25 July 2024
EMA/371773/2024
Committee for Medicinal Products for Human Use (CHMP)

Assessment report

Eksunbi

International non-proprietary name: ustekinumab

Procedure No. EMEA/H/C/006448/0000

Note

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

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Administrative information

Name of the medicinal product:	Eksunbi
Applicant:	Samsung Bioepis NL B.V. Olof Palmestraat 10 2616 LR Delft NETHERLANDS
Active substance:	Ustekinumab
International Non-proprietary Name/Common Name:	Ustekinumab
Pharmaco-therapeutic group (ATC Code):	immunosuppressants, interleukin inhibitors (L04AC05)
Therapeutic indication(s):	Plaque psoriasis Eksunbi is indicated for the treatment of moderate to severe plaque psoriasis in adults who failed to respond to, or who have a contraindication to, or are intolerant to other systemic therapies including ciclosporin, methotrexate (MTX) or PUVA (psoralen and ultraviolet A) (see section 5.1). Paediatric plaque psoriasis Eksunbi is indicated for the treatment of moderate to severe plaque psoriasis in children and adolescent patients from the age of 6 years and older, who are inadequately controlled by, or are intolerant to, other systemic therapies or phototherapies (see section 5.1). Psoriatic arthritis (PsA) Eksunbi, alone or in combination with MTX, is indicated for the treatment of active psoriatic arthritis in adult patients when the response to previous non-biological disease-modifying anti-rheumatic drug (DMARD) therapy has been inadequate (see section 5.1). Crohn’s Disease

	Eksunbi is indicated for the treatment of adult patients with moderately to severely active Crohn's disease who have had an inadequate response with, lost response to, or were intolerant to either conventional therapy or a TNFα antagonist or have medical contraindications to such therapies. Ulcerative colitis Eksunbi is indicated for the treatment of adult patients with moderately to severely active ulcerative colitis who have had an inadequate response with, lost response to, or were intolerant to either conventional therapy or a biologic or have medical contraindications to such therapies (see section 5.1).
Pharmaceutical form(s):	Concentrate for solution for infusion; Solution for injection
Strength(s):	45 mg, 90 mg and 130 mg
Route(s) of administration:	Subcutaneous use, Intravenous use
Packaging:	pre-filled syringe (glass) and vial (glass)
Package size(s):	1 pre-filled syringe and 1 vial

Table of contents

1. Background information on the procedure 9
1.1. Submission of the dossier 9
1.2. Legal basis, dossier content and multiples 9
1.3. Information on paediatric requirements 10
1.4. Information relating to orphan market exclusivity 10
1.4.1. Similarity 10
1.5. Scientific advice 11
1.6. Steps taken for the assessment of the product 11

2. Scientific discussion 12
2.1. Problem statement 12
2.2. About the product 12
2.3. Type of Application and aspects on development 12
2.4. Quality aspects 13
2.4.1. Introduction 13
2.4.1. Active Substance 13
2.4.2. Finished Medicinal Product 20
2.4.3. Discussion on chemical, pharmaceutical and biological aspects 33
2.4.4. Conclusions on the chemical, pharmaceutical and biological aspects 34
2.4.5. Recommendation(s) for future quality development 34
2.5. Non-clinical aspects 34
2.5.1. Introduction 34
2.5.2. Pharmacology 34
2.5.3. Pharmacokinetics 35
2.5.4. Toxicology 35
2.5.5. Ecotoxicity/environmental risk assessment 35
2.5.6. Discussion on non-clinical aspects 36
2.5.7. Conclusion on non-clinical aspects 37
2.6. Clinical aspects 38
2.6.1. Introduction 38
2.6.2. Clinical pharmacology 38
2.6.3. Discussion on clinical pharmacology 60
2.6.4. Conclusions on clinical pharmacology 65
2.6.5. Clinical efficacy 65
2.6.6. Discussion on clinical efficacy 117
2.6.7. Conclusions on clinical efficacy 126
2.6.8. Clinical safety 126
2.6.9. Discussion on clinical safety 148
2.6.10. Conclusions on clinical safety 155
2.7. Risk management plan 155
2.7.1. Safety Concerns 155
2.7.2. Pharmacovigilance plan 156
2.7.3. Risk minimisation measures 156
2.7.4. Conclusion 158

2.8. Pharmacovigilance 158
2.8.1. Pharmacovigilance system 158
2.8.2. Periodic Safety Update Reports submission requirements 159
2.9. Product information 159
2.9.1. User consultation 159
2.9.2. Additional monitoring 159

3. Biosimilarity assessment 159
3.1. Comparability exercise and indications claimed 159
3.2. Results supporting biosimilarity 162
3.3. Uncertainties and limitations about biosimilarity 165
3.4. Discussion on biosimilarity 166
3.5. Extrapolation of safety and efficacy 167
3.6. Conclusions on biosimilarity and benefit risk balance 168

4. Recommendations 169

List of abbreviations

Abbreviation	Definition
$\%AUC_{extrap}$	Percentage of AUC_{inf} due to extrapolation from time of last measurable concentration (T_{last}) to infinity
ADCC	Antibody-dependent cellular cytotoxicity
ANCOVA	Analysis of Covariance
ADA	Anti-drug Antibodies
AE	Adverse Event
AESI	Adverse Events of Special Interest
ALP	Alkaline Phosphatase
ALT	Alanine Transaminase
ANOVA	Analysis of Variance
ANS	1-Anilinonaphthalene-8-sulfonate
AST	Aspartate Transaminase
AUC_{inf}	Area under the concentration-time curve from time zero to infinity
AUC_{last}	Area under the concentration-time curve from time zero to the last quantifiable concentration
ATC	Anatomical Therapeutic Chemical
%RSE	Percent relative standard error
2-AB	2-aminobenzamide
2H1L	2 heavy 1 light chain
APC	Antigen-presenting Cells
AST	Aspartate Transaminase
$AUC_{0\text{-}264h}$	AUC from time zero to 264 hours
%BBD	% Bioanalytical Bias Difference
BA	Bioavailability
BE	Bioequivalence
BMI	Body Mass Index
BPCI	Biologics Price Competition and Innovation

%CFB	Percent Change from Baseline
%CV	Percent coefficient of variation
C1q	Complement component 1, q Subcomponent, A chain
C_{max}	Maximum serum concentration
$C_{trough,ss}$	Trough concentration at steady state
CCP	Confirmation Cut Point
C1q	Complement component 1, q Subcomponent, A chain
CD	Crohn's Disease
CD	Circular Dichroism
CDAI	Crohn's Disease Activity Index
CDC	Complement-dependent cytotoxicity
CFB	Change From Baseline
CHO	Chinese hamster ovary
CI	Confidence Interval
CL	Clearance
CL/F	Apparent clearance
COVID-19	Coronavirus Disease 2019
CRP	C-Reactive Protein
CSR	Clinical Study Report
CPK	Creatine Phosphokinase
CS	Clinically Significant
$C_{trough,ss}$	Trough concentration at steady state
DLQI	Dermatology Life Quality Index
DNA	Deoxyribonucleic acid
DP	Drug Product
DS	Drug Substance
eCRF	Electronic Case Report Form
ECL	Electrochemiluminescence
ECG	Electrocardiogram
ELISA	Enzyme-linked Immunosorbent Assay
EMA	European Medicines Agency

EPAR	European public assessment reports
ET	Early Termination
FAS	Full Analysis Set
FcγR	Fc gamma receptor
FcRn	Fc receptor
FDA	Food and Drug Administration
F/U	Follow-up
Geometric LSMean	Geometric Least Squares Mean
GI	Gastrointestinal
GMP	Good Manufacturing Practice
HC	Heavy chain
HCD	Host cell protein
HCP	Host cell DNA
HCPs	Health Care Professionals
HRP	Horseradish Peroxidase
HPC	High Positive Control
HQC	High Quality Control
IBD	Inflammatory Bowel Disease
ICH	International Conference on Harmonization
ICF	Informed Consent Form
IFNγ	Interferon Gamma
Ig	Immunoglobulin
IL	Interleukin
INN	International Non-proprietary Name
IP	Investigational Product
iPSP	initial Pediatric Study Plan
ISR	Incurred Sample Reanalysis
ITF	Intrinsic Tryptophan Fluorescence
IV	Intravenous

1. Background information on the procedure

1.1. Submission of the dossier

The applicant Samsung Bioepis NL B.V. submitted on 1 May 2024 an application for marketing authorisation to the European Medicines Agency (EMA) for Eksunbi, through the centralised procedure falling within the Article 3(1) and point 1 of Annex of Regulation (EC) No 726/2004.

The applicant applied for the following indications:

Plaque psoriasis

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

Paediatric plaque psoriasis

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

Psoriatic arthritis (PsA)

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

Crohn's Disease

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

Ulcerative colitis

Eksunbi is indicated for the treatment of adult patients with moderately to severely active ulcerative colitis who have had an inadequate response with lost response to, or were intolerant to either conventional therapy or a biologic or have medical contraindications to such therapies.

1.2. Legal basis, dossier content and multiples

The legal basis for this application refers to:

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

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

This application is submitted as a multiple of Pyzchiva authorised on 19 April 2024 in accordance with Article 82.1 of Regulation (EC) No 726/2004.

The chosen product is:

- Medicinal product which is or has been authorised in accordance with Union provisions in force for not less than 10 years in the EEA:

- Product name, strength, pharmaceutical form: Stelara (Ustekinumab), 45 mg, 90 mg, solution for injection in pre-filled syringe and Stelara (Ustekinumab) concentrate for solution for infusion 130mg
- Marketing authorisation holder: Janssen-Cilag International NV
- Date of authorisation: 15-01-2009
- Marketing authorisation granted by: Union
- Marketing authorisation number: EU/1/08/494/003, EU/1/08/494/004, EU/1/08/494/005

■ Medicinal product authorised in the Union/Members State where the application is made or European reference medicinal product:

- Product name, strength, pharmaceutical form: Stelara (Ustekinumab), 45 mg, 90 mg, Solution for injection in pre-filled syringe and Stelara (Ustekinumab) concentrate for solution for infusion 130mg
- Marketing authorisation holder: Janssen-Cilag International NV
- Date of authorisation: 15-01-2009
- Marketing authorisation granted by: Union
- Marketing authorisation number: EU/1/08/494/003, EU/1/08/494/004, EU/1/08/494/005

■ Medicinal product which is or has been authorised in accordance with Union provisions in force and to which comparability tests and studies have been conducted:

- Product name, strength, pharmaceutical form: Stelara (Ustekinumab), 45 mg, 90 mg, Solution for injection in pre-filled syringe 130mg
- Marketing authorisation holder: Janssen-Cilag International NV
- Date of authorisation: 15-01-2009
- Marketing authorisation granted by: Union
- Marketing authorisation number: EU/1/08/494/003, EU/1/08/494/004, EU/1/08/494/005

1.3. Information on paediatric requirements

Not applicable.

