior biologic treatment, n (%)			
Yes	17 (6.8)	19 (7.5)	36 (7.2)
No	232 (93.2)	235 (92.5)	467 (92.8)
History of psoriatic arthritis, n (%)			
Yes	64 (25.7)	54 (21.3)	118 (23.5)
No	185 (74.3)	200 (78.7)	385 (76.5)

Source: Reviewer
Abbreviation: BSA=Body surface area, DLQI=Dermatology Life Quality, PASI=Psoriasis Area and Severity, PGA=Physician's Global Assessment, SD=Standard deviation
Counts (percentages relative to randomized) or means (standard deviation) are presented.

Analysis of Primary Clinical Endpoint(s)

The primary efficacy endpoint was the percent improvement in PASI from baseline to Week 12. In this review, the primary analysis was conducted based on the FAS corresponding to Table 12. The total number of subjects in the FAS was 503 (249 for SB17 and 254 for EU-Stelara). Within the FAS, five subjects (three randomized to SB17 and two randomized to EU-Stelara) experienced Intercurrent events (IEs) resulting in no data available at Week 12. (See details in Table 18).

For the primary estimand, the IEs were handled using the principal stratum strategy, in which the subjects who experienced no IEs were included in the primary analysis. For the supportive estimand, the hypothetical strategy was applied where a multiple imputation method was employed to handle the missing data.

The treatment difference was estimated using ANCOVA with the baseline value of PASI as a covariate and country and treatment groups as factors. Two-sided 90% confidence intervals for the treatment difference were calculated using least squares means (LSMeans) and compared to margins of ±10%. Table 17 displays the results for the primary clinical endpoint, the percent change in PASI from baseline to Week 12. In the primary estimand analysis, of the subjects who did not have IEs, subjects randomized to SB17 had LSMean 85.7% change in PASI from baseline at Week 12 and subjects randomized to EU-Stelara had LSMean 86.3% change in PASI, for an estimated difference between treatments of -0.69% (90% CI: (-3.33%, 1.95%)). In the supportive estimand analysis, with the imputed dataset for the five subjects who had missing data, subjects had 85.7% change in PASI on the SB17 treatment arm and 86.4% change on the EU-Stelara arm at Week 12 (90% CI: (−3.34%, 1.93%)). The 90% CIs calculated using each analysis ruled out the margin of ±10%, that the Agency has determined.

Table 17 Difference in Percent Change of PASI from Baseline to Week 12

	Estimand Strategy	LSMeans, % (SE)		Difference, % LSMeans (SE)	Difference, % 90% CI
		SB17	EU-Stelara		
Primary Analysis	Principal stratum strategy[1]	85.7 (2.42)	86.3 (2.31)	-0.69	(-3.33, 1.95)
Supportive Analysis	Hypothetical strategy[2]	85.7 (2.43)	86.4 (2.32)	-0.7	(−3.34, 1.93)
Source: Reviewer and Study Report p75 and p76					

Abbreviations: LSMeans=least square means, SE=standard error, CI=confidence interval
Inferential statistics for percent change from baseline in PASI at Week 12 are based on analysis of covariance model with the baseline value of PASI as a covariate and country and treatment groups as factors.
[1]According to the principal stratum strategy, within FAS, subjects who did not experience IEs were included in the analysis.
[2]According to the hypothetical strategy, a multiple imputation method was used for the missing data.

Potential Effects of Missing Data

In the FAS, there were five subjects who did not have data at Week 12, all of which had IEs. Table 18 shows the disposition of missing observations at Week 12: withdrew from the study early (1), had protocol violation (1), had missing data at Week 12 (2), or was impacted by the war in Ukraine (1). For the primary analysis, the IEs were handled through the principal stratum strategy in which subjects who did not have IEs were only included. This approach could confound treatment differences in IE occurrence and PASI response, requiring further investigation of the missing data assumption. Also, in the supportive estimand analysis, the applicant assumed the monotone missing pattern for the missing data imputation, which requires sensitivity analyses to explore the effect of violations in assumptions about the missing data for the reliability of the results.

Although the amount of missing data was low, the statistical reviewer performed a tipping point analysis to assess the potential impact of assumptions about the missing data and to identify scenarios where altering these assumptions would lead to a change in conclusions, using multiple imputation method[6].

Figure 7 show the results from this analysis for the comparison of SB17 to EU-Stelara. In the figure, the horizontal axes show the postulated shift in the mean PASI change of the missing subjects compared to the non-missing subjects on the SB17 arm. The vertical axes correspond to the same values for the EU-Stelara arm. The black triangle indicates treatment difference in PASI percent change at Week 12 in the observed population on the SB17 and EU-Stelara arms, ignoring missingness. The yellow portion of the plot indicates areas where the 90% confidence interval is entirely contained within the ±10% margin, the orange portion indicates an upper confidence bound greater than 10% (favoring SB17), the red portion indicates an upper confidence bound greater than 10% (the applicant's margin, favoring SB17), the green portion indicates a lower confidence bound less than 10% (favoring Stelara), the blue portion indicates a lower

confidence bound greater than 15% (the applicant's margin, favoring Stelara). Within the ranges we investigated, there was no areas that both upper and lower bounds out of the margin at the same time. Numbers on diagonal lines indicate differences in the PASI percent change from baseline at Week 12 between SB17 and EU-Stelara, with including the imputed data.

Figure 7 varied the estimated shift in mean change from baseline in PASI in the missing subjects compared to the observed subjects on each arm from -60 to 60. This analysis indicates that large decreases in efficacy (i.e., 55 units) on SB17 compared to EU-Stelara can be ruled out, unless there is an assumption of much worse outcomes (50 units) on the SB17 arm and much better outcomes (50 units) on the EU-Stelara among the missing compared to the observed. This is evidenced by the large amount of yellow on the plot and small amount of green/orange. The tipping points for ruling out equivalence require large differences between response in the dropouts on each arm. These large differences in PASI change across arms (e.g., >100 unit) seem implausible, given the distribution of PASI change on each arm (Figure 8). These tipping point analysis was consistent with the applicant's tipping point analysis and provides further support for the conclusions on the primary efficacy endpoints.

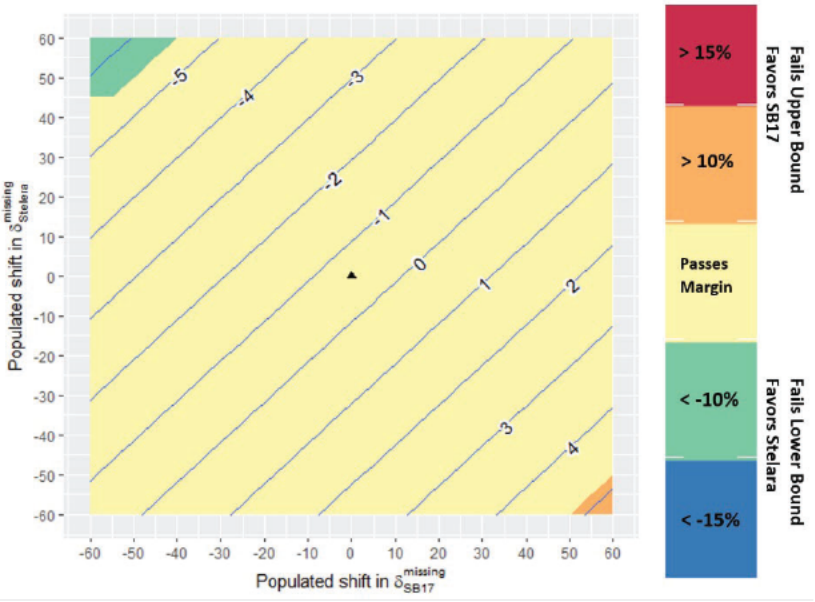
Table 18 Disposition and Missing Data in Full Analysis Set

	SB17 (N=249)	EU-Stelara (N=254)	Total (N=503)
Number of subjects with Week 12 data, n (%)	246 (98.8)	252 (99.2)	498 (99)
Completed all assessments	222	224	446
Missed at least one Assessment[1]	9	9	18
Discontinued the study	15	19	34
Adverse event	0	2	2

Consent withdrawal by subject	2	5	7
Lack of efficacy	1	0	1
Lost to follow-up	1	2	3
Other	11	10	21
Number of subjects without Week 12 data[2], n (%)	3 (1.2)	2 (0.8)	5 (1)
Missed assessment at Week 12	2	0	2
Discontinued the study	1	2	3
Protocol violation	1	0	1
Consent withdrawal by subject	0	1	1
Other	0	1	1

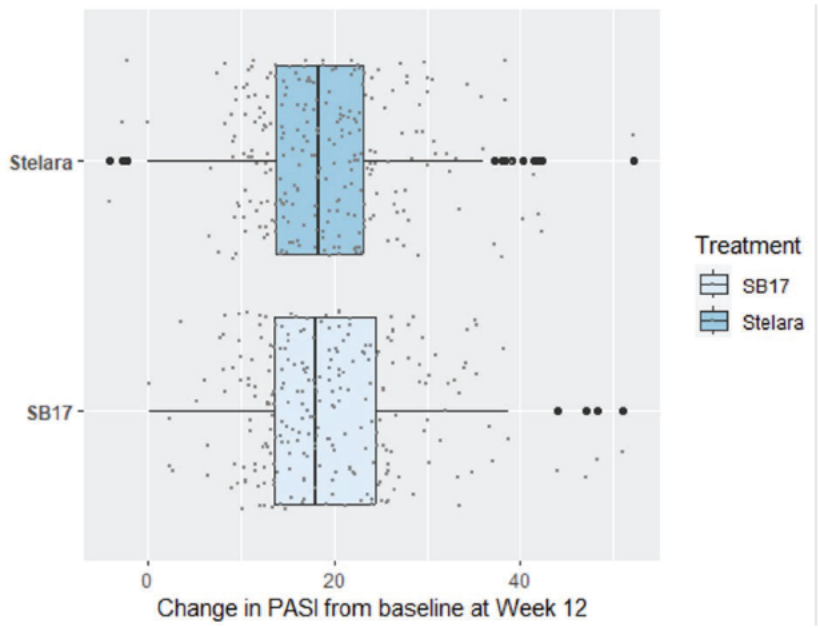
Source: Reviewer
[1]Missed at least one assessment at 2, 4, 8, 16, 20, 24, 28, 40, or 52 Week but completed the study.
[2]All subjects who missed Week 12 had intercurrent events defined in Table 12.

Figure 7 Tipping Point Analysis of Percent Change in PASI from baseline at Week 12 (90% Confidence Interval) in Full Analysis Set



Source: Reviewer
Numbers on diagonal lines indicate estimated treatment differences in PASI percent change between SB17 and EU-Stelera in all subjects, including those who have missing data.
The black triangle is the estimated treatment differences in PASI percent change using observed data only based on ANOVA with the baseline value of PASI as a covariate and country and treatment groups as factors.

Figure 8 Box Plots for Change in PASI at Week 12 in Full Analysis Set



Source: Reviewer
Summary statistics of PASI change at Week12 for SB17 arm: minimum=0.20, median=18.05, mean=19.45, maximum=51.00
Summary statistics of PASI change at Week12 for Stelara arm: minimum=-4.0, median=18.40, mean=19.24, maximum=52.20
No imputation was used. Jittered dots represent all observed data.