1.4. Information relating to orphan market exclusivity

1.4.1. Similarity

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

1.5. Scientific advice

The applicant received the following scientific advice on the development relevant for the indication subject to the present application:

Date	Reference	SAWP co-ordinators
14 December 2017	EMEA/H/SA/3705/1/2017/III	Christian Gartner, Rune Kjeken
19 September 2019	EMEA/H/SA/3705/1/FU/1/2019/II	Jeanette McCallion, Andrea Laslop
13 October 2022	EMA/SA/0000101942	Juha Kolehmainen, Livia Puljak

The scientific advice pertained to the following chemical, pharmaceutical and biological development, the toxico-pharmacological development and the clinical development of Eksunbi:

• the proposed quality assessment strategy, and the test items for the similarity assessment; studies planned to demonstrate comparability between the two PFSs; proposed stability studies;

• the acceptability of the structural and physicochemical analyses and in vitro non-clinical studies;

• the acceptability of proposed design of Phase I study is appropriate to demonstrate similarity in PK, safety, tolerability, and immunogenicity between SB17 and Stelara; the acceptability of proposed design of Phase III study in PsO patients using the SC PFS;

• the acceptability of the revised Phase I and Phase III clinical study;

• the agreement that no human factor (usability) studies are needed based on the use-related risk analysis results.

1.6. Steps taken for the assessment of the product

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

Rapporteur: Jayne Crowe Co-Rapporteur: Thalia Marie Estrup Blicher

CHMP Peer reviewer(s): N/A

The application was received by the EMA on	1 May 2024
The procedure started on	27 May 2024
The CHMP Rapporteur's first Assessment Report was circulated to all CHMP and PRAC members on	1 July 2024
The PRAC Rapporteur's first Assessment Report was circulated to all PRAC and CHMP members on	1 July 2024
The PRAC agreed on the PRAC Assessment Overview and Advice to CHMP during the meeting on	11 July 2024
The CHMP, in the light of the overall data submitted and the scientific discussion within the Committee, issued a positive opinion for granting	25 July 2024

a marketing authorisation to Eksunbi on	

2. Scientific discussion

2.1. Problem statement

Not applicable for biosimilars.

2.2. About the product

Ustekinumab is a fully human IgG1κ monoclonal antibody that binds with specificity to the shared p40 protein subunit of human cytokines interleukin (IL)-12 and IL-23. Ustekinumab inhibits the bioactivity of human IL-12 and IL-23 by preventing p40 from binding to the IL-12Rβ1 receptor protein expressed on the surface of immune cells. Ustekinumab cannot bind to IL-12 or IL-23 that is already bound to IL-12Rβ1 cell surface receptors. Thus, ustekinumab is not likely to contribute to complement- or antibody-mediated cytotoxicity of cells with IL-12 and/or IL-23 receptors. IL-12 and IL-23 are heterodimeric cytokines secreted by activated antigen presenting cells, such as macrophages and dendritic cells, and both cytokines participate in immune functions; IL-12 stimulates natural killer (NK) cells and drives the differentiation of CD4+ T cells toward the T helper 1 (Th1) phenotype, IL-23 induces the T helper 17 (Th17) pathway.

Eksunbi will be made available in the following dose forms, strengths, and pack sizes:

- 130 mg concentrate for solution for infusion (pack size: 1 vial)
- PFS DP is provided in the following two strengths: 45 mg/0.5 mL and 90 mg/1.0 mL solution for injection (pack size: 1 pre-filled syringe)

2.3. Type of Application and aspects on development

Eksunbi (ustekinumab) has been developed as a biosimilar to the EU reference product Stelara, (International Non-proprietary Name [INN]: Ustekinumab).

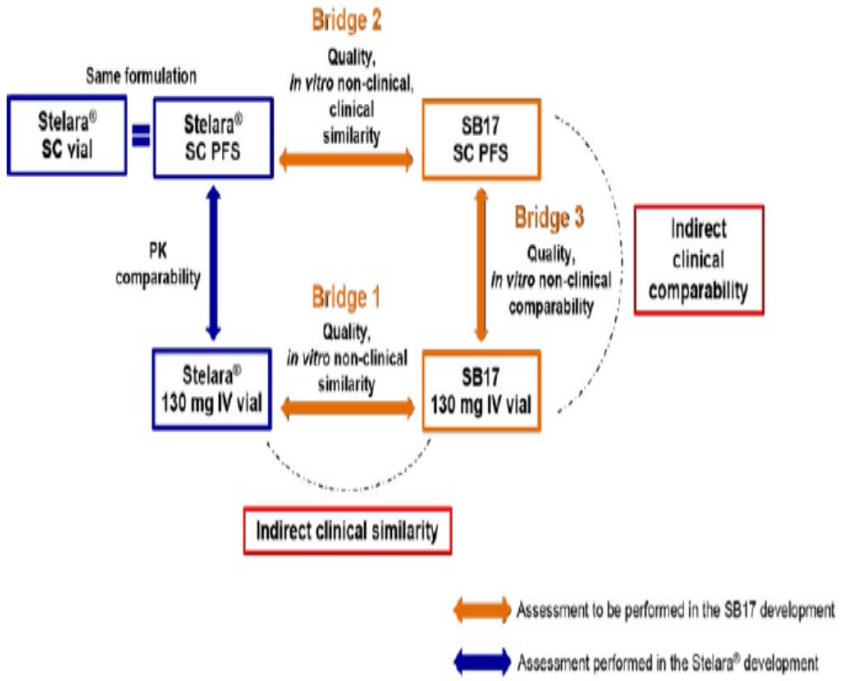
The quality and *in vitro* non-clinical similarity between Eksunbi IV vial and Stelara IV vial have been studied using physiochemical assays and *in vitro* biological assays (Bridge 1).

In addition to the direct comparison, comparability between the Eksunbi IV vial and Stelara IV vial has been made based on the indirect similarity comparison of SC PFS (Bridge 2), comparability exercise between Eksunbi SC PFS and IV vial (Bridge 3) and the established PK comparability between Stelara SC PFS and IV vial.

Furthermore, clinical similarity between the two PFS presentations has been evaluated:

- in the Phase I study (SB17-1001) - a randomised, double-blind, three-arm, parallel group, single-dose Phase I study in healthy subjects designed to demonstrate equivalence with respect to the PK profile of SB17 (ustekinumab) SB17 and Stelara. To support the global clinical development program, the study was also designed to assess the PK profiles of SB17, EU Stelara, and US Stelara.
- and in the Phase III study (SB17-3001) - a randomised, double-blind, multicentre study to evaluate the efficacy, safety, tolerability, PK and immunogenicity of SB17, compared to Stelara in patients with moderate to severe plaque PsO.

Figure 1. Clinical comparability



2.4. Quality aspects

2.4.1. Introduction

Eksunbi (SB17) contains ustekinumab, a fully human immunoglobulin G1 (IgG1) kappa monoclonal antibody composed of two identical heavy chains (449 amino acid residues each) and two identical light chains (214 amino acid residues each) that binds to the shared p40 protein subunit of IL-12 and IL 23. SB17 will be produced in Chinese hamster ovary (CHO) cell line.

The finished product is presented as a concentrate for solution for infusion containing 130 mg of ustekinumab as active substance, and as a solution for injection in pre-filled syringe (PFS) containing 45 mg/0.5 mL or 90 mg/1.0 mL of ustekinumab as active substance.

Other ingredients are: Histidine, Histidine hydrochloride monohydrate, Methionine (vial only), Disodium edetate (vial only), Sucrose, Polysorbate 80, Water for injections.

The vial presentation is available in a type I glass 30 mL vial closed with a chlorobutyl rubber stopper (pack size: 1 vial). The PFS presentation is available in a type I glass 1 mL syringe with a fixed stainless-steel needle and a needle cover containing rubber (pack size: 1 pre-filled syringe).

2.4.1. Active Substance

2.4.1.1. General Information

SB17 (ustekinumab) is a fully human IgG1 monoclonal antibody. Ustekinumab binds with specificity to the shared p40 protein subunit of human cytokines interleukin (IL)-12 and IL-23. Ustekinumab inhibits

the bioactivity of human IL-12 and IL-23 by preventing p40 from binding to the IL-12Rβ1 receptor protein expressed on the surface of immune cells. Details of antibody structure and the amino acid sequence is provided in the dossier.

2.4.1.2. Manufacture, process controls and characterisation

Description of manufacturing process and process controls

The manufacturing process is standard for the production of mAbs. Manufacturing starts from a vial of working cell bank (WCB), which is expanded through a series of flasks and bioreactors. For each of these steps the process parameters and performance parameters have been listed.

The purification process consists of 7 stages which includes affinity chromatography, low pH virus inactivation, neutralisation and depth filtration, cation exchange chromatography, mixed mode chromatography, viral filtration, ultrafiltration and diafiltration and drug substance (DS) formulation and dispensing. The manufacturing description for the purification stage is considered acceptable. For each of these steps the process parameters and performance parameters have been listed. The process parameters have been broken down into key process parameters (KPPs) and critical process parameters (CPPs) while the performance parameters include in-process gateways (IPGs), critical in-process gateways (CIPGs), in-process tests (IPTs), and critical in-process tests (CIPTs).

Control of materials

The list of raw materials and their specifications has been provided for both the cell culture and purification stage. Non compendial raw materials are either tested in-house or are accepted based on the supplier's Certificate of Analysis (CoA). The non-compendial raw materials acceptance criteria have been registered to the dossier.

The host cell line is a Chinese hamster ovary (CHO). The characteristics of the major genetic elements of the plasmid are described, the cDNA and amino acid sequence translated from the nucleotide sequence of the SB17 genes is provided. The coding sequences of the antibody genes were confirmed. The construction process is described in line with Ph. Eur. 0784 products of recombinant DNA technology and in line with ICH Q5B.

Establishment and characterisation of cell banks are described in accordance with the ICH Q5D. Appropriate testing has been done on cell banks in line with ICH Q5A. Testing of the cell banks included identity, microbiological tests (sterility, mycoplasma and bacteriostasis/fungistasis), genotypic tests (gDNA and cDNA sequencing of the product gene) and virus safety tests.

Testing was performed in line with the requirements of ICH Q5A. Genetic stability testing was performed; the results show they met the acceptance criteria.

Control of critical steps and intermediates

The dossier lists the registered controls for the DS manufacturing process. The process controls are split between process parameters and performance parameters. Process parameters are considered to be inputs that are used to control the manufacturing process, and they consist of key process parameters (KPP) or critical process parameters (CPP). The KPP are classified as parameters that do not influence critical quality attributes (CQAs). CPPs are classified due to their impact on CQAs and both have operating ranges and action ranges. Performance parameters are measurements from the process to determine if the process is operating as expected based on development experience and risk assessments. They have been classified as in-process gateways (IPGs), critical in-process gateways (CIPGs), in-process tests (IPTs), and critical in-process tests (CIPTs).

In the early stages of the cell culture process, there is appropriate controls to ensure sufficient healthy cells are obtained to proceed to the next expansion step and ensure enough cells are produced to inoculate the production bioreactor. Appropriate controls are in place for the production bioreactor, including standard controls such as temperature, pH, dissolved oxygen, and culture duration, as well as the expected microbial controls for adventitious viruses, bioburden and mycoplasma. The chromatography steps have controls registered for load ratio, linear velocity, and peak collection. The low pH step includes the expected critical controls for inactivation time, pH and temperature. The viral filter has the expected critical controls for load ratio, pressure, and filter integrity.