Analysis of Secondary Clinical Endpoint(s)

The secondary efficacy endpoints were percent change from baseline in Psoriasis Area and Severity (PASI), Physician's Global Assessment (PGA) score, PASI50, PASI75, PASI90, and PASI100 response rate, percent change from baseline in PASI, and change from baseline in Dermatology Life Quality Index (DLQL). The applicant provided summary statistics on the secondary efficacy endpoints by treatment group and visit for the FAS and PPS, which were reproduced by the statistical reviewer. For the analysis of secondary clinical endpoints, the continuous secondary endpoints were analyzed using the FAS and an ANCOVA model with treatment group and country as factors and using the corresponding baseline value as a covariate. The binary and categorical secondary endpoints were analyzed using the FAS and Cochran-Mantel-Haenszel chi-squared test.

Percent Change from baseline in PASI at Week 2, 4, 8, 16, 20, 24, 28, 40 and 52

The ANCOVA model with adjusting treatment group and country as factors and using the corresponding baseline value as a covariate was performed for the percent change in PASI other than Week 12 for the FAS. For evaluation of the treatment difference between SB17 and EU-Stelara, the least squares difference, standard error, and two-sided 95% confidence interval were reported in Table 19. The analysis of these continuous endpoints uses the FAS with an observed data (available cases only) analysis. At every week, percent change from baseline in PASI were similar and the confidence intervals were appropriately small for SB17 and EU-Stelara. For each analysis, the difference between SB17 and EU-Stelara was less than 2%. The time-response curve (Figure 9) is similar between the treatment groups supporting the robustness of the primary efficacy analysis.

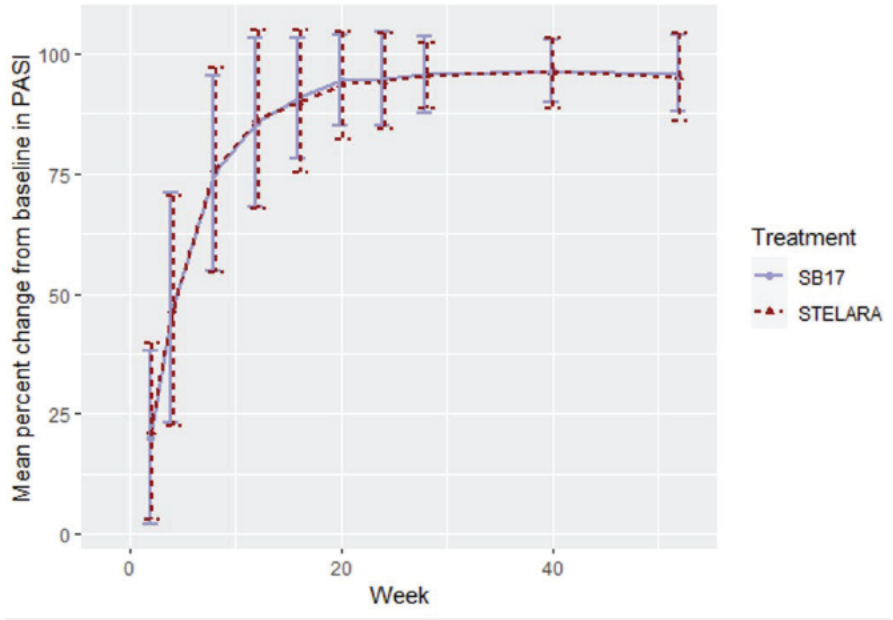
Table 19 Percent Change from baseline in PASI at Week 2, 4, 8, 16, 20, 24, 28, 40 and 52 in Full Analysis Set

	SB17		EU-Stelara		
	N[1]	LSMeans[2] (SE)	N[1]	LSMeans[2] (SE)	Difference in LSMeans[2] (95% CI)[2]
Week 2	249	18.2 (2.40)	254	19.7 (2.29)	-1.51 (-4.61, 1.60)
Week 4	249	44.0 (3.12)	254	43.7 (2.99)	0.31 (-3.74, 4.35)
Week 8	248	75.4 (2.74)	253	76.1 (2.62)	-0.70 (-4.26, 2.85)
Week 16	244	90.2 (1.84)	249	89.5 (1.76)	0.74 (-1.67, 3.14)
Week 20	231	93.2 (1.40)	242	92.2 (1.34)	0.99 (-0.87, 2.85)
Week 24	235	94.6 (1.32)	244	93.9 (1.26)	0.67 (1.08, 2.42)
Week 28	238	94.7 (0.99)	245	94.6 (0.95)	0.19 (-1.12, 1.50)
Week 40	235	94.3 (0.90)	240	94.0 (0.86)	0.32 (-0.88, 1.51)
Week 52	233	94.0 (1.12)	235	93.3 (1.07)	0.70 (-0.80, 2.20)

Source: Reviewer
Abbreviations: LSMeans=Least square means, SE=standard error, CI=confidence interval
[1]Number of subjects with complete data included in analysis
[2]LS means, standard errors, difference, and confidence intervals calculated from analysis of covariance model with treatment group and country as factors and corresponding baseline value as a covariate.

The Stelara treatment group was re-randomized at Week 28 in a 1:1 ratio to switch to SB17 (Stelara+SB17) or continue to receive Stelara (Stelara+Stelara).

Figure 9 Mean Percent Change in PASI over Time in Full Analysis Set



Source: Reviewer
Vertical Error bars show standard deviation of percent change in PASI in each week. Subjects with complete data were included. The EU-Stelara treatment group was re-randomized at Week 28 in a 1:1 ratio to switch to SB17 (EU-Stelara+SB17) or continue to receive EU-Stelara (Stelara+Stelara).

Change from baseline in DLQL at Week 4, 12, 16, 28, 40, and 52

At every week, percent change from baseline in DLQL_were similar and the confidence intervals were appropriately small for SB17 and EU-Stelara, using FAS

(Table 20). For each analysis, the difference between SB17 and EU-Stelara was less than 0.5.

Table 20 Change from baseline in DLQL at Week 4, 12, 16, 28, 40, and 52 in Full Analysis Set

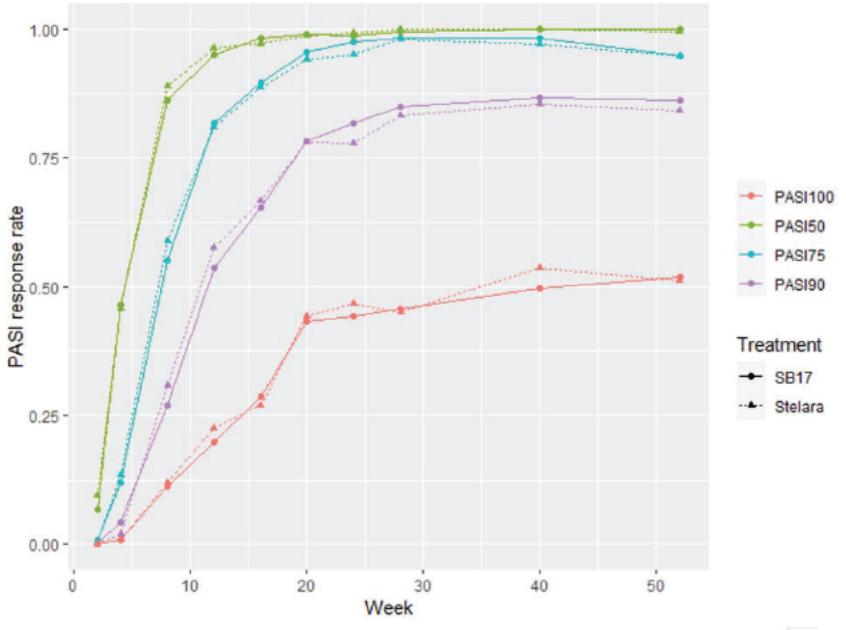
	SB17		EU-Stelara		
	N[1]	LSMeans[2] (SE)	N[1]	LSMeans[2] (SE)	Difference in LSMeans[2] (95% CI)[2]
Week 4	247	5.24 (0.59)	254	4.90 (0.56)	0.34 (-0.43, 1.11)
Week 12	246	9.74 (0.51)	252	9.76 (0.49)	-0.02 (-0.69, 0.66)
Week 16	244	10.3 (0.56)	249	10.0 (0.53)	0.31 (-0.42, 1.04)
Week 28	238	11.3 (0.48)	247	11.2 (0.46)	0.08 (-0.55, 0.72)
Week 40	235	11.4 (0.43)	240	11.4 (0.41)	-0.06 (-0.63, 0.51)
Week 52	233	11.6 (0.44)	235	11.5 (0.42)	0.02 (-0.58, 0.62)

Source: Reviewer
Abbreviations: LSMeans=Least square means, SE=standard error, CI=confidence interval
[1]Number of subjects with complete data included in analysis.
[2]LS means, standard errors, difference, and confidence intervals calculated from analysis of covariance model with treatment group and country as factors and corresponding baseline value as a covariate.
The EU-Stelara treatment group was re-randomized at Week 28 in a 1:1 ratio to switch to SB17 (EU-Stelara+SB17) or continue to receive EU-Stelara (Stelara+Stelara).

PASI50, PASI75, PASI90, and PASI100 response rate at Week 2, 4, 8, 12, 16, 20, 24, 28, 40 and 52

The proportion of patients with PASI50, PASI75, PASI90, and PASI100 response over time were similar across treatment arms (Figure 10). The statistical reviewer performed a Cochran-Mantel-Haenszel chi-squared test. There was no evidence of association between the treatment and PASI response rate, while taking into account the week as a stratification factor (p-value = 0.515 for PASI50, p-value = 0.815 for PASI75, p-value = 0.851 PASI90 and p-value = 0.578 PASI100).

Figure 10 PASI50, PASI75, PASI90, and PASI100 Responses over Time in Full Analysis Set

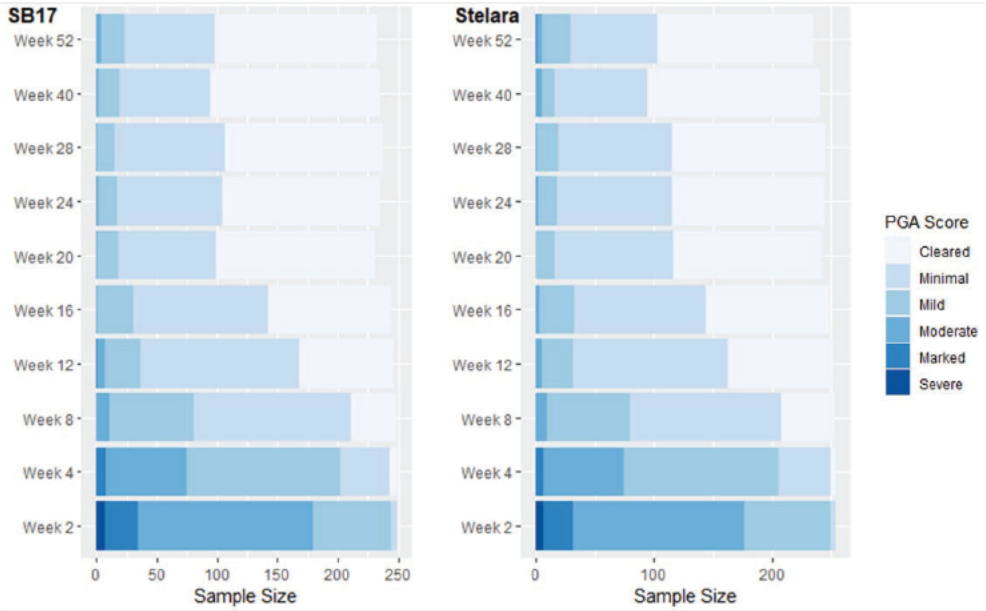


Source: Reviewer
Abbreviations: PASI=Psoriasis Area and Severity Index, PASI50=50% improvement of PASI score from baseline, PASI75=75% improvement of PASI score from baseline, PASI90=90% improvement of PASI score from baseline, PASI100=100% improvement of PASI score from baseline
Subjects with complete data were included. The EU-Stelara treatment group was re-randomized at Week 28 in a 1:1 ratio to switch to SB17 (EU-Stelara+SB17) or continue to receive EU-Stelara (Stelara+Stelara).

PGA score at Week 2, 4, 8, 12, 16, 20, 24, 28, 40, and 52

The Cochran-Mantel-Haenszel chi-squared test showed there was no evidence of association between the treatment and PGA score, while taking into account the week as a stratification factor (*p*-value = 0.979).

Figure 11 PGA score at Week 2, 4, 8, 12, 16, 20, 24, 28, 40, and 52 in Full Analysis Set



Source: Reviewer
Abbreviations: PGA=Physician's Global AssessmentSubjects with complete data were included.
The EU-Stelara treatment group was re-randomized at Week 28 in a 1:1 ratio to switch to SB17 (EU-Stelara+SB17) or continue to receive EU-Stelara (Stelara+Stelara).

Other Clinical Endpoints

Subgroup Analyses

The subgroup analyses compared PASI percent change efficacy results across treatment arms within different subgroups defined by sex, age, region, race, use of prior treatment for psoriasis and use of prior biologic treatment. Table 21 shows these results for the primary endpoint (percent change in PASI at Week 12) comparing SB17 vs. EU-Stelara within the confirmatory study. As would be expected, there was considerable heterogeneity in the estimated differences between SB17 and EU-Stelara across the subgroups with very small size. However, estimated differences were largely centered around similarity for the subgroups with sufficient sample size, and there were no

striking trends. The number of subjects located in Latvia (country) was too small and isolated to the EU-Stelara group, making it impossible to calculate sufficiently reliable estimates for the treatment effects, though we provide the tabulation of least square mean percent change in PASI within each subgroup. In general, Table 21 indicates the subgroup efficacy results were comparable to the overall sample results.

Table 21 Subgroup Analyses in Study SB17-3001 (Difference in Percent Change in PASI at Week 12 for SB17 vs. EU-Stelara)

	SB17		EU-Stelara		Difference	
	N[1]	LSMean[2] (SE)	N[1]	LSMean[2] (SE)	LSMeean[2] (SE)	90% CI[2]
All patients	246	85.7 (2.42)	252	86.3 (2.31)	-0.69	(-3.33, 1.95)
Sex						
Male	147	82.5 (2.79)	161	84.9 (2.65)	-2.46 (1.98)	(-5.72, 0.81)
Female	99	88.4 (3.24)	91	85.7 (3.13)	2.69 (2.75)	(-1.85, 7.23)
Age						
≤65 years	234	85.3 (2.92)	236	85.4 (2.84)	-0.11 (1.63)	(-2.8, 2.58)
>65 years	12	79.7 (6.13)	16	80.9 (5.05)	-1.19 (5.97)	(-11.5, 9.11)
Country[3]						
Czech Republic	26	84.4 (3.27)	25	78.6 (3.34)	5.84 (4.7)	(-2.04, 13.7)
Estonia	10	94.5 (3.45)	12	91.6 (3.15)	2.82 (4.68)	(-5.28, 10.9)
Poland	119	86.8 (1.54)	120	87.9 (1.54)	-1.05 (2.18)	(-4.65, 2.55)
Ukraine	73	84.0 (2.50)	72	86.5 (2.51)	-2.48 (3.58)	(-8.34, 3.39)
Hungary	2	67.9 (3.53)	3	103.7 (2.48)	-35.7 (5.63)	(-52.2, -19.3)
Korea	2	67.9 (9.43)	4	70.0 (5.89)	-2.15 (12.8)	(-32.2, 27.9)
Lithuania	14	82.8 (3.52)	14	84.4 (3.52)	-1.68 (5)	(-10.2, 6.86)
Latvia	0	-	2	-	-	-
Race						
Asian	2	67.9 (9.43)	4	70.0 (5.89)	-2.15 (12.8)	(-32.2, 27.9)
White	244	87.9 (2.51)	248	88.5 (2.41)	-0.67 (1.62)	(-3.33, 2)
Use of prior treatment for psoriasis						
Yes	116	85.7 (2.54)	132	86.7 (2.37)	-1.01 (2.35)	(-4.89, 2.88)
No	130	83.6 (3.68)	120	83.7 (3.47)	-0.12 (2.28)	(-3.88, 3.64)
Use of prior biologic treatment						

Yes	17	87.3 (3.8)	19	89.6 (4.08)	-2.3 (4.37)	(-9.72, 5.12)
No	229	85.8 (2.51)	233	86.2 (2.38)	-0.38 (1.69)	(-3.17, 2.4)

Source: Reviewer
Abbreviations: LSMeans=Least square means, SE=standard error, CI=confidence interval
[1]Number of subjects with complete data included in analysis.
[2]LS means, standard errors, difference, and confidence intervals calculated from analysis of covariance model with treatment group and country as factors and corresponding baseline value as a covariate.
[3]Subgroup analysis for country is based on analysis of covariance model with treatment group as factors and corresponding baseline value as a covariate.

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Authors:

Junghi Kim, PhD — Clinical Statistical Reviewer

Jessica Kim, PhD — Clinical Statistics Team Leader

6.3. Review of Safety Data

6.3.1. Methods

To evaluate comparative safety, adverse events, laboratory examination, vital signs, hypersensitivity, and immunogenicity were reviewed. The primary safety evaluation is based on a single comparative clinical study, SB17-3001, 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 SB17 in order to assess for potential safety issues from the transition. In addition, safety data from the PK comparability study (SB17-1001) in healthy volunteers were reviewed as supportive of the primary safety assessment.

Clinical Studies Used to Evaluate Safety

The Applicant collected safety data from two clinical studies, as listed in Section 2.2 and summarized below. In the two studies, subjects received at least one SC dose of either SB17, US-Stelara, or EU-Stelara. The primary saety data was derived from the conduct of Study SB17-3001.

In the PK similarity study (SB17-1001), a total of 201 subjects received a single dose of 45 mg SC of either SB17 (67 subjects), US-Stelara (67 subjects) or EU-Stelara (67 subjects) with a follow-up period of 14 weeks (99 days). This study was conducted in healthy subjects and had limited follow-up. Therefore, only limited safety information could be obtained from this study and are not captured in this review.

The primary safety data was derived from the comparative clinical study SB17-3001, which was conducted in two periods. See Figure 1 for the study schema. In the first stage, 503 subjects were randomized in a 1:1 ratio to either SB17 (249 subjects) or EU-Stelara (25 subjects). Subjects were administered SB17 or Stelara 45 mg at Week 0, Week 4, followed by every 12 weeks up to Week 40. If the subject gained weight and became > 100 kg in subsequent dosing visits the subject received two doses of 45 mg (total of 90 mg). The primary efficacy endpoint (PASI percent improvement from baseline) was evaluated at Week 12.

At Week 28, subjects who achieved PASI50 response and were considered eligible entered into the transition period. In the transition period, subjects that received EU-Stelara were randomized again in a 1:1 ratio to either continue on EU-Stelara (EU-Stelara to EU-Stelara; 122 subjects) or were transitioned to SB17 (EU-Stelara to SB17; 122 subjects), until Week 40. Subjects that received SB17 continued to receive SB17 (237 subject) until Week 40, but they followed the randomization procedure in order to maintain blinding.

The primary safety analysis set (SAF1) consisted of all subjects who received at least one dose of the investigational product during the study period. The Safety Set 2 (SAF2) consisted of all subjects in the SAF1 who received at least one dose of the investigational product after re-randomization at Week 28. Subjects were analyzed according to the IP received. As a result, of the 503 subjects randomized, a total of 503 (100.0%) subjects were included in the SAF1 and 481 (95.6%) subjects were included in the SAF2.

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

Categorization of Adverse Events

An adverse event (AE) was defined as any untoward medical occurrence in a subject administered the medicinal (investigational) product or other protocol-imposed

intervention and which did not necessarily have to have a causal relationship with this treatment or intervention.

A serious AE (SAE) was defined as any untoward medical occurrence that met at least 1 of the following serious criteria:

- Resulted in death.
- Was life-threatening (refers to an event in which the subject was at risk of death at the time of the event. It does not refer to an event that hypothetically might have caused death if it were more severe).
- Required inpatient hospitalization or prolongation of existing hospitalization.
- Resulted in persistent or significant disability/incapacity.
- Resulted in congenital anomaly/birth defect.
- Was medically important.

A treatment-emergent adverse event (TEAE) was defined as any adverse event (AE) that emerged during treatment with an investigational product.

Adverse events of specific interest (AESIs) were defined based on the known risks associated with treatment with US-Stelara and other IL-12 and -23 antagonists including systemic hypersensitivity, infections, pulmonary events, and injection site reactions.

Safety Analyses

6.3.2. Major Safety Results

Relevant Characteristics of the Population Evaluated for Safety

Table 22: Population Demographics of Study SB17-3001

Characteristic	SB17 (N=249)	EU-Stelara (N=254)	Total (N=503)
Sex, n (%)			
F	99 (39.8)	92 (36.2)	191 (38.0)
M	150 (60.2)	162 (63.8)	312 (62.0)
Age (years) Mean (SD) Median (Min, Max)	 44.0 (13.21) 43.0 (19, 77)	 44.3 (12.42) 44.0 (18, 76)	 44.2 (12.81) 43.0 (18, 77)
Age groups, n (%)			
< 65 Years	234 (94.0)	235 (92.5)	469 (93.2)
>= 65 Years	15 (6.0)	19 (7.5)	34 (6.8)
Race, n (%)			
ASIAN	2 (0.8)	4 (1.6)	6 (1.2)
WHITE	247 (99.2)	250 (98.4)	497 (98.8)
Ethnicity, n (%)			
KOREAN	2 (0.8)	4 (1.6)	6 (1.2)

Characteristic	SB17 (N=249)	EU-Stelara (N=254)	Total (N=503)
MIXED ETHNICITY	0	1 (0.4)	1 (0.2)
OTHER	247 (99.2)	249 (98.0)	496 (98.6)
Country of participation, n (%)			
CZE	26 (10.4)	25 (9.8)	51 (10.1)
EST	10 (4.0)	12 (4.7)	22 (4.4)
HUN	2 (0.8)	3 (1.2)	5 (1.0)
KOR	2 (0.8)	4 (1.6)	6 (1.2)
LTU	14 (5.6)	14 (5.5)	28 (5.6)
LVA	0	2 (0.8)	2 (0.4)
POL	122 (49.0)	121 (47.6)	243 (48.3)
UKR	73 (29.3)	73 (28.7)	146 (29.0)
Weight (kg) Mean (SD) Median (Min, Max)	 80.7 (11.78) 83.0 (46.7, 95)	 79.9 (12.02) 82.1 (46.7, 95)	 80.3 (11.90) 82.2 (46.7, 95)

Characteristic	SB17 (N=249)	EU-Stelara (N=254)	Total (N=503)
BMI (kg/m^2)			
Mean (SD)	27.2 (3.94)	26.8 (3.66)	27.0 (3.81)
Median (Min, Max)	27.3 (16.8, 39.1)	27.2 (16.7, 35.5)	27.2 (16.7, 39.1)

Source: OCS Analysis Studio, Custom Table Tool.
Columns - Dataset: Demographics; Filter: SAF1FL = 'Y'.
Sex, n (%) - Dataset: Demographics; Filter: SAF1FL = 'Y'.
Age (years) - Dataset: Demographics; Filter: SAF1FL = 'Y'.
Age groups, n (%) - Dataset: Demographics; Filter: SAF1FL = 'Y'.
Race, n (%) - Dataset: Demographics; Filter: SAF1FL = 'Y'.
Ethnicity, n (%) - Dataset: Demographics; Filter: SAF1FL = 'Y'.
Country of participation, n (%) - Dataset: Demographics; Filter: SAF1FL = 'Y'.
Weight (kg) - Dataset: Demographics; Filter: SAF1FL = 'Y'.
BMI (kg/m2) - Dataset: Demographics; Filter: SAF1FL = 'Y'.
SD = Standard Deviation.