Process validation and/or evaluation

To validate the drug substance (DS) manufacturing process, three process performance qualification (PPQ) batches were manufactured at commercial scale or suitable scale-down models were used for supportive studies. A standard approach to process validation has been taken which is in accordance with the Guideline on process validation for the manufacture of biotechnologically derived active substance and data to be provided (EMA/CHMP/BWP/187338/2014). The results presented for the PPQ batches include all tests registered i.e., CPPs, KPPs, CIPTs, IPTs, CIPGs, and IPGs.

The majority of the results for the process parameters and performance were within the established acceptance criteria. However, a discrepancy was noted for the addition of the 100X formulation for batch CMC-P-0101, it was agreed there was no impact to quality as the protein concentration, pH, osmolarity and polysorbate 80 were within specification and the excipients of the drug product batches manufactured from this DS batch were shown to be within their expected range.

The clearance of the following impurities was addressed in validation studies. The details provided are considered sufficient.

A description of each hold time has been provided. Hold times are registered for the several manufacturing steps. Individual hold times are proposed for both 15 – 25°C and 2 – 8°C. Data from intermediate samples taken from PPQ batches, held in small scale representative containers has been provided for the majority of the hold times which consisted of testing for quality attributes and purity.

The applicant proposes to reuse the chromatography resins during commercial manufacturing. This is based on scale-down studies which tested the consistency of process performance parameter, process-related impurities and product quality attributes. The scale down results for each resin met the acceptance criteria at each cycle.

The DS is transported to the DP manufacturing site ensuring the product is kept at appropriate temperature. The shipping qualification studies were performed in consideration of worst-case shipping conditions. Only brief shipping qualification data has been provided to support the conclusion that the shipping validation testing met the acceptance criteria, but the information is considered acceptable.

Manufacturing process development

A quality attribute risk assessment was performed to identify the critical quality attributes (CQAs) and the non-CQAs.

The applicant has provided a detailed overview of the development of the SB17 DS manufacturing process, which was developed based on pilot, clinical and PPQ batches. Once the clinical manufacturing process had been identified, a process risk assessment 1 (PRA1) was performed, followed by process characterisation, a process risk assessment 2 (PRA2) and then process validation where finally the process control parameters were re-evaluated and then finalised. This approach was split between the cell culture and the purification process.

For the cell culture stage, it was initially developed at laboratory and pilot scale before the process was scaled up to a scale for clinical and commercial manufacturing. The differences between the pilot and clinical cell culture manufacturing process have been highlighted and were limited to the scale of the bioreactor at the seed train and production bioreactor stages. For the clinical manufacturing process, a PRA1 was performed to determine the level of process characterisation required to understand the impact of each process parameter on quality attributes and process consistency. Based on the PRA1, process characterisation studies were performed using qualified scale-down models (SDMs). The operating parameters were matched between the laboratory, pilot and commercial manufacturing scales. Process characterisation followed a relatively standard approach based on univariate and multivariate statistical design of experiments (DoE) process characterisation studies. Based on the process characterisation studies, a pilot confirmation run was conducted and the results show that all the tested product qualities were within the acceptance criteria. Subsequently, another risk assessment, PRA2 was conducted which was a failure mode and effect analysis (FMEA) that evaluated the severity, occurrence and likelihood of detection of parameter failures and their impact on CQAs by establishing individual scores for severity, occurrence and detectability and then multiplying them together to generate an RPN. Finally, based on all this information process validation was performed, no changes were made to the control strategy following this procedure.

From the PRA1 a large number of parameters were identified as high risk, these can be agreed. As above for the cell culture stage, the process characterisation followed a relatively standard approach based on univariate and multivariate statistical DoE process characterisation studies. For the process characterisation studies of the purification stage, the process parameters listed in S.2.4 have been studied along with additional process parameters deemed to have no impact on quality. Based on the studies the parameters were deemed to have an impact on product quality or not using statistical analysis. Overall, the studies performed are considered sufficient and the results have identified KPPs, N-KPPs and CPPs, these are considered acceptable. After the process characterisation studies a PRA2 was performed and a risk mitigation and control strategy for the process performance qualification was determined, the classifications are deemed acceptable. Process validation was performed as described in S.2.5, from these studies some additional modifications were made, the changes are mainly to hold times, resin lifetimes, the elution solution pH for the affinity chromatography step and the VF load ratio for the viral filtration step, these are deemed acceptable. The UF1 intermediate processing and UF/DF recovery intermediate processing parameters have been reclassified from CPPs to N-KPPs as the process is continuous without a static hold, hence, it is deemed not to impact product quality by the Applicant. This change has been adequately justified.

The applicant has provided an extensive comparability study to demonstrate that the SB17 manufacturing process throughout the development is comparable to the commercial manufacturing process. The comparability study complies with ICH Q5E and included testing of quality attributes from the release specifications as well as extended characterisation tests and stability studies. A summary of the data, including chromatograms, electropherograms etc. has been presented.

The panel of analytical methods included in the comparability evaluation is considered sufficient and includes primary structure and post-translational modification.

For the pilot and clinical phase comparability exercise the comparability range was set based on historical representative SB17 pilot DS batches and historical DP batch. The comparability acceptance criteria were based on the mean ± 3SD using a one-sided or two-sided limits as the batch number was considered too low for tolerance interval analysis, this is approach can be agreed as this is an earlier development phase comparability study.

The majority of the comparability data provided to demonstrate that pilot and clinical phase batches shows that the two processes are comparable in terms of primary structure and post-translational

modification, glycan profiles, purity and impurity, charge heterogeneity, higher order structure, quantity and biological properties.

For the clinical phase and commercial manufacturing process comparability exercise, clinical phase DS batch and PPQ batches were used. The comparability range was set based on tolerance intervals that cover 99% proportion of population with 95% confidence level using mean ± *k*SD for one- or two-sided tolerance limits. For this comparability study, the comparability range was established using representative pilot and clinical phase batches, this is endorsed. The comparability exercise was based on clinical DP batches and PPQ DP batches, given that the DP batches were manufactured from the DS batches used in the comparability study and the formulation has not changed, this can be accepted as sufficient to demonstrate comparability.

The majority of the comparability data provided demonstrates that the clinical and commercial batches are comparable in terms of primary structure and post-translational modification, glycan profiles, purity and impurity, charge heterogeneity, higher order structure, quantity and biological properties.

Comparative stability studies were performed on pilot, clinical and PPQ DP batches to determine if the degradation patterns were similar among all the SB17 DP batches. No degradation comparability studies were performed on DS batches. The analytical methods tests were performed. The results show similar degradation patterns for all the batches.

An updated comparability study has been provided which now includes all available batches. The comparability was now performed by directly comparing DS batches while DP batches were compared separately. Overall, the updated comparability approach is considered sufficient.

Characterisation

The applicant has provided elucidation of structure and other characteristics details section. The information covers determination of the structures (primary, post-translational modification, glycan profile, and higher order), purity/impurities, charge heterogeneity, quantity, cellular potency, and binding activity. For some of the tests, only the drug product (DP) was characterised but since the DS and DP have an identical active ingredient, it is agreed that the characterisation data with the DP can be considered to be equivalent.

Impurities

The description of the potential product- and process-related impurities for the SB17 DS is considered brief, with merely a list of the impurities and a table for each impurity outlining the amount detected in the DS for PPQ batches and in some cases the amount detected in clinical batches. Process-related impurities include host cell protein and host cell DNA, protein A leachate. The batch data from the PPQ batches shows removal of the impurities below their LoQ which implies the clearance is sufficient.

The product-related impurities have been stated as high molecular weight (HMW) and low molecular weight (LMW) species. They are tested at release by size exclusion-high performance liquid chromatography (SE-HPLC) and capillary electrophoresis-sodium dodecyl sulphate (CE-SDS) (non-reducing). The information provided is quite limited, nonetheless, the batch data shows both are consistently below the acceptance criteria and the different size impurities have been characterised in the comparability studies.

A risk assessment for the presence of nitrosamines in the DS has been presented and the applicant concludes that there is no risk of nitrosamines. The evaluation performed is deemed sufficient.

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

Specifications

The proposed active substance specification includes tests for identity (IL-23 binding and icIEF), quantity (protein concentration), purity (CE-SDS reduced, CE-SDS non-reduced and SE-HPLC), potency (IL-23 binding and IL-23 neutralisation), general tests (appearance, osmolality and pH), charge heterogeneity (icIEF) and safety (endotoxin and microbial enumeration).

In general, the panel of tests are in line with ICH Q6B and are considered appropriate for routine control of a monoclonal antibody both at release and end of shelf life.

Analytical procedures

Compendial analytical procedures are performed in accordance with the Ph. Eur. method descriptions are provided for non-compendial methods. The method descriptions include details regarding equipment, reagents, operating conditions, sample and standard preparation, assay controls and system of suitability, thus, they can be regarded as acceptable.

The analytical procedures have been appropriately validated in accordance with ICH Q2(R1). For the non-compendial methods, summary validation reports have been submitted for each assay and the testing performed included linearity, accuracy, range, precision (repeatability, intermediate precision, reproducibility), detection limit, quantitation limit, robustness and system suitability. In addition to the standard validation requirements of ICH Q2(R1), for several methods extensive robustness studies have been described. For a number of the methods, co-validation has been done between Samsung Bioepis and testing sites, this is deemed acceptable.

Batch analysis

Batch analysis data is provided for pilot batches manufactured at Samsung Bioepis Co., Ltd, clinical batches at AGC Biologics A/S and PPQ manufactured at commercial scale at AGC Biologics A/S. All batches comply with the specifications in place at the time of testing. The data demonstrate that the commercial process is capable of manufacturing a consistent drug substance.

Justification of specification

The specifications have been based on commercial acceptance criteria from batch analysis data of commercial scale DS batches. Issues raised during the procedure on the justification of specifications have been addressed and proposed limits are considered acceptable.

Reference standards

The applicant has established four reference standards throughout the development of SB17 and depending on where the reference standard was prepared from, a different classification has been listed. The different reference classes defined by the applicant include research reference standards (RRS), the interim reference standard (IRS), the clinical reference standard (CRS), the primary reference standard (PRS) and the working reference standard (WRS), although it is noted that there is no CRS or WRS. The PRS was established from the SB17 clinical DS batch CMC-O-0001 which was manufactured. The qualification testing included primary structure, carbohydrate structure (N-glycan profile), quantity, identity, physicochemical properties (purity and impurities, charge heterogeneity), biological activity and all the results met the pre-defined acceptance criteria. The PRS will be tested annually to allow for an extension of the expiry date by additional 12 months. If there is no out-of-specification, then the extension will be done without a notification to the EMA.

The applicant has stated there will be a WRS which will be selected from a SB17 PPQ or commercial DS batch, however, currently there is no WRS. The applicant has registered the details for introducing the WRS with defined testing and acceptance criteria, this is deemed acceptable.

Container closure

The container closure system for the DS is a Celsius FFT 6 L bag (Sartorius Stedim Biotech). The bag is covered by a protective shell of high-density polyethylene (HDPE) as a secondary packaging. The bags are sterilised by gamma irradiation and are certified BSE/TSE free. The CoA for the specifications of the container closure system(s) has been provided. The applicant registered the CoA in the dossier, hence, any change from the specifications listed in this CoA will require a variation. Extractable studies have

been performed. No leachable study was performed as the applicant argues that a high enough safety margin has been demonstrated during the extractables study to conclude there is a low toxicological risk.T he proposal to omit the leachable study is accepted.

2.4.1.4. Stability

Stability studies have been performed in accordance with ICH guidelines in terms of testing frequency and storage conditions. For the stability studies, pilot, clinical and PPQ DS batches have been tested. Long-term stability studies were performed and data have been provided for pilot, clinical and commercial batches respectively, at this storage condition. In addition, studies were also performed at intermediate conditions and at accelerated conditions.

Stability testing included appearance, purity, heterogeneity, potency, and general testing. The methods used are the same as used for release testing and have been appropriately validated. At the long-term storage conditions, there were no trends or out specification results seen for any of the tests performed on the pilot batch, for the clinical batches or for the PPQ batches.

A shelf-life is being proposed based on the long-term and intermediate stability data of clinical phase DS batches. Real time data has been provided for clinical batches, considering the comparability data and minimal changes made to the manufacturing process between the clinical and commercial manufacturing process, the shelf life can be agreed.

2.4.2. Finished Medicinal Product

2.4.2.1. Description of the product and Pharmaceutical Development

Description of the product

Eksunbi (SB17) has two presentations covering three strengths. The pre-filled syringe (PFS) drug product (DP) is provided as 45 mg/0.5 mL and 90 mg/1.0 mL of ustekinumab solution for injection as a single-use safety PFS for subcutaneous injection. The vial DP is presented as a single-use vial containing 130 mg/26 mL concentrate for solution for infusion of ustekinumab for intravenous infusion. Both presentations are a clear, colourless to light yellow, sterile and preservative-free solution. There are no overages or overfills in either presentation.

Pharmaceutical development

The applicant has based their formulation development on the reference medicinal product, Stelara. The formulations of Eksunbi vial DP and Stelara vial are identical. For the Eksunbi PFS DP, the applicant has used a higher concentration of sucrose compared to the reference medicinal product. Otherwise, the formulation is same as the reference medicinal product.

A sucrose concentration robustness study has been provided to demonstrate that the higher sucrose concentration doesn't affect CQAs. The study included DP with different sucrose concentrations. The study showed there were no effects on CQAs due to varying the sucrose concentration following thermal stress, long-term storage conditions, freeze-thaw cycles or agitation stress. The study demonstrates that the change in sucrose concentration in SB17 does not negatively impact the quality of the DP and therefore the change to sucrose concentration is acceptable.

The manufacturing process development history, from clinical development and onto commercial development has been presented. There have only been minor changes between clinical and commercial process manufacturing. Comparability has been demonstrated between Eksunbi clinical DP batches and Eksunbi commercial DP batches. And additionally, comparability has been demonstrated between Eksunbi commercial PFS DP and Eksunbi commercial vial DP. The comparability studies were extensive and comparability was demonstrated.

The primary packaging material for Eksunbi 45 mg and 90 mg PFS DP consists of a syringe and a stopper. The choice of container is adequately justified based on the primary packaging of the reference medicinal product, extractable studies, leachable studies, silicone oil studies, a tungsten interaction study and stability studies. The primary packaging material for Eksunbi 130 mg vial DP consists of a glass vial and rubber stopper. The choice of container is adequately justified based on the primary packaging of the reference medicinal product, extractable studies, leachable studies and stability studies.

2.4.2.2. Manufacture of the product and process controls

Manufacture

Manufacture, primary packaging and QC release testing (endotoxin and sterility only) are conducted by finished product manufacturing site. The remainder of QC release testing is conducted at another testing site. A testing site is registered as an additional site where potency (IL-23 binding and IL-23 neutralisation) release testing can be performed. Secondary packaging site is registered as the site where labelling and packaging of SB17 vial and labelling, assembly and packaging of SB17 PFS is conducted. The site of EU batch release is Samsung Bioepis NL B.V., Netherlands.

The target batch size for Eksunbi 45 mg PFS is defined. The target batch size for SB17 90 mg PFS is defined. The target batch size for SB17 130 mg vial is defined.

The process is a standard drug product manufacturing process for a monoclonal antibody. A high-level description of the manufacturing process has been provided but this is acceptable as the process is relatively straightforward. The PFS DP manufacturing process is divided into steps that consist of thawing, filtration, filling and stoppering followed by assembly of the PFS, labelling and storage. The SB17 vial DP manufacturing process consists of thawing, compounding, dilution, filtration, filling, stoppering and crimping. Relevant process parameters and in process tests are provided with ranges or acceptance criteria.

Process controls

The control strategy is similar for Eksunbi PFS and vial DP. The control strategy is divided into process parameters and performance parameters. Process parameters include critical process parameters (CPP), key process parameters (KPP) and non-key process parameters (NKPP). Performance parameters include in process gateways (IPG) and in process tests (IPT). Critical IPTs are identified at step 3 (sterilising filtration). One CPP and 4 critical IPGs are identified in step 4 filling. The proposed ranges and acceptance criteria are supported by process validation.

The risk assessment performed following PPQ runs has been provided to justify the process and performance parameters.

Process Validation

Process validation was conducted at commercial scale and includes manufacturing process validation, filter validation, aseptic filling validation, cleaning validation and shipping validation.

Three consecutive Eksunbi 45 mg PFSs, three consecutive Eksunbi 90 mg PFSs and three consecutive Eksunbi 130 mg vials were successfully manufactured for process validation and lots met the pre-determined protocol acceptance criteria for the study, demonstrating that the DP manufacturing processes can produce DP of a consistent quality.

The aseptic filling process was validated by representative media fills that exceeded the maximum fill times of both the SB17 PFS and SB17 vial filling times. The maximum fill time for the SB17 PFS is defined. The maximum fill time for SB17 vial is defined.

Shipping qualification has been performed on bulk and final packaging. The shipping qualification is acceptable.

2.4.2.3. Product specification, analytical procedures, batch analysis

Specifications

The finished product specifications include tests for appearance, osmolality, pH, identity (IL-23 binding activity, icIEF), extractable volume, protein concentration, biological activity (IL-23 biding activity, IL-23 neutralisation activity), purity and impurity (CE-SDS non reduced, CE-SDS reduced, SE-HPLC), charge heterogeneity (icIEF), container closure integrity, bacterial endotoxins (Ph. Eur.), particulate matter (Ph. Eur.) and sterility (Ph. Eur.).

The acceptance criteria for both drug products are largely harmonised, however for SB17 vial, osmolality, protein concentration and extractable volume are specific to the vial presentation. Testing of the DP is in compliance with ICH Q6B and Ph. Eur. monographs for Monoclonal Antibodies for Human Use (2031) and Parenteral Preparations (0520).

The specifications include functionality testing of the PFS.

The approach to establishing specifications is inconsistent as tolerance intervals, defined ranges and analysis of the reference medicinal product have all been used on various quality attributes to justify the specifications. However, the proposed specifications have been suitably justified. Both DP presentations contain PS80 and stability data has been provided demonstrating that the PS80 levels remain stable.

A nitrosamine risk assessment has been provided. The risk assessment concluded that there was no risk of nitrosamines in Eksunbi drug product from the raw materials, manufacturing components, packaging or cleaning processes at the manufacturing site.

Analytical procedures

The compendial methods used for analysis of Eksunbi DP have been listed and their associated Ph. Eur. monograph used for testing referenced. Non-compendial methods used for analysis of Eksunbi DP are the same as those used for the drug substance, which have been previously described and appropriately validated.

However, as the DP vial formulation contains a combination of a surfactant and a chelator, low endotoxin recovery (LER) was detected for the vial presentation (no LER was detected for the PFS presentations). The proposed LER mitigation strategy is acceptable.

Batch Analysis

For the Eksunbi PFS, batch data has been provided from batches, which covers all batches manufactured to date. The data presented includes pilot batches, engineering run, clinical batches and PPQ batches for each of the DP 45 mg PFS and DP 90 mg PFS. For SB17 vial, batch data has been provided from batches from the DP vial manufacturing process. The data presented includes pilot batches and PPQ batches.

All batch data provided, for both presentations, were within the proposed specification and show that the manufacturing process can product SB17 to a consistent quality.

Reference Materials

The reference standards used for release are the same as those used for DS and have discussed previously.

Container Closure

The primary packaging material for Eksunbi consists are of glass syringe and a rubber stopper. The materials of construction are Ph. Eur. compliant and technical drawings have been provided. The syringe and stopper are the only components in direct contact with the DP and the sterilisation sites for the syringe and stopper have been registered. The glass syringe is sterilised by ethylene oxide according to ISO 11135 and the stopper has been sterilised by gamma irradiation according to ISO 11137. ISO certification for the sterilisation sites registered in the dossier have been provided.

During the procedure a major objection (MO) was raised as a Notified Body opinion relating to the PFS was missing. In response the Notified Body opinion has been provided. The PFS conforms to the relevant general requirements in Chapter I, the requirements regarding design and manufacture in Chapter II, and requirements regarding the information supplied with the device in Chapter III of Annex I of regulation (EU) 2017/745.

For the Eksunbi vial, the container closure system consists of a 30 mL, clear type I glass vial with a 20 mm rubber stopper that is sealed with a 20 mm aluminium cap. The description of the components is brief but adequate. All contact materials comply with Ph. Eur. 3.2.1 (glass vial) and Ph. Eur. 3.2.9 (rubber stopper). The container closure system is standard for monoclonal antibodies. The vial is sterilised by depyrogenation and the stopper sterilised by steam at the finished product manufacturing site in line with Ph. Eur. 5.1.1. Representative drawings of the vial and stopper have been provided.

2.4.2.4. Stability of the product

Eksunbi *PFS DP*

The shelf-life for the Eksunbi 45 mg PFS DP and the Eksunbi 90 mg PFS DP is 24 months at 5 ±3°C. Individual pre-filled syringes may be stored at room temperature up to 30°C for a maximum single

period of up to 1 month in the original carton to protect from light. The period of 1 month must not exceed the original expiry date printed on the carton.

Long-term stability data is available from the PPQ batches and the applicant is leveraging data from clinical batches, which have up to 24 months long-term stability data. A comparability study has been provided that demonstrates comparability between clinical and commercial product. Additionally, stressed stability studies show that clinical and commercial product have similar degradation profiles. Therefore, the proposal to leverage long-term stability data from clinical batches to establish a 24-month shelf-life is acceptable.