Deaths

There were no deaths reported in the clinical program for SB17.

Treatment Emergent Adverse Events

Serious Adverse Events (SAEs)

No SAEs were reported during the phase 1 PK comparability trial (SB17-1001).

The incidence of SAEs was comparable across the treatment groups in the overall period. A total of 13 (2.6%) subjects (7 [2.8%] subjects in the SB17, 6 [2.4%] subjects in

the Stelara Overall, 2 [1.6%] subjects in the EU-Stelara+SB17, and 3 [2.5%] subjects in the Stelara+Stelara treatment groups) had 14 SAEs in the overall period. None of the SAEs were considered related to the investigational product.

Main Period:

A total of 9 (1.8%) subjects (6 [2.4%] patients in the SB17 treatment group, and 3 [1.2%] patients in the EU-Stelara treatment group) had 9 serious TEAEs in the main period. The SAEs are summarized in the table below.

Table 23: Summary of SAEs in Study SB17-3001 in the Main Period

System Organ Class Preferred Term	SB17 N = 249		EU-STELARA N = 254	
	n	(%)	n	(%)
Any SAE	6	(2.4)	3	(1.2)
Cardiac disorders	1	(0.4)	1	(0.4)
Acute myocardial infarction	1	(0.4)	0	(0.0)
Atrial fibrillation	0	(0.0)	1	(0.4)

System Organ Class Preferred Term	SB17 N = 249 n	(%)	EU-STELARA N = 254 n	(%)
Any SAE	6	(2.4)	3	(1.2)
Infections and infestations	0	(0.0)	1	(0.4)
Pneumonia	0	(0.0)	1	(0.4)
Injury, poisoning and procedural complications	3	(1.2)	1	(0.4)
Fibula fracture	1	(0.4)	0	(0.0)
Joint dislocation	1	(0.4)	0	(0.0)
Meniscus injury	1	(0.4)	0	(0.0)
Tibia fracture	0	(0.0)	1	(0.4)
Musculoskeletal and connective tissue disorders	1	(0.4)	0	(0.0)

System Organ Class Preferred Term	SB17 N = 249 n	(%)	EU-STELARA N = 254 n	(%)
Any SAE	6	(2.4)	3	(1.2)
Musculoskeletal chest pain	1	(0.4)	0	(0.0)
Renal and urinary disorders	1	(0.4)	0	(0.0)
Prerenal failure	1	(0.4)	0	(0.0)
Source: OCS Analysis Studio, Safety Explorer.				
Filters: TRT01A = "SB17" and SAF1FL = "Y" (SB17); TRT01A = "STELARA" and SAF1FL = "Y" (STELARA); TRTEMFL = "Y" and APERIOD = 1 to 1 and AESER = "Y" (Adverse Events).				

Selected SAE narratives for subjects who recieved SB17 in the Main Period:

- **Acute myocardial infarction:** Subject (b) (6) is a 52-year-old white male diagnosed with plaque psoriasis in 1995. On Study Day 167, the subject presented to the emergency room due to reduced exercise tolerance and

tightness in chest. On the same day, the subject was hospitalized with Acute myocardial infarction (Reported Term: myocardial infarction [NSTEMI]) of moderate intensity. Laboratory investigations also demonstrated hyperlipidemia. On the same day, a single vessel procedure of percutaneous angioplasty and vascular stent insertion of the right coronary artery was performed. On (Study Day 169), the subject's laboratory investigations showed lipoprotein A of 0.52 g/L (big risk > 0.5) and apolipoprotein B of 0.79 g/L (big risk 0.8). On Study Day 170, the subject underwent another single vessel procedure of percutaneous coronary angioplasty and vascular stent insertion of the left circumferential branch of the coronary artery. The procedure was successful with no complications. No action was taken with the IP due to the event of Acute myocardial infarction. The outcome of the event was reported to be resolved on Study Day 172, and the subject was discharged from the hospital on the same day. The Investigator assessed the event Acute myocardial infarction as moderate in intensity and not related to IP. The site stated the event as a result of atherosclerosis.

- **Musculoskeletal chest pain:** Subject (b) (6) is a 69-year-old white female diagnosed with plaque psoriasis in 2013. On Study Day 151, the subject visited the emergency room (ER) with chest discomfort, left leg pain and cough. At the ER, physical examination revealed a larger left limb circumference with no evidence of thrombosis. A chest computerized tomography scan ruled out pulmonary embolism. The subject was reported with Musculoskeletal chest pain (Reported Term: musculoskeletal chest pain related to COVID-19) of mild intensity. No treatment was reported for the event of Musculoskeletal chest pain. The outcome of the event was reported to be resolved on Study Day 152, and the subject was discharged from the hospital on the same day without any complaints. The Investigator assessed the event Musculoskeletal chest pain as mild in intensity and not related to IP. The Investigator considered cough related to COVID-19 to be the most likely cause for the event chest pain.

- **Prerenal failure:** Subject (b) (6) is 55-year-old white female diagnosed with plaque psoriasis in 1987. On Study Day 43, the subject experienced vomiting of moderate intensity. He was treated with activated charcoal for 4 days, and the vomiting resolved. On Study Day 47, he experienced diarrhea of moderate intensity. On Study Day 48, the subject presented to the hospital with diarrhea along with dizziness and weakness. On the same day, laboratory test results demonstrated hyponatremia, elevated C-reactive protein, and elevated

creatinine levels. The subject was diagnosed with Prerenal failure (Reported Term: prerenal kidney failure) of severe intensity and was hospitalized. The PI stated that the preceding vomiting and diarrhea that contributed to the subject's dehydration were due to food poisoning. The dehydration then resulted in prerenal kidney failure. No action was taken with the IP due to the event of Prerenal failure. The outcome of the AEs of Diarrhea and Prerenal failure were reported to be resolved Study Day 54. On the same day, the subject was discharged from hospital. The Investigator assessed the SAE Prerenal failure as severe in intensity and not related to IP.

Transition Period:

A total of 4 (0.8%) subjects (1 [0.4%] subject in the SB17+SB17, 3 [1.2%] subjects in the Stelara Overall, 1 [0.8%] subject in the EU-Stelara+SB17, and 2 [1.6%] subjects in the Stelara+Stelara treatment groups) had 5 serious TEAEs in the transition period. The SAEs are summarized in the table below.

Table 24: Summary of SAEs in Study SB17-3001 in the Transition Period

System Organ Class Preferred Term	SB17 + SB17 N = 237 n	 (%)	Stelara Overall N = 244 n	 (%)	EU-Stelara + SB17 N = 122 N	 (%)	Stelara + Stelara N = 122 n	 (%)
Any SAE	1	(0.4)	3	(1.2)	1	(0.8)	2	(1.6)
Gastrointestinal disorders	0	(0.0)	1	(0.4)	1	(0.8)	0	(0.0)
Salivary gland calculus	0	(0.0)	1	(0.4)	1	(0.8)	0	(0.0)
Neoplasms benign, malignant and unspecified (incl cysts and polyps)	0	(0.0)	1	(0.4)	0	(0.0)	1	(0.8)
Prostate cancer	0	(0.0)	1	(0.4)	0	(0.0)	1	(0.8)
Nervous system disorders	1	(0.4)	0	(0.0)	0	(0.0)	0	(0.0)
Ischaemic stroke	1	(0.4)	0	(0.0)	0	(0.0)	0	(0.0)
Reproductive system and breast disorders	0	(0.0)	1	(0.4)	0	(0.0)	1	(0.8)

System Organ Class Preferred Term	SB17 + SB17 N = 237 n	(%)	Stelara Overall N = 244 n	(%)	EU-Stelara + SB17 N = 122 N	(%)	Stelara + Stelara N = 122 n	(%)
Any SAE	1	(0.4)	3	(1.2)	1	(0.8)	2	(1.6)
Ovarian cyst torsion	0	(0.0)	1	(0.4)	0	(0.0)	1	(0.8)
Pelvic adhesions	0	(0.0)	1	(0.4)	0	(0.0)	1	(0.8)
Source: OCS Analysis Studio, Safety Explorer.								
Filters: TRTTNLBL = "SB17+SB17" and SAF2FL = "Y" (SB17 + SB17); TRTTNLBL = "Stelara+SB17" or "Stelara+Stelara" and SAF2FL = "Y" (Stelara Overall); TRTTNLBL = "Stelara+SB17" and SAF2FL = "Y" (Stelara + SB17); TRTTNLBL = "Stelara+Stelara" and SAF2FL = "Y" (Stelara + Stelara); TRTEMFL = "Y" and APERIOD = 2 to 2 and AESER = "Y" (Adverse Events).								

The SAE narratives for the subjects who received SB17 in the transition eriod are provided below:

- **Ischemic Stroke:** Subject (b) (6) was a 60-year-old white male diagnosed with plaque psoriasis in 1991. On Study Day 362, the subject was hospitalized for sudden right upper extremity paresis, dysarthria, cranial

nerve VII paresis, and loss of visual field on the right. On the same day, a computed tomography (CT) scan of the brain revealed findings of older post-ischemic changes, an angiography showed no significant stenosis of the cerebral arteries, and the subject was reported with Ischemic stroke (Reported Term: acute ischemic stroke) of severe intensity. The subject was a current smoker, which was a risk factor for the event; the subject was a current drinker, and vital signs suggested high blood pressure, such as reporting blood pressure of 158/78 mmHg at Week 28 and 142/79 mmHg at Week 40. On Study Day 363, the subject's neurological deficit improved but the paresis of the fingers of the right hand persisted. On the same day, a control CT scan of the brain showed no new findings. On Study Day 369, the subject was transferred to the rehabilitation department within the same hospital for occupational therapy, physiotherapy, and speech therapy. No action was taken with IP due to the event of Ischemic stroke. The outcome of the event was reported to be resolved on Study Day 376, and the subject was discharged from hospital. The Investigator assessed the event of Ischaemic stroke as severe in intensity and not related to IP.

- **Salivary gland calculus:** Subject (b) (6) a 23-year-old white female diagnosed with plaque psoriasis in (b) (6) On an unspecified date in (b) (6) the subject experienced parotitis of mild intensity. On (b) (6) (Study Day 288; during transition period), an ultrasound scan of the salivary gland showed increased density of the tissue and the subject was diagnosed with Salivary gland calculus (Reported Term: sialolithiasis) of mild intensity. The subject's signs and symptoms at event onset included enlargement and tenderness of the salivary glands. The event was serious as it required hospitalization and was considered to be medically important. On (b) (6) the subject was hospitalized, and an elective surgery of extirpation of the right submandibular salivary gland was performed the following (b) (6) The subject was treated with amoxicillin, 1,000 mg orally twice daily from (b) (6) (Study Day 304) to (b) (6) (Study Day 306). The Investigator clarified that the subject had a few episodes of parotitis that were treated with systemic antibiotics, and it was quite common for sialolithiasis to develop due to recurrent inflammation of the parotid gland which led to constriction of salivary ducts, therefore creating blockage and stone formation. The subject had reported medical history of Parotitis started from (b) (6) and ended at (b) (6) On (b) (6) (Study Day 306), the event of Parotitis resolved. No action was taken with the IP due to the event of Salivary gland calculus. The outcome of the event was reported to be resolved with no symptoms on (b) (6) (Study Day 308); the subject was discharged from the hospital the same day. The

Investigator assessed the event Salivary gland calculus as mild in intensity and not related to IP. The Investigator considered the subject's previous problems with salivary glands to be the cause of the event.

Reviewer Comment: This reviewer agrees with the assessments that the SAEs were not treatment-related.

Dropouts and/or Discontinuations

Of the 503 randomized patients, 481 (95.6%) subjects completed 28 weeks of the study, and 466 (96.9%) subject completed 52 weeks of the study. In both treatment groups, the most common reason for discontinuation was 'Other' and all related to war in Ukraine. There were no discontinuations in the SB17 cohort due to TEAEs. The reasons for discontinuation are summarized in the tables below.

Table 25: Summary of Discontinuations in the Safety Population in Study SB17-3001 in the Main Period

	SB17 (N=249)	EU-Stelara (N=254)	Total (N=503)
Consent withdrawn by subject	2 (0.8)	4 (1.6)	6 (1.2)
Subject lost to follow-up	0	1 (0.4)	1 (0.2)
Protocol violation	1 (0.4)	0	1 (0.2)
Lack of efficacy	1 (0.4)	0	1 (0.2)

	SB17 (N=249)	EU-Stelara (N=254)	Total (N=503)
Other			
Subject discontinuation from IP on or before Week 28 (Main period) related to war in Ukraine	8 (3.2)	5 (2.0)	13 (2.6)

Source: OCS Analysis Studio, Custom Table Tool.
Columns - Dataset: Demographics; Filter: SAF1FL = 'Y'.
Consent withdrawn by subject - Dataset: Demographics; Filter: DCP01RS = 'CONSENT WITHDRAWAL BY SUBJECT'.
Subject lost to follow-up - Dataset: Demographics; Filter: DCP01RS = 'SUBJECT LOST TO FOLLOW-UP'.
Protocol violation - Dataset: Demographics; Filter: DCP01RS = 'PROTOCOL VIOLATION'.
Lack of efficacy - Dataset: Demographics; Filter: DCP01RS = 'LACK OF EFFICACY'.
Other - Dataset: Demographics; Filter: DCP01RS = 'OTHER'.

Prior to Week 28, a total of 22 (4.4%) subject discontinued treatment: 12 (4.8%) subjects from the SB17 treatment group and 10 (3.9%) subjects from the Stelara Overall treatment group. No subjects discontinued due to TEAEs in the Main Period.

Table 26: Summary of Discontinuations in the Safety Population in Study SB17-3001 in the Transition Period

	SB17+SB17 (N=237)	EU-Stelara+ SB17 (N=122)	Stelara+Stelara (N=122)	Total (N=481)
Adverse Events	0	0	2 (1.6)	2 (0.4)
Consent withdrawn by subject	0	2 (1.6)	0	2 (0.4)
Subject lost to follow-up	1 (0.4)	1 (0.8)	0	2 (0.4)
Other				
<NO DATA>	0	1 (0.8)	0	1 (0.2)
Y	3 (1.3)	1 (0.8)	4 (3.3)	8 (1.7)

Source: OCS Analysis Studio, Custom Table Tool.
Columns - Dataset: Demographics; Filter: SAF2FL = 'Y'.
Adverse Events - Dataset: Demographics; Filter: DCSREAS = 'ADVERSE EVENT'.
Consent withdrawn by subject - Dataset: Demographics; Filter: DCSREAS = 'CONSENT WITHDRAWAL BY SUBJECT'.
Subject lost to follow-up - Dataset: Demographics; Filter: DCSREAS = 'SUBJECT LOST TO FOLLOW-UP'.
Other - Dataset: Demographics; Filter: DCSREAS = 'OTHER'.

A total of 15 (3.1%) subjects discontinued treatment after Week 28: 4 (1.7%) subjects from the SB17 and 11 (4.5%) patients from the Stelara Overall treatment groups (5 [4.1%] subjects from the EU-Stelara+SB17 and 6 [4.9%] subjects from the Stelara+Stelara treatment groups).

Common Adverse Events

Main Period:

A total of 244 (48.5%) subjects (120 [48.2%] subjects in the SB17, and 124 [48.8%] subjects in the EU-Stelara treatment groups) experienced at least one AE during the main period. The TEAEs with incidence ≥1 % of subjects by SOC or PT in the main period are presented below.

Table 27: Summary of Common TEAEs by ≥1% of Subjects in Study SB17-3001 in the Main Period

System Organ Class Preferred Term	SB17 N = 249 n	(%)	EU-Stelara N = 254 n	(%)
Any AE	120	(48.2)	124	(48.8)
Infections and infestations	71	(28.5)	76	(29.9)
Nasopharyngitis	22	(8.8)	21	(8.3)
Covid-19	16	(6.4)	23	(9.1)

System Organ Class Preferred Term	SB17 N = 249		EU-Stelara N = 254	
	n	(%)	n	(%)
Any AE	120	(48.2)	124	(48.8)
Upper respiratory tract infection	10	(4.0)	13	(5.1)
Asymptomatic covid-19	5	(2.0)	1	(0.4)
Respiratory tract infection	5	(2.0)	4	(1.6)
Bronchitis	4	(1.6)	5	(2.0)
Urinary tract infection	3	(1.2)	3	(1.2)
Pharyngitis	1	(0.4)	5	(2.0)
Investigations	21	(8.4)	19	(7.5)
Alanine aminotransferase increased	9	(3.6)	7	(2.8)

System Organ Class Preferred Term	SB17 N = 249		EU-Stelara N = 254	
	n	(%)	n	(%)
Any AE	120	(48.2)	124	(48.8)
Aspartate aminotransferase increased	7	(2.8)	1	(0.4)
Blood glucose abnormal	0	(0.0)	3	(1.2)
Gastrointestinal disorders	12	(4.8)	6	(2.4)
Abdominal pain upper	4	(1.6)	0	(0.0)
Skin and subcutaneous tissue disorders	12	(4.8)	10	(3.9)
Pruritus	6	(2.4)	3	(1.2)
Psoriasis	3	(1.2)	1	(0.4)
Musculoskeletal and connective tissue disorders	11	(4.4)	10	(3.9)

System Organ Class Preferred Term	SB17 N = 249		EU-Stelara N = 254	
	n	(%)	n	(%)
Any AE	120	(48.2)	124	(48.8)
Psoriatic arthropathy	3	(1.2)	1	(0.4)
Nervous system disorders	11	(4.4)	9	(3.5)
Headache	7	(2.8)	6	(2.4)
Injury, poisoning and procedural complications	10	(4.0)	11	(4.3)
Vaccination complication	0	(0.0)	4	(1.6)
Vascular disorders	10	(4.0)	7	(2.8)
Hypertension	8	(3.2)	6	(2.4)
Respiratory, thoracic and mediastinal disorders	5	(2.0)	6	(2.4)

System Organ Class Preferred Term	SB17 N = 249		EU-Stelara N = 254	
	n	(%)	n	(%)
Any AE	120	(48.2)	124	(48.8)
Rhinorrhoea	3	(1.2)	2	(0.8)
Catarrh	0	(0.0)	3	(1.2)
Blood and lymphatic system disorders	4	(1.6)	6	(2.4)
Leukopenia	3	(1.2)	5	(2.0)
General disorders and administration site conditions	4	(1.6)	3	(1.2)
Metabolism and nutrition disorders	4	(1.6)	8	(3.1)
Diabetes mellitus	0	(0.0)	4	(1.6)
Psychiatric disorders	3	(1.2)	4	(1.6)

System Organ Class Preferred Term	SB17 N = 249 n	(%)	EU-Stelara N = 254 n	(%)
Any AE	120	(48.2)	124	(48.8)
Renal and urinary disorders	2	(0.8)	4	(1.6)
Leukocyturia	0	(0.0)	4	(1.6)
Hepatobiliary disorders	1	(0.4)	3	(1.2)
Source: OCS Analysis Studio, Safety Explorer.				
Filters: TRT01A = "SB17" and SAF1FL = "Y" (SB17); TRT01A = "STELARA" and SAF1FL = "Y" (Stelara); TRTEMFL = "Y" and APERIOD = 1 to 1 (Adverse Events).				
Percent Threshold: Any Column ≥ 1%.				

At the SOC level, the most frequent TEAEs during the main period belonged to “infections and infestations” and “investigations”. The most frequently occurring TEAEs at the PT level were all from SOC “infections and infestations”, which were ‘nasopharyngitis’ in 43 (8.5%) subjects (22 [8.8%] subjects in the SB17, and 21 [8.3%] subjects in the Stelara treatment groups), ‘COVID-19’ in 39 (7.8%) subjects (16 [6.4%] subjects in the SB17, and 23 [9.1%] subjects in the Stelara treatment groups), and

'upper respiratory tract infection' in 23 (4.6%) subjects (10 [4.0%] subjects in the SB17, and 13 [5.1%] subjects in the EU-Stelara treatment groups).

In general, the incidences and frequency of the majority of the TEAEs by PT were comparable between two treatment groups. In the SB17 treatment group during the Main Period, there was a higher incidence of several TEAEs (e.g., nasopharyngitis, asymptomatic Covid-19, respiratory tract infection, elevated alanine/aspartate aminotransferase, upper abdominal pain, pruritis, psoriasis, psoriatic arthropathy, headache, hypertension, and rhinorrhea). However, given the relatively small sample size of this single study, it is difficult to interpret these findings and come to a definitive conclusion that these are meaningful differences between SB17 and EU-Stelara. Additionally, external factors, such as concomitant Covid-19 infections, may have contributed to some of these findings, such as elevated aspartate aminotransferase levels.

Transition Period:

A total of 85 (17.7%) subjects (39 [16.5%] subjects in the SB17+SB17, 46 [18.9%] subjects in the Stelara Overall, 17 [13.9%] subject in the EU-Stelara+SB17, and 29 [23.8%] subjects in the Stelara+Stelara treatment groups) experienced at least one AE in the transition period. The TEAEs with incidence ≥1 % of subjects by SOC or PT in the transition period are presented below.