Stability studies have been carried out in accordance with ICH Q1E, Q5C and photostability studies were carried out in accordance with ICH Q1B. Long-term (5 ±3°C), Accelerated (25 ±2°C/60 ±5% RH) and Stressed (40 ±2°C/75 ±5% RH) were provided for batches that comprised of pilot batches, clinical DP batches and PPQ batches. The methods used have been described and validated. The shelf-life specifications applied throughout the stability studies are not in line with the commercial specifications registered in P.5.1, however all currently provided data comply with the registered stability acceptance criteria. It has been requested that registered specifications should be used for on-going studies. The applicant has committed to updating the specifications for ongoing stability studies and it is requested that this be completed by closing sequence.

A short-term cycling study, supply chain cycling study, room temperature study and photostability study were also conducted. The short-term cycling study consisted of exposure of the Eksunbi DP to low and high temperatures. Results provided in the dossier show there is no impact to CQAs following the temperature cycling. A supply chain study was conducted to address non-routine excursions that may be encountered in the supply chain. Results remained within specification demonstrating that SB17 DP can tolerate temporary non-routine excursions that may occur within the supply chain. A room temperature study investigated the effects of storing DP at room temperature (30 ± 2°C/65 ± 5% RH) for 2 months following storage at 24 months at 5 ± 3°C.

The photostability study exposed PPQ DP Batch 45 mg 0001 to at least 1.2 million lux hours of white fluorescent lamp light and at least 200 watt hours per square meter of near UV lamp light at 25 ± 2°C/60 ± 5% RH. Notable changes were observed in a quality attribute following light exposure. Data presented demonstrates that the commercial pack can protect from these light-induced effects.

In order to ensure blinding during the clinical trial period, a PFS is used that is different than the final commercial PFS. The materials of construction for the syringe and stopper are similar and a comparability study has been provided demonstrating that both syringes and stoppers are comparable.

SB17 Vial DP

The shelf-life for the Eksunbi 130 mg vial is 18 months at 5 ±3°C and the product should not be frozen. After dilution, chemical and physical in-use stability of the diluted solution has been demonstrated for up to 72 hours at 30°C. If necessary, the diluted infusion solution may be kept at 2 °C to 8 °C for up to 1 month and at room temperature up to 30°C for an additional 72 hours after removal from refrigeration including the infusion period.

The applicant proposes a shelf-life of 18-months and real time stability data has been provided to support this shelf-life.

Stability studies have been carried out in accordance with ICH Q1E, Q5C and photostability studies were carried out in accordance with ICH Q1B. Long-term (5 ±3°C), Accelerated (25 ±2°C/60 ±5% RH) and Stressed (40 ±2°C/75 ±5% RH) were provided for batches that comprised of pilot batches and PPQ batches. The methods used have been described and validated. The shelf-life specifications applied throughout the stability studies are not in line with the registered commercial specifications,

however all currently provided data comply with the registered stability acceptance criteria. It has been requested that registered specifications should be used for on-going studies.

A supply chain study was conducted to address non-routine excursions that may be encountered in the supply chain. results remained within acceptance criteria. The study demonstrates the DP can withstand short, non-routine excursions within the supply chain should they occur.

In line with ICH Q1B, the photostability study exposed PPQ Vial DP (130 mg, batch 0001) to at least 1.2 million lux hours of white fluorescent lamp light and at least 200 watt hours per square meter of near UV lamp light at 25 ± 2°C/60 ± 5% RH. when stored in the commercial packaging, these changes were not observed. This demonstrates that Eksunbi is light sensitive and that the commercial packaging provides sufficient light protection.

In-use stability studies were performed to demonstrate compatibility with polyolefin IV bags when DP is diluted to either 1.04 mg/mL or 2.08 mg/mL in 0.9% NaCl or 0.45% NaCl solutions. The in-use stability studies are complete and met all stability release specifications. The in-use study demonstrated that, following dilution in 0.9% or 0.45% NaCl solution, the DP is stable for up to 1 month at 5 ±3°C plus an additional 72 hr at 30 ±2°C/60 ±5% RH.

2.4.2.5. Biosimilarity

Overview

The biosimilarity of Eksunbi (SB17) to the EU Stelara reference medicinal product (RMP) was assessed using a range of state-of-the-art analytical tests in line with the EMA *Guideline on Similar Biological Medicinal Products containing Biotechnology-derived proteins as active substance* (EMA/CHMP/BWP/247713/2012). Two separate biosimilarity exercises were presented for the PFS (45 mg subcutaneous) and vial (130 mg IV) presentations. The characterisation for the similarity assessment involved the determination of physicochemical and biological properties of SB17 and EU Stelara. Data have been presented to support the suitability of the analytical methods used.

The QTPP to identify the relevant product quality attributes (QAs) of the RMP and the associated risk assessments to rank criticality of QAs are described. The testing panel includes primary and higher order structure, post-translational modifications, size and charge variants, protein concentration, as well as Fab and Fc-mediated biological functions. Overall, appropriate quality attributes have been selected for inclusion in the analytical similarity exercise and the assignment of criticality to QAs is agreed. FcRγ binding is evaluated but is designated as a non-CQA on the basis that effector function is not relevant to the mechanism of action of ustekinumab. This is agreed. Functional comparison data for delivered volume and activation force of the PFS presentations is presented in and is acceptable.

Depending on the degree of risk assigned to QAs, different acceptance ranges were applied for the determination of similarity. For low-risk attributes or attributes that cannot be quantitatively measured, a comparison of raw data or graphical results was performed. For moderate- and high- risk attributes, quality ranges of mean ± X SD were applied. There is no particular justification presented for the statistical approach used to determine similarity ranges. However, with reference to the raw data, the defined similarity ranges are generally appropriate for the purpose of evaluating similarity. Thus, no queries are raised regarding the statistical approach used.

PFS biosimilarity

For the PFS, the reference ranges for moderate- to high- risk quality attributes were defined using 29 – 38 lots of EU Stelara RMP. This is a sufficient number of RMP lots to establish the basis for similarity

analysis and can be assumed to encompass a range of DS batches. It is also noted that two of the reference EU Stelara lots were included in the phase I and phase III studies (KCS11MI and KHS25MQ).

The side-by-side similarity analysis was performed using lots of the 45 mg presentation of SB17 compared against lots of EU Stelara. As the only difference between the 45 mg and 90 mg PFS is the fill volume, it is proposed to establish similarity solely using the 45 mg presentation of SB17. This approach is agreed and is justified on the basis of a risk assessment to evaluate any impact of the manufacturing process on the relevant quality attributes and on the results of an extended side-by-side comparability exercise for the 45 mg and 90 mg PFS presentations of Eksunbi. While the number of SB17 lots included in the side-by-side analysis is relatively low, the batches were manufactured using different DS lots and are either PPQ lots or are representative of the commercial manufacturing process. Furthermore, data is also presented for lots of the 130 mg vial presentation in a separate analytical similarity exercise which is discussed further below. Overall, sufficient lots of Eksunbi have been evaluated against EU Stelara for the purpose of establishing analytical similarity.

All reference and test lots were tested prior to expiry. In addition, the selection of reference batches to determine the similarity ranges has been with respect to batch age at time of testing and how the batches were suitable to generate a representative quality profile. Similarly, the age of the test batches (SB17) vs the reference batches included in the side-by-side analysis has been justified.

A summary of the characterisation results for the PFS similarity assessment is presented below in Table 1.

Table 1. Similarity assessment results for PFS

Category	Test Item	Data Analysis Method	Similarity Assessment Result
Physicochemical Properties: Primary structure and post translational modification	Molecular weight	Raw data/graphical comparison	Similar
	Amino acid sequence	Raw data/graphical comparison	Similar
	Peptide mapping	Raw data/graphical comparison	Similar
	N-terminal sequence	Raw data/graphical comparison	Similar
	C-terminal sequence	Raw data/graphical comparison	Minor differences (Justified in Section 2.3.1.5)
	Extinction coefficient	Raw data/graphical comparison	Similar
	Oxidation	Raw data/graphical comparison	Similar
	Deamidation	Raw data/graphical comparison	Similar
Physicochemical Properties: Glycan profiles	N-linked glycosylation site	Raw data/graphical comparison	Similar
	N-glycan identification	Raw data/graphical comparison	Minor differences (Justified in Section 2.3.2.2)

Category	Test Item	Data Analysis Method		Similarity Assessment Result
	N-glycan profile	%G0F	Raw data/graphical comparison	Minor differences (Higher than Stelara, Justified in Section 2.3.2.3)
		%G1F	Raw data/graphical comparison	Minor differences (Lower than Stelara, Justified in Section 2.3.2.3)
		%G2F	Raw data/graphical comparison	Minor differences (Lower than Stelara, Justified in Section 2.3.2.3)
		%Afucose	Raw data/graphical comparison	Minor differences (Lower than Stelara, Justified in Section 2.3.2.3)
		%Charged glycan	Raw data/graphical comparison	Minor differences (Lower than Stelara, Justified in Section 2.3.2.3)
		%High mannose	Quality range (Mean ± X SD)	Within similarity range
		%α-Gal	Raw data/graphical comparison	Minor differences (Lower than Stelara, Justified in Section 2.3.2.3)
	Total sialic acid contents	Raw data/graphical comparison		Minor differences (Lower than Stelara, Justified in Section2.3.2.4)
Physicochemical Properties: Purity and Impurities	SE-HPLC	%HMW	Quality range (Mean + X SD)	Within similarity range

Category	Test Item	Data Analysis Method		Similarity Assessment Result
		%Monomer	Quality range (Mean – X SD)	Within similarity range
		%LMW	Quality range (Mean + X SD)	Within similarity range
	CE-SDS (non-reduced)	%2H1L	Quality range (Mean + X SD)	Within similarity range
		%IgG	Quality range (Mean – X SD)	Within similarity range
	CE-SDS (reduced)	%LC+%HC	Quality range (Mean – X SD)	Within similarity range
		%NGHC	Quality range (Mean + X SD)	Partly out of similarity range (Justified in Section 2.3.3.3)
Physicochemical Properties: Charge heterogeneity	CEX-HPLC	%Acidic	Quality range (Mean ± X SD)	Within similarity range
		%Main	Quality range (Mean ± X SD)	Partly out of similarity range (Justified in Section 2.3.4.1)
		%Basic	Quality range (Mean ± X SD)	Out of similarity range (Justified in Section 2.3.4.1)
	icIEF	pI of Main	Quality range (Mean ± X SD)	Within similarity range
		%Acidic	Quality range (Mean ± X SD)	Out of similarity range (6/6) (Justified in Section 2.3.4.2)
		%Main	Quality range (Mean ± X SD)	Out of similarity range (6/6) (Justified in Section 2.3.4.2)