Table 28: Summary of Common TEAEs by ≥1% of Subjects in Study SB17-3001 in the Transition Period

Preferred Term	SB17 + SB17		Stelara Overall		EU-Stelara + SB17		Stelara + Stelara	
	N = 237		N = 244		N = 122		N = 122	
	n	(%)	n	(%)	N	(%)	n	(%)
Any AE	39	(16.5)	46	(18.9)	17	(13.9)	29	(23.8)
Covid-19	3	(1.3)	6	(2.5)	3	(2.5)	3	(2.5)
Respiratory tract infection	3	(1.3)	1	(0.4)	0	(0.0)	1	(0.8)
Upper respiratory tract infection	3	(1.3)	3	(1.2)	1	(0.8)	2	(1.6)
Nasopharyngitis	2	(0.8)	6	(2.5)	2	(1.6)	4	(3.3)
Aspartate aminotransferase increased	1	(0.4)	3	(1.2)	1	(0.8)	2	(1.6)
Bronchitis	1	(0.4)	2	(0.8)	2	(1.6)	0	(0.0)
Psoriasis	1	(0.4)	2	(0.8)	0	(0.0)	2	(1.6)
Hypertransaminasaemia	0	(0.0)	2	(0.8)	2	(1.6)	0	(0.0)

Preferred Term	SB17 + SB17		Stelara Overall		EU-Stelara + SB17		Stelara + Stelara	
	N = 237		N = 244		N = 122		N = 122	
	n	(%)	n	(%)	N	(%)	n	(%)
Any AE	39	(16.5)	46	(18.9)	17	(13.9)	29	(23.8)
Leukocyturia	0	(0.0)	3	(1.2)	0	(0.0)	3	(2.5)
Source: OCS Analysis Studio, Safety Explorer.								
Filters: TRTTNLBL = "SB17+SB17" and SAF2FL = "Y" (SB17 + SB17); TRTTNLBL = "Stelara+SB17" or "Stelara+Stelara" and SAF2FL = "Y" (Stelara Overall); TRTTNLBL = "Stelara+SB17" and SAF2FL = "Y" (Stelara + SB17); TRTTNLBL = "Stelara+Stelara" and SAF2FL = "Y" (Stelara + Stelara); TRTEMFL = "Y" and APERIOD = 2 to 2 (Adverse Events).								
Percent Threshold: Any Column ≥ 1%.								

Adverse Reactions (ARs)

Main Period:

The proportion of TEAEs related to the investigational product were comparable between the two treatment groups (11 [4.4%] subjects in the SB17 and 15 [5.9%] subjects in the EU-Stelara treatment groups).

Table 29: Adverse Reactions in the Safety Population in Study SB17-3001 in the Main Period

System Organ Class Preferred Term	SB17 N = 249 n	(%)	EU-Stelara N = 254 n	(%)
Any AE	11	(4.4)	15	(5.9)
Investigations	4	(1.6)	4	(1.6)
Alanine aminotransferase increased	3	(1.2)	3	(1.2)
Aspartate aminotransferase increased	2	(0.8)	0	(0.0)
Blood bilirubin increased	0	(0.0)	1	(0.4)
Blood and lymphatic system disorders	3	(1.2)	2	(0.8)
Leukopenia	2	(0.8)	2	(0.8)
Neutropenia	2	(0.8)	1	(0.4)
Infections and infestations	2	(0.8)	4	(1.6)

System Organ Class Preferred Term	SB17 N = 249		EU-Stelara N = 254	
	n	(%)	n	(%)
Any AE	11	(4.4)	15	(5.9)
Nasopharyngitis	1	(0.4)	3	(1.2)
Respiratory tract infection	1	(0.4)	1	(0.4)
Skin and subcutaneous tissue disorders	2	(0.8)	3	(1.2)
Pruritus	1	(0.4)	1	(0.4)
Psoriasis	1	(0.4)	2	(0.8)
Gastrointestinal disorders	1	(0.4)	1	(0.4)
Paraesthesia oral	1	(0.4)	0	(0.0)
Abdominal pain	0	(0.0)	1	(0.4)

System Organ Class Preferred Term	SB17 N = 249 n	(%)	EU-Stelara N = 254 n	(%)
Any AE	11	(4.4)	15	(5.9)
Hepatobiliary disorders	1	(0.4)	0	(0.0)
Drug-induced liver injury	1	(0.4)	0	(0.0)
Nervous system disorders	1	(0.4)	0	(0.0)
Hypersomnia	1	(0.4)	0	(0.0)
General disorders and administration site conditions	0	(0.0)	2	(0.8)
Injection site erythema	0	(0.0)	1	(0.4)
Injection site pain	0	(0.0)	1	(0.4)
Injury, poisoning and procedural complications	0	(0.0)	1	(0.4)

System Organ Class Preferred Term	SB17 N = 249		EU-Stelara N = 254	
	n	(%)	n	(%)
Any AE	11	(4.4)	15	(5.9)
Post procedural complication	0	(0.0)	1	(0.4)
Metabolism and nutrition disorders	0	(0.0)	1	(0.4)
Hyperglycaemia	0	(0.0)	1	(0.4)
Musculoskeletal and connective tissue disorders	0	(0.0)	1	(0.4)
Pain in extremity	0	(0.0)	1	(0.4)
Psychiatric disorders	0	(0.0)	1	(0.4)
Dyssomnia	0	(0.0)	1	(0.4)
Source: OCS Analysis Studio, Safety Explorer.				

System Organ Class Preferred Term	SB17 N = 249		EU-Stelara N = 254	
	n	(%)	n	(%)
Any AE	11	(4.4)	15	(5.9)
Filters: TRT01A = "SB17" and SAF1FL = "Y" (SB17); TRT01A = "STELARA" and SAF1FL = "Y" (Stelara); TRTEMFL = "Y" and AEREL = "RELATED" (Adverse Events).				

Transition Period:

The majority of the TEAEs were not IP related, and the proportion of TEAEs related to the investigational product were similar across the treatment groups (2 [0.8%] subjects in the SB17+SB17, 4 [1.6%] subjects in the Stelara Overall, none in the EU-Stelara+SB17, and 4 [3.3%] subjects in the Stelara+Stelara treatment groups).

Table 30: Adverse Reactions in the Safety Population in Study SB17-3001 in the Transition Period

Preferred Term	SB17 + SB17		Stelara Overall		EU-Stelara + SB17		Stelara + Stelara	
	N = 237		N = 244		N = 122		N = 122	
	n	(%)	n	(%)	N	(%)	n	(%)
Any AE	2	(0.8)	4	(1.6)	0	(0.0)	4	(3.3)
Leukopenia	1	(0.4)	0	(0.0)	0	(0.0)	0	(0.0)
Neutropenia	1	(0.4)	0	(0.0)	0	(0.0)	0	(0.0)
Psoriasis	1	(0.4)	2	(0.8)	0	(0.0)	2	(1.6)
Hyperglycaemia	0	(0.0)	1	(0.4)	0	(0.0)	1	(0.8)
Post procedural complication	0	(0.0)	1	(0.4)	0	(0.0)	1	(0.8)
Respiratory tract infection	0	(0.0)	1	(0.4)	0	(0.0)	1	(0.8)
Source: OCS Analysis Studio, Safety Explorer.								
Filters: TRTTNLBL = "SB17+SB17" and SAF2FL = "Y" (SB17 + SB17); TRTTNLBL = "Stelara+SB17" or "Stelara+Stelara" and SAF2FL = "Y" (Stelara Overall); TRTTNLBL = "Stelara+SB17" and SAF2FL = "Y" (Stelara + SB17); TRTTNLBL = "Stelara+Stelara"								

Preferred Term	SB17 + SB17		Stelara Overall		EU-Stelara + SB17		Stelara + Stelara	
	N = 237		N = 244		N = 122		N = 122	
	n	(%)	n	(%)	N	(%)	n	(%)
Any AE	2	(0.8)	4	(1.6)	0	(0.0)	4	(3.3)
and SAF2FL = "Y" (Stelara + Stelara); TRTEMFL = "Y" and APERIOD = 2 to 2 and AEREL = "RELATED" (Adverse Events).								

Adverse Events of Special Interest (AESIs)

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

The following AEs were classified as AEs of special interest (AESI) in Study SB17-3001:

- Systemic hypersensitivity
- Infections
- Pulmonary events
- Injection site reaction

Although not listed as an AESI in the protocol, malignancies are included among the warnings and precautions for US-Stelara. Therefore, this reviewer included malignancies in the AESI analyses.

Main Period:

Table 31: Summary of AESIs in the Safety Population in Study SB17-3001 in the Main Period

Summary of AESIs in the Safety Population in Study SB17-3001 in the Main Period		
	SB17 (N=249)	EU-Stelara (N=254)
Hypersensitivity Reactions		
Abdominal pain	0	1 (0.4)
Dermatitis allergic	0	1 (0.4)
Infections		
Non-serious	70 (28.1)	75 (29.5)
Serious	0	1 (0.4)
Injection Site Reactions		
Injection site erythema	0	1 (0.4)

Summary of AESIs in the Safety Population in Study SB17-3001 in the Main Period		
	SB17 (N=249)	EU-Stelara (N=254)
Injection site pain	0	1 (0.4)

Source: OCS Analysis Studio, Custom Table Tool.
Columns - Dataset: Demographics; Filter: SAF1FL = 'Y'.
Hypersensitivity Reactions - Dataset: Adverse Events; Filter: APERIOD = '1' - '1', TRTEMFL = 'Y', AESI = 'SYSTEMIC HYPERSENSITIVITY'.
Infections - Dataset: Adverse Events; Filter: APERIOD = '1' - '1', TRTEMFL = 'Y', AESI = 'INFECTIONS'.
Injection Site Reactions - Dataset: Adverse Events; Filter: APERIOD = '1' - '1', TRTEMFL = 'Y', AESI = 'INJECTION SITE REACTION'.

With regards to hypersensitivity reactions, 2 (0.8%) subjects in the EU-Stelara treatment group reported 3 events (2 events of 'abdominal pain' in 1 subject, and 1 event of 'dermatitis allergic' in 1 subject) during the main period. The subject who reported 'abdominal pain' was determined as ADA positive at Week 8 and 12. The subject with 'dermatitis allergic' was determined as ADA negative up to Week 52. No serious hypersensitivity reactions such as anaphylactic shock or angioedema were reported during the study.

During the main period, 70 (28.1%) subjects in the SB17, and 75 (29.5%) subjects in the EU-Stelara treatment groups had AESI of 'infections.' Only 1 subject, who was in the EU-Stelara treatment group, experienced a serious infection (pneumonia).

Two subjects in the EU-Stelara treatment group experienced injection site reactions; none were reported in the SB17 treatment group during the main period.

There were no pulmonary events or malignancies reported during the main period.

There were no meaningful differences between treatment groups during the main period.

Transition Period:

During the transition period, 20 (8.4%) subjects in the SB17+SB17, 9 (7.4%) subjects in the EU-Stelara+SB17, and 11 (9.0%) subjects in the Stelara+Stelara treatment groups had AESI of 'infections'. None were serious infections.

There were no reports of systemic hypersensitivity, injection site reactions or pulmonary events during the transition period.

One subject in the Stelara+Stelara group reported a malignancy (prostate cancer) during the transition period. The event led to permanent IP discontinuation.

There were no meaningful differences between treatment groups during the transition period.

6.3.3. Additional Safety Evaluations

Laboratory Evaluations

No clinically meaningful changes over time or differences between treatment groups were observed for hematology or clinical chemistry parameters in Study SB17-3001. The incidences of clinically significant abnormalities were low and were comparable between treatment groups.

Vitals Signs

No clinically relevant changes were observed in any vital sign parameters across treatment groups in either Study SB17-1001 or Study SB17-3001.

ECGs

There were no clinically meaningful changes over time or differences between treatment groups in 12-lead ECG parameters in either Study SB17-1001 or Study SB17-3001.