Category	Test Item	Data Analysis Method		Similarity Assessment Result
		%Basic	Quality range (Mean ± X SD)	Out of similarity range (6/6) (Justified in Section 2.3.4.2)
Physicochemical Properties: Higher order structure	Disulfide bond	Raw data/graphical comparison		Similar
	Free sulfhydryl group quantification	Raw data/graphical comparison		Similar
	CD	Raw data/graphical comparison		Similar
	ITF	Raw data/graphical comparison		Similar
	ANS	Raw data/graphical comparison		Similar
	FTIR	Raw data/graphical comparison		Similar
	DSC	Raw data/graphical comparison		Similar
	H/DX-MS	Raw data/graphical comparison		Similar
	SEC-MALS	Raw data/graphical comparison		Similar
	SV-AUC	Raw data/graphical comparison		Similar
	DLS	Raw data/graphical comparison		Similar
	MFI	Raw data/graphical comparison		Minor differences (Lower than Stelara, Justified in Section 2.3.5.12)
Physicochemical Properties: Quantity	Protein concentration (mg/mL)	Quality range (Mean ± X SD)		Within similarity range
Biological properties	IL-23 neutralisation assay	%Relative potency	Quality range (Mean ± X SD)	Within similarity range
	IL-12 neutralisation assay	%Relative potency	Quality range (Mean ± X SD)	Within similarity range
	IL-23 binding assay	%Relative binding activity	Quality range (Mean ± X SD)	Within similarity range
	IL-12 binding assay	%Relative binding activity	Quality range (Mean ± X SD)	Within similarity range

Category	Test Item	Data Analysis Method		Similarity Assessment Result
	FcRn binding assay	%Relative binding activity	Quality range (Mean ± X SD)	Within similarity range
Additional biological properties	FcγRIa binding assay	%Relative binding activity	Raw data/graphical comparison	Similar
	FcγRIIa binding assay	%Relative binding activity	Raw data/graphical comparison	Similar
	FcγRIIb binding assay	%Relative binding activity	Raw data/graphical comparison	Similar
	FcγRIIIa binding assay	%Relative binding activity	Raw data/graphical comparison	Similar
	C1q binding assay	%Relative binding activity	Raw data/graphical comparison	Similar
	ADCC assay	Raw data/graphical comparison		Similar
	CDC assay	Raw data/graphical comparison		Similar

Results

Eksunbi and EU Stelara have the same molecular weight (intact protein analysis and deglycosylated protein analysis), amino acid sequence (100% coverage), extinction coefficient, N-terminal sequence and deamidation levels. The results of peptide mapping and PTM analysis did not indicate any significant difference in primary structure. The C-terminal ends of SB17 and EU Stelara differ in that Eksunbi has a higher content of the Lys- removed form and low levels of an α-amidated proline variant. It is agreed that these minor differences in C-terminal variants do not impact on the conclusion of analytical similarity. Oxidation levels of Met_{51} and Met_{254} were similar but not fully aligned. As levels of oxidated variants are quite low, it is agreed that these minor differences are unlikely to be relevant. An appropriate panel of tests were used to evaluate the higher order structure and results support the conclusion of biosimilarity.

The N-linked glycosylation profile of Eksunbi and Stelara is similar but, some differences were noted. N-acetylneuraminic acid (NANA) was detected only in Eksunbi while α-galactosylated or N-glycoylneuraminic acid (NGNA) were detected only in Stelara. These differences are expected due to the difference in host cell expression system but are not expected to have an adverse impact on immunogenicity as the species present in Stelara are known to be more immunogenic. The relative contents of G0F trended higher for Eksunbi than Stelara which is attributed to the difference in galactosylation between Eksunbi and the reference product and is not considered clinically meaningful given that neither molecule has CDC activity. The levels of G1F and G2F were inside the defined similarity range (mean ± X SD) although slightly below the min-max range observed for the reference product. The difference in afucosylation is not considered significant as both molecules exhibit similar FcγRIIIa binding activities and ustekinumab is not associated with ADCC or CDC. This is agreed. For the

relative contents of charged glycans, there is a significant difference between SB17 and Stelara. This difference is attributed to the different sialic acid forms; SB17 contains NANA whereas Stelara contains NGNA and α-Gal. As discussed already, there is no expected negative impact on immunogenicity arising from this difference and ustekinumab has no Fc-mediated activity. The differences in the N-glycan profile align to the differences in the charge variant profile as discussed further below are not considered to be clinically meaningful.

From the results of CEX-HPLC without enzyme pretreatment, there is a significant difference in terms of %acidic peaks, %main peak and %basic peaks between Eksunbi and Stelara. Eksunbi contains lower levels of acidic variants vs Stelara, lower levels of basic fractions vs Stelara and higher levels of main peak vs Stelara. Given the difference in charge variant profile, a structure activity relationship study was performed to analyse the different charge variant fractions present in biosimilar and reference product. Peptide mapping was performed along with SE-HPLC. The charge variant fractions were also analysed by biological characterisation (IL-23 neutralisation, IL-23 binding activity and FcRn binding activity). Overall, the difference in acidic variants between Eksunbi and Stelara is mainly attributed to the difference in sialic acid content and the results of biological characterisation were comparable between acidic and load fractions for both Eksunbi and Stelara. The differences in basic variants between the Eksunbi and Stelara products is attributed to C-terminal lysine differences. As C-terminal lysines are removed *in vivo* shortly after administration, there is no expected clinical impact. Similarly, the α-amidation of proline in the C-terminal region of SB17 contributes to the slight difference in basic peaks observed with CEX-HPLC (without enzyme treatment) but this difference is not considered clinically meaningful as this is a well-known modification in CHO cells and does not impact with respect to antibody binding or effector function. The biological characterisation of the basic fractions indicate that basic peaks were comparable to load sample with respect to IL-23 neutralisation and binding properties for both Stelara and Eksunbi. For FcRn binding, the basic fractions showed higher activity but, the difference was minor and not considered significant. The results of icIEF analysis are also presented and are consistent with the results of CEX-HPLC discussed above. The conclusion that the observed difference in charge variant profile does not have a clinically meaningful impact is agreed.

The results of SE-HPLC, CE-SDS non-reduced and CE-SDS reduced are consistent with a conclusion of biosimilarity. The results of %HMW and %LMW size variants are slightly lower in Eksunbi than in Stelara but, this would not preclude a conclusion of analytical similarity. The results of %2H1L by CE-SDS non-reduced are within the similarity range but trend slightly higher for SB17 than for Stelara. However, with reference to the min-max ranges observed for the Stelara lots, it is agreed that the difference is minor and not significant. The results of %NGHC by CE-SDS reduced are slightly higher for Eksunbi than the Stelara similarity range. However, on the basis that there is no expected immunogenic impact and given the absence of any ustekinumab Fc effector function, it is agreed that this minor difference is not clinically significant.

The relative IL-23 neutralisation potency, IL-23 binding activity, IL-12 neutralisation potency, IL-12 binding activity and FcRn binding activity of Eksunbi fell within the similarity range as defined for the EU RMP. In the case of FcRn binding, the results from Eksunbi lots trend lower than those of the EU Stelara lots although they fall within the min-max range for the reference lots. This lower trend in FcRn binding for Eksunbi is attributed to the difference in C-terminal lysine variants. This claim has been supported by data demonstrating that the difference in FcRn binding is neutralised when reference product and Eksunbi lots are treated with carboxypeptidase B (CPB) to remove the C-terminal variants. Based on the provided results of the CPB treatment study and the provided actual k_a, k_d, or K_D values for the FcRn binding assay, it is considered that there are no significant grounds for concern that administered test lots and RMP lots would behave significantly differently with respect to FcRn binding. The results of the additional biological activity characterisation support the biosimilarity of the Eksunbi

and Stelara products (FcγR binding, C1q binding, ADCC and CDC). There was no ADCC or CDC activity observed for either SB17 or Stelara.

Vial biosimilarity

Analytical similarity of the Eksunbi vial was assessed in a comprehensive similarity exercise using EU Stelara as the reference medicinal product (RMP). The reference ranges for moderate- to high- risk quality attributes were defined using lots of the EU Stelara RMP. The use of only vial RMP lots to set similarity ranges results in slightly narrower acceptance criteria for the vial biosimilarity exercise than for the PFS biosimilarity exercise. However, the results from the two similarity exercises (PFS and vial) are highly consistent. In addition, it is acknowledged that a large number of EU Stelara PFS lots were used to establish the similarity ranges for the comparison of the PFS presentation and that the PFS study should encompass a sufficient number of Stelara DS lots. Furthermore, comparability has been demonstrated between the Eksunbi PFS and vial presentations. As such, the approach to establish biosimilarity for the vial presentation using a lower number of RMP lots is acceptable.

The side-by-side similarity analysis was performed using lots of the vial presentation of Eksunbi 130 mg vial compared against lots of EU Stelara 130 mg vial. The SB17 lots are pilot scale. The pilot scale process for SB17 has been demonstrated to be comparable to the commercial process. As such, the inclusion of vial lots from the non-commercial Eksunbi process/site, while unusual, can be agreed. All reference and test lots were tested prior to expiry.

The results for the vial presentation are largely aligned to the results for the PFS. While some minor differences are noted between the results for the PFS and vial presentations, this can be attributed to the difference in the number of reference lots used to derive similarity ranges. Overall, the results of biosimilarity for the vial are highly consistent with those discussed above for the PFS presentation. In the case of FcRn binding, the results for the vial fall below the similarity range, but as described above for PFS, the differences in FcRn binding have been adequately justified.

Comparative stability studies

Comparative stability studies were carried out on Eksunbi and Stelara to assess similarity in terms of degradation profiles. The studies were performed under heat stress, basic stress, acidic stress, oxidative stress and photostress conditions. Minor differences were observed between Eksunbi and Stelara under oxidative stress conditions. A decrease in %IgG was observed by CE-SDS (non-reduced) for Stelara in comparison to Eksunbi. These results do not give rise to any concern as the trends observed are worse in the case of Stelara. Overall, the results of all comparative stability studies for both the PFS and vial showed similar degradation profiles supporting similarity between Eksunbi and Stelara.

2.4.2.6. Post approval change management protocol(s)

Not applicable.

2.4.2.7. Adventitious agents

The applicant provided a comprehensive overview of the strategy to minimise the risk of contamination by adventitious agents. The strategy consists of controlling potential sources of virus contamination both to the cell bank system and the production process, and viral clearance processes.

No animal-derived raw materials are used during the routine manufacturing process nor has there been any animal-derived raw material used during the development of the cell banks. Certificates have

been provided from the manufacturer of cell bank that state they are from a non-animal source and pose no risk of BSE/TSE.

The cell banks are tested for mycoplasma and the results are presented in the DS section and show there was no presence of mycoplasma while the unprocessed bulk is routinely tested for mycoplasma. Testing for bacterial and fungal contaminants is routinely done for the unprocessed bulks and the results for clinical batches and PPQ batches showed that there were no bacterial or fungal contaminants present.

A summary of the viral clearance studies has been provided and in general is acceptable and complies with ICH Q5A. The primary viral clearance steps are the: low pH inactivation, viral filtration, and chromatography steps including protein A affinity, and mixed mode chromatography. The model viruses were selected and the panel is considered as appropriate. The virus validation studies have been performed on a validated scale down model operating at worst-case conditions such as virus inactivation temperature, virus inactivation pH, protein A resin bed height, load ratio, column volume for washing and elution, these are considered acceptable. For the chromatography steps, virus validation data is presented from fresh resin and aged resin. The summary data presented implies there is no difference in clearance between the new and old resin. The overall approach to the viral clearance studies is considered acceptable.

Overall, the results of viral clearance study at set point conditions demonstrated the production process has sufficient capacity to inactivate or remove viruses.