Pregnancies

In Study SB17-1001, there was one case of pregnancy reported for female subject (Subject [redacted]) on [redacted]. The subject received SB17 treatment on [redacted]. Fetal ultrasound revealed isolated right aortic arch on [redacted] and [redacted] respectively by ultrasound performed by cardiopediatrician. No other anomalies were observed. The subject delivered a healthy female infant on [redacted]. Both mother and the newborn baby were reported as healthy on [redacted]. The subject was discontinued from the study in accordance with the protocol.

In Study SB17-3001, there was 1 subject whose female partner got pregnant during the study. The female partner refused to consent for providing information about the pregnancy. Thus, no further information was available on this female partner.

There was 1 subject, a 33-year-old female, who had a positive pregnancy test at the Week 52 visit. The subject denied the possibility of pregnancy and left the site, refusing any further evaluation. The patient was lost to follow-up thereafter.

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

6.4. Clinical Conclusions on Immunogenicity

The immunogenicity evaluation included qualitative and quantitative measurement of anti-drug antibody (ADA) and neutralizing antibody (NAb) in healthy subjects (from a single-dose PK similarity study) and in subjects with plaque psoriasis (multiple doses up to 52 weeks in a comparative clinical study), and an assessment of the impact of ADA on PK, efficacy, and safety.

In Study SB17-1001, the incidence of post-dose ADA between SB17 and US-Stelara and EU-Stelara was comparable in healthy subjects.

In Study SB17-3001, the incidence of positive ADA status up to Week 52 was lower for SB17 than for the EU-Stelara treatment group. However, the incidence of overall ADA after transition was comparable. There were no meaningful differences between the frequency of TEAEs in the SB17/SB17 group versus the other treatment arms (EU-Stelara/SB17 and EU-Stelara/EU-Stelara), regardless of ADA or NAb status. This reviewer concludes that there were no clinically significant differences between SB17 and 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.

Authors:

Shera Schreiber, MD

Clinical Reviewer

David Kettl, MD

Clinical Team Leader

6.5. [redacted] (b) (4)

[redacted] (b) (4)

(b) (4)

6.6. Extrapolation

The Applicant submitted data and information in support of a demonstration that SB17 is highly similar to US-Stelara notwhithstanding minor differences in clinically inactive components, and that there are no clinically meaningful differences between SB17 and US-Stelara in terms of safety, purity and potency in patients with plaque psoriasis (Study SB17-3001). In addition, the totality of evidence submitted in the application sufficiently demonstrates that SB17 can be expected to produce the same clinical results as US-licensed Stelara in any given patient (b) (4)

The Applicant is seeking licensure of SB17 for the following indication(s) for which US-Stelara has previously been licensed and for which SB17 has not been directly studied:

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

The Applicant provided a justification for extrapolating data and information submitted in the application to support licensure of SB17 as (b) (4) biosimilar for each

such indication for which licensure is sought and for which US-Stelara has been previously approved. This Applicant's justification was evaluated and considered adequate, and is summarized below.

Therefore, the totality of the evidence provided by the Applicant supports licensure of SB17 for each of the following indication(s) for which US-Stelara has been previously licensed and for which the Applicant is seeking licensure of SB17:

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

6.6.1. The Applicant is not seeking licensure of SB17 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 SB17 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 (b) (4) .Division of Gastroenterology

Executive Summary: Consistent with the principles of the FDA guidance for industry *Scientific Considerations in Demonstrating Biosimilarity to a Reference Product* (April 2015),[8] 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 SB17 as (b) (4) biosimilar to US licensed Stelara, under section 351(k) of the PHS Act, for the non-studied indications of Crohn's

[8] Guidance for Industry – Scientific Considerations in Demonstrating Biosimilarity to a Reference Product.

disease (CD), and ulcerative colitis (UC) in adults. The scientific justification based on the mechanism of action, pharmacokinetics (PK), immunogenicity, and safety supporting this conclusion are summarized in the following paragraphs.

Mechanism of Action: The mechanisms of action of ustekinumab that are relevant to moderate to severe active plaque psoriasis (PsO; the studied clinical study population) are also relevant to inflammatory bowel disease (IBD) (i.e., CD and UC). The Applicant provided data to support that SB17 has the same known and potential mechanisms of action as US-Stelara, which supports extrapolation to indications not directly studied in the SB17 clinical program. Ustekinumab belongs to the pharmacologic class of interleukin (IL)-23 and IL-12 antagonists. It is a human IgG1κ monoclonal antibody that binds with specificity to the p40 protein subunit used by both the IL-12 and IL-23 cytokines that are involved in inflammatory and immune responses, such as natural killer cell activation and CD4+ T-cell differentiation and activation. In the *in vitro* models, ustekinumab was shown to disrupt IL-12 and IL-23 mediated signaling and cytokine cascades by disrupting the interaction of these cytokines with a shared cell-surface receptor chain, IL-12Rβ1. The cytokines IL-12 and IL-23 have been implicated as important contributors to the chronic inflammation that is a hallmark of CD and UC.[9]

The biological activities of SB17 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 binding and neutralization, were similar across SB17 vs. US- Stelara. A similar lack of ADCC, and CDC activities was also demonstrated. Overall, these data support the determination that SB17 and US- Stelara are highly similar. Data support the conclusion that SB17 and US- Stelara utilize the same mechanism(s) of action, to the extent such mechanism(s) are known.

Pharmacokinetics (PK): Study SB17-1001 was a randomized, double-blind, parallel group, single dose, PK similarity study conducted in healthy adult subjects. The clinical pharmacology reviewers concluded that the data from this study support a demonstration of PK similarity between SB17 vs. US-Stelara, SB17 vs. EU-Stelara, and US-Stelara vs. EU-Stelara in healthy subjects (refer to Section 5 Clinical Pharmacology Evaluation and Recommendations). Available data on US-Stelara do not indicate any

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

major differences in PK based on disease state. Therefore, it is reasonable to conclude that PK for SB17 is expected to be similar between patients with PsO (the studied population) and those with IBD.

Immunogenicity: In the SB17 development program, immunogenicity was evaluated in populations that were considered sensitive for detecting meaningful differences (healthy subjects and PsO). While some differences were noted in the incidence of ADAs and/or NAbs across the treatment groups in both study populations, per the Clinical Pharmacology reviewers, the impact of immunogenicity on PK, efficacy, and/or safety between SB17 and US-/EU-Stelara was generally comparable and not considered to be clinically meaningful. Additionally, there were no meaningful differences in the rates of ADA in those subjects that underwent a single transition from EU-Stelara to SB17 in Study SB17-3001, compared to those that remained on their randomized treatment (EU-Stelara or SB17). Therefore, it is reasonable to conclude that immunogenicity in patients with IBD receiving SB17 would be similar to that observed in patients with PsO receiving US-Stelara. Refer to Section 5 Clinical Pharmacology Evaluation and Recommendations of this review for further details.

Safety: The safety of SB17 compared to EU-Stelara was assessed in the comparative clinical study SB17-3001 conducted in patients with PsO, and supported by a single dose, PK similarity study SB17-1001 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 SB17 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 addition, as previously noted, a single transition from EU-Stelara to SB17 was assessed as part of the study. No meaningful differences in the incidence of adverse events, including hypersensitivity, were observed in patients with PsO that underwent a single transition, compared to those that remained on their randomized treatment (SB17 or EU-Stelara). 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 SB17 has been shown to be similar to that of EU-Stelara in patients with PsO, combined with an adequate PK bridging between US-Stelara and EU-Stelara from the healthy subject study SB17-1001 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 PsO.

Regulatory Recommendations: DG concludes that sufficient scientific justification was provided to support licensure of SB17 for the following indications:

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

Authors:

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

6.6.2. Division of Rheumatology and Transplant Medicine

In addition to the plaque psoriasis indication, the Applicant is seeking licensure of SB17 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 SB17 as [redacted] (b) (4) biosimilar for the above indication for which licensure is sought and for which US-Stelara has been previously licensed and SB17 has not been directly studied.

First, as summarized above, the Applicant submitted data and information to demonstrate that SB17 is highly similar to US-Stelara and/or EU-Stelara and that there are no clinically meaningful differences in PK between SB17 and US-Stelara, SB17 and EU-Stelara, and between EU-Stelara and US-Stelara in healthy subjects (Study SB17-1001), and that there are no clinically meaningful differences in terms of efficacy, safety, and immunogenicity between SB17 and EU-Stelara in patients with plaque psoriasis (PsO) (Study SB17-3001). In addition, the totality of evidence submitted in the application sufficiently demonstrates that SB17 can be expected to produce the same clinical results as US-licensed Stelara in any given patient [redacted] (b) (4)

The additional points considered in the scientific justification for extrapolation of data and information to support licensure of SB17 for the treatment of PsA are described below.

Mechanism of Action (MOA)

In comprehensive in vitro comparative testing, SB17 has been shown to be functionally similar to US-Stelara. These data demonstrate that the biologic activity and potency of SB17 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 SB17 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 SB17 and US-Stelara in Study SB17-1001, a randomized, double-blind, single-dose PK similarity study in health adult subjects, as reviewed in the Clinical Pharmacology section. Importantly, SB17 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 SB17 and US-Stelara in the rheumatology indication for licensure (PsA). Thus, a similar PK profile would be expected between SB17 and US-Stelara in patients with PsA.

The Applicant provided adequate justification that a similar PK profile is expected between SB17 and US-Stelara for PsA.

Immunogenicity

Immunogenicity of SB17 was examined in the PK similarity study in healthy subjects (Study SB17-1001) and comparative clinical study in subjects with PSO (Study SB17-3001). The impact of immunogenicity on PK, efficacy, and safety between SB17 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 SB17 in Study SB17-3001.

The Applicant provided adequate justification that there are no clinically significant differences in immunogenicity expected between SB17 and US-Stelara for PsA.

Toxicity

The Applicant demonstrated that there are no clinically meaningful differences in safety between SB17 and EU-Stelara in patients with PsO and between SB17, 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 SB17, US-Stelara, and EU-Stelara, a similar safety profile would be expected between SB17 and US-Stelara in patients with PsA.

The Applicant provided adequate justification that a similar safety profile would be expected between SB17 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 SB17 for the rheumatologic indication of psoriatic arthritis for which US-Stelara has been previously licensed and for which the Applicant is seeking licensure.

The Applicant is not seeking licensure of SB17 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 SB17 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 (b) (4) (b) (4)

Authors:

Susanne Anderson, MD	Nadia Habal, MD	Raj Nair, MD
Primary Clinical Reviewer	Clinical Team Leader	Acting Division Director

7. Labeling Recommendations

7.1. Nonproprietary Name

The Applicant's proposed nonproprietary name, ustekinumab-ttwe, was found to be conditionally acceptable by the Agency (DMEPA review dated January 26, 2024).

7.2. Proprietary Name

The proposed proprietary name for SB17 is conditionally approved as PYZCHIVA. The name has been reviewed by DMEPA, who concluded the name was acceptable (DMEPA review dated June 14, 2023).

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:

Shera Schreiber, MD — Clinical Reviewer

David Kettl, MD — 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.

The Applicant has adequately disclosed financial interests and arrangements with the investigators. Form 3454 is noted in Section 14.1 and verifies that no compensation is linked to study outcome. The Principal Investigators (PIs) did not disclose any proprietary interest to the sponsor.

Authors:

Shera Schreiber, MD

Clinical Reviewer

David Kettl, 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:

Shera Schreiber, MD

Clinical Reviewer

10. Pediatrics

The Applicant submitted an Initial Pediatric Study Plan (iPSP) on August 30, 2022. After receiving comments from the Agency on February 9, 2023, the Applicant submitted an Agreed Initial Pediatric Study Plan on February 17, 2023.

In this application, the Applicant included assessment via extrapolation for pediatric patients ages 6-17 years with plaque psoriasis and psoriatic arthritis weighing at least 60 kg. See Section 6.6 for review of the assessments.

Currently, there is no dosage form for SB17 that allows for weight-based dosing for patients weighing less than 60 kg. (b) (4)

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

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

This Application was discussed at the Pediatric Review Committee (PeRC) meeting on November 14, 2023. The PeRC recommended that a 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. (b) (4)

Authors:

Shera Schreiber, MD	David Kettl, MD
Clinical Reviewer	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 Applicant agreed to the following PMR:

PMR 4572-1: Develop a presentation that can be used to accurately administer SB17 to pediatric patients who weigh less than 60 kg.

Final Report Submission: December 2024

PMC 4651-1: Develop an endotoxin testing method for the 5 mg/mL drug product that mitigates the low endotoxin recovery (LER) effect, submit method qualification results with 3 lots of 5 mg/mL drug product, and provide results of a LER study performed with the updated method using 3 lots of drug product. The USP <151> pyrogen test will be replaced by a suitable in vitro endotoxin method upon approval of the supplement.

Final Report Submission: January 2026

Authors:

Shera Schreiber	David Kettl, MD
Clinical Reviewer	Clinical Team Leader

12. Comments to Applicant

None

13. Division Director Comments

13.1. Division Director (OND – Clinical) Comments

I concur with the team's assessment of the data and information submitted in these BLAs. The data and information submitted by the Applicant, including adequate justification for extrapolation of data and information, demonstrate that SB17 is biosimilar to US-Stelara. (b) (4)

(b) (4)

(b) (4)

The Applicant is not seeking licensure of SB17 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 SB17 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 above for more information (b) (4)

(b) (4)

(b) (4)

Author:

Tatiana Oussova, MD, MPH

Deputy Director for Safety

14. Appendices

14.1. Financial Disclosure

Covered Clinical Study: SB17-3001

Was a list of clinical investigators provided:	Yes ☒	No ☐ (Request list from Applicant)

Total number of investigators identified: 149		
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) _____		
Is an attachment provided with the reason:	Yes ☐	No ☐ (Request explanation from Applicant)

14.2. Clinical Pharmacology Appendices

14.2.1. Summary of Bioanalytical Method Validation and Performance

- **PK assays: Bioanalytical methods for determination of ustekinumab in human serum**

The Applicant developed and validated an enzyme-linked immunosorbent assay (ELISA) for measurement of study drug concentrations in human serum samples obtained from the PK similariy study (SB17-1001) and the comparative clinical study (SB17-3001). The method is applicable for the quantitation of study drug within a nominal range of 150 to 1500 ng/mL, with LLOQ of 150 ng/mL. In the assay, test samples including calibration standards and quality controls were incubated with recombinant human IL-12p70-coated wells of a ELISA plate. After incubation, unbound material was washed away, SB17, US-Stelara, and EU-Stelara were detected using horseradish peroxidase conjugated mouse anti-human IgG (Fcγ). After excess unbound conjugate was removed by washing, the bound conjugate with SB17 or Stelara (US or EU) was then visualized by adding the substrate tetramethylbenzidine to the plate. The color development was stopped upon addition of the stopping solution, and the intensity of the color was measured at 450 nm. The intensity of color is proportion to the concentration of ustekinumab. The concentration of study drug in clinical samples was back calculated off of the non-linear regression of the standard curve. The vadliation parameters and performance of the ELISA are summarized in Table 32.

Table 32 Summary of Validation Parameters of the ELISA for Measurement of Study Drug Concentrations in Human Serum

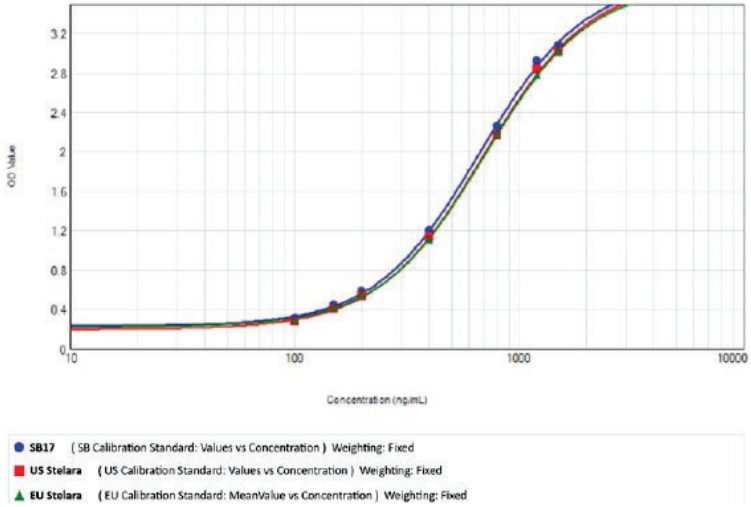
Validation Parameter	Results	
Analytical procedure number	TM.3086.03	
This analytical method was used in the following study:	SB17-1001	SB17-3001
Analyte	Ustekinumab in normal healthy human serum	Ustekinumab in plaque psoriasis (Ps) patient serum
Method of detection	Enzyme-linked Immunosorbent Assay (ELISA)	
Calibration model	4 Parameter Logistic (4-PL)	
Weighting factor	No weighting	
Quantifiable working range	150 ng/mL to 1500 ng/mL	
Quality control (QC) levels	LLOQ: 150 ng/mL LQC: 300 ng/mL MQC: 500 ng/mL HQC: 1150 ng/mL ULOQ: 1500 ng/mL	
Minimum Required Dilution (MRD)	1 in 50	
MRD solution	Low Cross Buffer	
Precision and accuracy (≤ 20% at LQC, HQC, MQC and ≤ 25% at LLOQ and ULOQ)	Requirements fulfilled	
Selectivity (matrix)	Requirements fulfilled using serum from normal healthy individuals	Requirements fulfilled using serum from Ps patient individuals

Validation Parameter	Results
Hemolyzed serum interference (up to 2% hemolysis)	Requirements fulfilled
Lipemic serum interference (up to 696 mg/dL)	Requirements fulfilled
Dilution linearity/hook effect	125-fold/no hook effect observed
Specificity/Interference (IL-12p70, IL-12p40, IL-23)	No interference detected with IL-12p70, IL-12p40 and IL-23 up to 10,000 pg/mL at 150 ng/mL and 1500 ng/mL of SB17, US Stelara and EU Stelara.
Short-term stability	EU Stelara: 48 hours at ambient temperature (~25°C). SB17 and US Stelara: 72 hours at ambient temperature (~25°C)
Freeze-thaw matrix stability	SB17 and US Stelara: 8 cycles at < −80°C (−80°C nominal) EU Stelara: 4 cycles at < −80°C (−80°C nominal)
Frozen matrix stability at −80°C nominal	SB17, US Stelara, and EU Stelara: 448 days
Frozen matrix stability at −20°C nominal	SB17, US Stelara, and EU Stelara: 448 days

IL=interleukin; HQC=high quality control; LLOQ=lower limit of quantification; LQC=low quality control; MQC=medium quality control; MRD=minimum required dilution; PL=parameter logistic; Ps=psoriasis; QC=quality control; ULOQ=upper limit of quantification
Source: Summary of Biopharmaceutic Studies, Table 4

An additional comparablility test was performed to justify whether the use of SB17 as the reference standard is appropriate to measure US-Stelara or EU-Stelara. The comparability of bioanalytical method of SB17 PK assay was evaluated with 18 accuracy and precision runs using the calibration standards and QCs prepared from SB17, US-Stelara or EU-Stelara. All validation parameters for either SB17 or US-/EU-Stelara met pre-defined criteria. Moreover, each calibration standard curves of three comparison groups are highly overlapped as shown in Figure 13.

Figure 12 Comparison of Calibration Standard Curve (SB17 vs US-/EU-Stelara)



Source: Summary of Biopharmaceutic Studies, Figure 2

Source: Summary of Biopharmaceutic Studies Table 14

Validation Parameter	Results

14.3. Statistical Appendices

14.3.1. Major Protocol Deviation (PD)

Table 38 presents a list of major protocol deviations (PDs) and Table presents reasons for exclusion from PPS regarding eleven subjects.

Table 33 List of major protocol deviation (PD)

Category	Details of PDs
Study Procedures Criteria	Blood or urine samples for clinical laboratory test (Haematology, Chemistry, and Urinalysis) were not collected at scheduled visit
	Blood sample for immunogenicity was not collected at scheduled visit
	Blood sample for PK was not collected at scheduled visit
	Body weight was not measured at scheduled visit
	DLQI assessment was not completed at scheduled visit
	Other major GCP non-compliances which might have an impact on data quality
	Out of visit window for non-dosing visit
	PASI assessment was not done at scheduled visit
	Psoriasis PGA was not completed at scheduled visit
	Tuberculosis evaluation was not performed at scheduled visit
	Urine pregnancy test was not performed at scheduled visit
Inclusion criteria	Body weight => 95 kg at Screening or at Randomisation
IP Compliance	Date of IP injection at Week 0 is not same as the date of Randomisation
	IP administration was skipped
	IP dispense error (Actually used IP kit number and IWRS dispensed kit number are not the same.)
	Out-of-window administration of IP
Exclusion criteria	Have current uncontrolled psychiatric disease or at risk of suicide at Screening
	Have received any disease-modifying anti-rheumatic drugs (DMARDs), any systemic immunosuppressants or any other injectable or enema corticosteroids, within 4 weeks prior to Randomisation
	Have received phototherapy or conventional systemic therapy for psoriasis within 4 weeks prior to Randomisation
	Have received topical therapy for psoriasis within 2 weeks prior to Randomisation
	Have used any IL-12 or IL-23 inhibitor biologics, IL-17 inhibitor, rituximab, or integrin inhibitor biologics at any time prior to Randomisation
	Positive chest X-ray findings determined by a qualified physician such as radiologist or pulmonologist, including active TB, untreated or inadequately treated old, inactive or healed TB
	Provided informed consent after any study related procedures start
	Women who are pregnant or nursing at Screening
Concomitant Medication Criteria	Use of topical therapy for psoriasis

Source: Reviewer

Table 34 Reason for exclusion from Per-Protocol Set

Category	Reason for exclusion from Per-Protocol Set	Subject ID
Study Procedures Criteria	Other major GCP non-compliances which might have an impact on data quality	(b) (6)
	PASI assessment was not done at scheduled visit	
Exclusion criteria	Have received topical therapy for psoriasis within 2 weeks prior to Randomisation	
	Have received any disease-modifying anti-rheumatic drugs (DMARDs), any systemic immunosuppressants or any other injectable or enema corticosteroids, within 4 weeks prior to Randomisation	
	Have used any IL-12 or IL-23 inhibitor biologics, IL-17 inhibitor, rituximab, or integrin inhibitor biologics at any time prior to Randomisation	
	Have received phototherapy or conventional systemic therapy for psoriasis within 4 weeks prior to Randomisation	
IP Compliance	IP not received at Week 4, PASI assessment result missing at Week 12	

Source: Reviewer

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

/s/

DAVID L KETTL
06/28/2024 05:06:24 PM