2.4.3. Discussion on chemical, pharmaceutical and biological aspects

The drug substance manufacturing process is standard for the production of monoclonal antibodies. Details of developmental genetics and the establishment of the MCB and WCB are described and acceptable. The control strategy for the drug substance is comprehensive with sufficient control of each manufacturing step. The manufacturing process has been appropriately validated. The lists of raw materials have been provided and are acceptable. The characterisation data is considered sufficient. The panel of release tests covers relevant aspects of purity, potency, and safety. Batch data provided demonstrate that the commercial process is capable of manufacturing a consistent drug substance. Reference standards are sufficiently described. The container closure system for the for the DS is a Celsius FFT 6 L bag (Sartorius Stedim Biotech). A shelf-life is acceptable based on the long-term and intermediate stability data of clinical phase DS batches.

Three presentations are proposed for the DP, a 45 mg pre-filled syringe, a 90 mg pre-filled syringe and a 130 mg/26 mL vial. The DP manufacturing process is standard for a monoclonal antibody. The formulation is based on the reference medicinal product and its composition is suitable to maintain the quality of the DP, which is supported by stability studies. The control strategy for the manufacturing process has been outlined. Process validation has been completed successfully. The panel of release tests covers relevant aspects of purity, potency and safety. The batch data demonstrates that the commercial process is capable of manufacturing DP of a consistent quality. A shelf life of 24 months for the pre-filled syringes has been supported by leveraging stability data from clinical batches. Individual pre-filled syringes may be stored up to 30°C for up to 1 month. A shelf-life of 18 months has been proposed for the 130 mg DP vial and can be accepted based on the data provided.

During the procedure a major objection (MO) was raised as the notified body opinion relating to the PFS was missing. In response, the notified body opinion has been provided and the MO is considered resolved.

Overall, a comprehensive analytical similarity exercise has been performed for both the PFS and the vial presentations of Eksunbi against the EU reference product, Stelara. The results of the individual tests support a conclusion of biosimilarity.

2.4.4. Conclusions on the chemical, pharmaceutical and biological aspects

The quality of this product is considered to be acceptable when used in accordance with the conditions defined in the SmPC. Physicochemical and biological aspects relevant to the uniform clinical performance of the product have been investigated and are controlled in a satisfactory way. Data have been presented to give reassurance on viral/TSE safety.

2.4.5. Recommendation(s) for future quality development

Not applicable.

2.5. Non-clinical aspects

2.5.1. Introduction

Ustekinumab is a human immunoglobulin (Ig)G1κ monoclonal antibody which inhibits the bioactivity of human IL-12 and IL-23 by preventing p40 from binding to the IL-12Rβ1 receptor protein expressed on surface of immune cells. Literature data is provided as supporting evidence of the primary pharmacodynamics/mechanism of action of ustekinumab. By binding to the shared p40 subunit of IL-12 and IL-23, the clinical effects of ustekinumab are exerted in psoriasis, psoriatic arthritis, Crohn's disease and ulcerative colitis through interruption of the Th1 and Th17 cytokine pathways. The sought presentations of Eksunbi have identical amino acid sequence, formulations, dosage forms, and product strengths as reference product Stelara, with the exception of sucrose contents in Eksunbi versus 7.6% in Stelara for the PFS presentation. The most relevant difference between Eksunbi and Stelara is that Eksunbi is manufactured in Chinese hamster ovary cell line, whereas Stelara is manufactured in murine myeloma (Sp2/0) cell line.

2.5.2. Pharmacology

2.5.2.1. Primary pharmacodynamic studies

The applicant carried out a series of comparative *in vitro* studies as the pharmacology study program to evaluate similarity between Eksunbi and EU-Stelara inclusive of binding assays to IL-12 and IL-23 (ELISA), neutralisation assays to same, an ADCC and CDC assay, in addition to the following binding assays: FcγR1a, FCγRIIa, FCγRIIb, FCγRIIIa, C1q. The aforementioned was carried out using batches of Eksunbi, including pilot batches and process performance qualification (PPQ) batches, both with the concentrate solution for infusion (vial) 130 mg presentation, as well as the solution for subcutaneous (SC) injection in a pre-filled syringe (PFS) 45 mg presentation. The tests were conducted side-by-side with batches of the reference product Stelara (EU) for each presentation, respectively. When defining the similarity ranges for each biological attribute, the applicant differentiated attributes into high risk and moderate risk, applying a standard deviation (SD) multiplier. Similarity ranges were established for the biological attributes based on batches of EU Stelara per presentation. All performed assays

were within the similarity range except for the FcRn assay for the IV vial 130 mg presentation. Thus, Eksunbi (IV vial) binds slightly less to FcRn than Stelara.

Based on results of these studies, the applicant has concluded that Eksunbi and EU-Stelara are similar in terms of their pharmacodynamic (PD) behaviour and concluded that in vitro studies provide evidence to support the similarity of Eksunbi and Stelara with respect to pharmacological activity.

2.5.2.2. Secondary pharmacodynamic studies

No secondary PD studies were conducted based on EMA guideline [EMA/CHMP/BMWP/403543/2010] as well as the recommendations from the EMA [EMA/CHMP/SAWP/791150/2017].

2.5.2.3. Safety pharmacology programme

No safety PD studies were conducted based on EMA guideline [EMA/CHMP/BMWP/403543/2010] as well as the recommendations from the EMA [EMA/CHMP/SAWP/791150/2017].

2.5.2.4. Pharmacodynamic drug interactions

No pharmacodynamic PD studies were conducted based on EMA guideline [EMA/CHMP/BMWP/403543/2010] as well as the recommendations from the EMA [EMA/CHMP/SAWP/791150/2017].

2.5.3. Pharmacokinetics

Since no noted differences were observed in biological activity between Eksunbi and EU Stelara, following a stepwise and risk-based approach, *in vivo* animal studies are deemed unnecessary for the development of Eksunbi as agreed by the EMA [EMA/CHMP/SAWP/791150/2017]. As similarity has been sufficiently documented in the *in vitro* pharmacology studies, further non-clinical pharmacokinetic studies are not considered warranted.

2.5.4. Toxicology

No *in vivo* studies (single dose, repeat dose toxicity, genotoxicity, carcinogenicity or reproductive and development toxicity studies) have been carried out.

2.5.5. Ecotoxicity/environmental risk assessment

Eksunbi is a proposed biosimilar to Stelara having ustekinumab as the active substance. It has been approved and on market *via* centralised procedure as Stelara since 2009. The approval of Eksunbi is expected to lead to substitution for the reference medicinal product and therefore it should not result in an increase in total consumption of ustekinumab. Ustekinumab is a monoclonal antibody and therefore is broken down naturally by proteolytic enzymes into polypeptides and amino acids. No other intermediates are reported and therefore are not anticipated to pose toxic or accumulative risk to the environment. The current guideline EMEA/CHMP/SWP/4447/00 corr 21* states that for protein pharmaceuticals, an ERA should be provided, but may consist of justification for not submitting ERA studies since protein biopharmaceuticals are unlikely to pose risk to environment.

2.5.6. Discussion on non-clinical aspects

No additional *in vivo* pharmacodynamic effect studies were carried out. However, the comparability assessment between Eksunbi and EU-Stelara using lots from clinical phase and PPQ batches of the 45 mg PFS versus independent lots of EU-Stelara demonstrated similarity in terms of C-terminal sequence, *N*-glycan profile, % charge heterogeneity, and higher order structure, with some but not all experimental approaches. All deviations have been justified by the applicant and were considered acceptable to the CHMP. Both *in vitro* ligand binding assays and cell-based potency/neutralisation assays have been carried out in addition to analysis of additional biological effects (ADCC and CDC). Both relative potency and binding activity are reported as similar for Eksunbi and EU-Stelara. IL-23 neutralisation assays employed IL12Rβ1/IL23R-STAT3/Luc HEK293 cells expressing luciferase reporter gene upon activation of IL-23 dependent signalling. IL-12 neutralisation assays employed IL12Rβ1/IL12Rβ2-STAT4/Secreted Embryonic Alkaline Phosphatase (SEAP) HEK-Blue cells which express a reported gene induced by IL-12 binding. Similarity ranges are reported as 80-113% and 77-121% respectively. IL-23 and IL-12 binding were measured using enzyme linked immunoassay (ELISA) with similarity ranges of 83-118% and 85-114% respectively to EU-Stelara.

Binding activity to FcRn for Eksunbi ranged from 98-102% whereas the similarity range has been established between 107-127%. Thus, Eksunbi (IV vial) binds slightly less to FcRn than Stelara. The differences can be considered not clinically meaningful and related to the relative contents of basic variant (Lys variant), which was also shown in QC testing to differ between Eksunbi and Stelara batches. Stronger FcRn binding activity may enhance the half-life of the antibody, thus implying that increased plasma concentrations of Stelara could be expected. However, in light of only marginal differences between IV vial of Eksunbi and Stelara batches, and as no difference was observed for the SC PFS presentation, the CHMP concluded that that the differences are not expected to result in a biological meaningful impact.

Secondary pharmacology, safety pharmacology and pharmacodynamic drug interaction studies, pharmacokinetic analysis, *in vivo* toxicology/toxicokinetic, or any addition studies were not carried out. It was agreed between applicant and EMA during SA that the aforementioned omitted studies for Eksunbi were not required if the data from the comparative structural analyses, physicochemical analyses, as well as *in* vitro non-clinical studies and functional assays demonstrated similarity between Eksunbi and EU-sourced Stelara (hereafter referred to as, 'EU Stelara) [EMA/CHMP/SAWP/791150/2017]. This is also in agreement with the EMA Guideline on similar biological medicinal products (CHMP/437/04 Rev 1; 2014) and the EMA Guideline on similar biological medicinal products containing biotechnology-derived proteins as active substance: non-clinical and clinical issues (EMEA/CHMP/BMWP/42832/2005 Rev 1).

Omission of genotoxicity, carcinogenicity and reproduction toxicology (including fertility and early embryonic development, embryofoetal development and pre- and post-natal development), is acceptable to the CHMP as EMA guidance on ICH S6 [EMA/CHMP/ICH/731268/1998] states that carcinogenicity studies are not routinely conducted for biotechnology derived pharmaceuticals. Similarly, the "Guideline on similar biological medicinal products containing monoclonal antibodies: non-clinical and clinical issues" [EMA/CHMP/BMWP/403543/2010] states that reproduction toxicology is not required in non-clinical program for biosimilars. Absence of all other toxicity studies are acceptable to the CHMP.

Since no noted differences were observed in biological activity between Eksunbi and EU Stelara, following a stepwise and risk-based approach, *in vivo* animal studies were not deemed necessary for the development of Eksunbi. This is acceptable to the CHMP and considered appropriate.

The active substance ustekinumab is a protein monoclonal antibody and therefore is broken down naturally by proteolytic enzymes into polypeptides and amino acids. No other intermediates are reported and therefore are not anticipated to pose toxic nor accumulative risk to the environment. The applicant provided a valid justification for the absence of dedicated ERA studies, which is agreed by the CHMP.

2.5.7. Conclusion on non-clinical aspects

The available non-clinical primary pharmacodynamic *in vitro* data for Eksunbi support the pharmacological mechanism of action of ustekinumab in acceptable similarity ranges with reference product EU-Stelara. The absence of pharmacokinetic, toxicology and toxicokinetic studies is agreed by the CHMP.

The applicant has provided a valid justification for the absence of dedicated ERA studies, which is agreed by the CHMP.

Overall, the non-clinical package of Eksunbi is adequate to support the approval as a biosimilar to Stelara.

2.6. Clinical aspects

2.6.1. Introduction

GCP aspects

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

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

Table 2. Tabular overview of clinical studies

Study ID (Country)	Study Objective	Study Design/Duration	Study Population	Primary Endpoint
SB17-1001 **Phase I** (France)	Comparative PK, safety, tolerability, and immunogenicity Primary objective: For EMA: To demonstrate PK similarity of SB17 and EU Stelara in healthy subjects For FDA: To demonstrate PK similarity between SB17 and EU Stelara, between SB17 and US Stelara, and between EU Stelara and US Stelara in healthy subjects	Randomized, double-blind, three-arm, parallel group, single-dose study Total duration of approximately 18 weeks including 28-days screening period	Healthy subjects	PK • Area under the concentration-time curve from time zero to infinity (AUC_{inf}) • Maximum serum concentration (C_{max})
SB17-3001 **Phase III** (Czech Republic, Estonia, Hungary, Latvia, Lithuania, Poland, Republic of Korea, and Ukraine)	Comparative efficacy, safety, tolerability, PK, and immunogenicity Primary objective: To demonstrate the equivalence of SB17 to Stelara, in terms of the percent change from baseline in Psoriasis Area and Severity Index (PASI) at Week 12 in patients with moderate to severe plaque psoriasis (PsO)	Randomized, double-blind, multicentre study Total duration of approximately 56 weeks of study treatment period including 4 weeks of screening period and 24 weeks transition period.	Patients with moderate to severe plaque PsO	• Percent change from baseline in PASI at Week 12

AUC_{inf} = area under the concentration-time curve from time zero to infinity; C_{max} = maximum serum concentration; PASI = psoriasis area and severity index; PK = pharmacokinetic(s); PsO = psoriasis

2.6.2. Clinical pharmacology

2.6.2.1. Pharmacokinetics

Bioequivalence

Clinical Phase I study (SB17-1001)

Methods

Study design

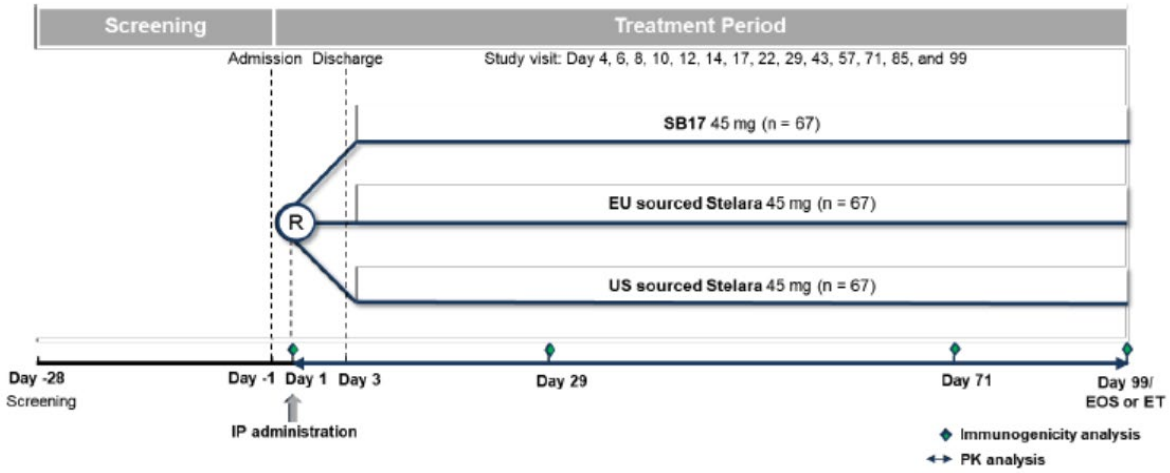
Study SB17-1001 is a randomised, double-blind, three-arm, parallel group, single-dose Phase I study in healthy subjects designed to demonstrate equivalence with respect to the PK profile of Eksunbi (ustekinumab) and Stelara. To support the global clinical development program the study was also designed to assess the PK profiles of Eksunbi, EU Stelara, and US Stelara.

Phase I study SB17-1001 was conducted entirely within the EU in France.

The total study duration was approximately 18 weeks (including the 4-week Screening period).

373 subjects were screened, and a total of 201 healthy subjects aged 18-55 years were randomised 1:1:1 to receive a single dose of either Eksunbi, EU sourced Stelara, or US sourced Stelara. All investigational products (IPs) were administered subcutaneously in the abdomen.

Figure 2. Schematic of study design



EOS: End of study; ET: Early termination; EU: European Union; IP: Investigational product; PK: Pharmacokinetic; R: Randomisation; US: United States of America.

Key inclusion criteria

Subjects had to meet all the following criteria to be eligible for the study:

1. Healthy male or female, aged **18-55 years** (inclusive) on the day of signing the informed consent.

2. Had a body weight between **60.0-90.0 kg** (inclusive) and a body mass index (BMI) between **19.0-29.9 kg/m^2** (inclusive) at Screening and Day −1.

3. Had 12-lead electrocardiogram (ECG) results without clinically significant abnormal findings confirmed by the Investigator at Screening and Day −1.

4. Had vital sign results without clinically significant abnormal findings confirmed by the Investigator at Screening and Day −1.

5. Had physical examination results without clinically significant abnormal findings confirmed by the Investigator at Screening and Day −1.

6. Female subjects who were not pregnant or nursing at Screening and Day −1, and subjects who were not planning to become pregnant during study period and until 15 weeks after the IP administration.

7. Female subjects of non-childbearing potential

Key exclusion criteria

Subjects meeting any of the following criteria were not eligible for the study:

1. Had a history and/or current presence of clinically significant atopic allergy, hypersensitivity, or

- allergic reactions (either spontaneous or following drug administration), also including known or

- suspected clinically relevant drug hypersensitivity to ustekinumab or to any of the excipients.

2. Had a history of and/or current clinically significant gastrointestinal, renal, hepatic, cardiovascular, haematological, neurologic (including reversible posterior leukoencephalopathy syndrome), metabolic (including known diabetes mellitus), psychiatric disorder, drug or alcohol abuse, or allergic disease excluding mild asymptomatic seasonal allergies.

3. Had a history of significant respiratory disorder (including asthma, non-infectious pneumonia).

4. Had a history of malignancy (including lymphoma, leukaemia, and skin cancer).

5. Had either active or latent tuberculosis (TB) as indicated by a positive test result for Mycobacterium tuberculosis at Screening or who had a history of TB.

6. Had a history of serious infection (associated with hospitalisation and/or which required intravenous [IV] antibiotics) within 8 weeks prior to randomisation.

Treatments

Subjects received a single dose of 45 mg/0.5 mL of either Eksunbi, EU-approved Stelara, or US-licensed Stelara on Day 1 as an SC injection.

Objectives

Primary objective:

To compare the PK of Eksunbi with EU- and US- Stelara and the PK of EU- Stelara with US- Stelara in terms of C_{max} and $AUC_{0\text{-}inf}$ following a single 45 mg/0.5 mL SC injection in healthy subjects.

The PK similarity of Eksunbi versus EU-Stelara, Eksunbi versus US-Stelara, and US-Stelara versus EU-Stelara would be demonstrated if, for all pairwise comparisons, the 90% CIs of the GMRs for both $_{Cmax}$ and $AUC_{0\text{-}inf}$ were entirely contained within the equivalence margin of 0.8 to 1.25 (i.e., 80% to 125% when the ratio was expressed as a percentage).

Secondary objectives:

The secondary objectives were to investigate and compare the safety, tolerability, and immunogenicity between Eksunbi and EU sourced Stelara in healthy subjects.

Outcomes/endpoints

Primary endpoints

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

Secondary endpoints:

- Secondary PK Endpoints
  - Area under the concentration-time curve from time zero to the last quantifiable concentration (AUC_{last})
  - Area under the concentration-time curve 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 (Vz/F)

- Terminal rate constant (λz).
- 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 ($\%AUC_{extrap}$)

– The safety parameters assessed included AEs, clinical laboratory assessments (haematology, clinical chemistry, coagulation, urinalysis, and urine microscopy), vital signs, ECG, physical examination findings, and injection site reactions.

– Immunogenicity assessments included antidrug antibodies (ADAs) and neutralising antibodies (Nabs).

Sampling time points

Blood samples for PK analysis were collected on Day 1 at 0 hour (pre-dose), 12, 24, 48, and 72 hours post-dose, then on Day 6 (120 hours), Day 8 (168 hours), Day 10 (216 hours), Day 12 (264 hours), Day 14 (312 hours), Day 17 (384 hours), Day 22 (504 hours), Day 29 (672 hours), Day 43 (1008 hours), Day 57 (1344 hours), Day 71 (1680 hours), Day 85 (2016 hours), and Day 99 (2352 hours) post-dose.

Blood samples for immunogenicity assessment were collected on Day 1 (pre-dose), Day 29, Day 71, and Day 99, for determination of ADAs and NAbs to ustekinumab.

Sampling schedule

Intensive daily sampling was carried out from Day 1 to Day 4, then every second day to day 14. It had been advised during the EMA SA that the sampling time-points should be selected sufficiently tight to provide a reliable estimate of peak exposure and to adequately characterise the whole PK profile, especially time-points around T_{max}. The range of t_{max} values is noted to be large in the study results.

Sample size

The sample size was calculated based on an estimated inter-subject coefficient of variation (CV%) of 33.9% which was reported in the previously published data [Stelara, Clinical Pharm and biopharma review]. With a sample size of 63 in each of 3 treatment arms (i.e., a total sample size of 189), a parallel study design would have 90% power, assuming a true geometric mean ratio of 1.05, to be able to reject both the null hypotheses that 1) the true geometric mean ratio of the test to the reference was less than 0.80 and 2) the true geometric mean ratio of the test to the reference was greater than 1.25, where both of these null hypotheses could be rejected simultaneously if the 90% CIs for the true geometric mean ratio lay completely between 0.80 and 1.25. Assuming a 5% drop-out rate, a total of 201 subjects (67 in each of three treatment arms) were required for study enrolment. Each subject was randomly allocated to one of the three treatment groups. In each cohort, 67 randomly selected subjects received a single dose of either Eksunbi 45 mg, EU Stelara 45 mg, or US Stelara 45 mg.

Randomisation

Randomisation to Eksunbi, EU-approved Stelara, or US-licensed Stelara was performed in a 1:1:1 ratio. The method of randomisation was not described, including details of block size.

The Phase I study was a subject-, investigator- and sponsor-blinded study. Blinding of the patient as a blinding cap was applied to the IP.

Statistical methods

According to the SAP: the statistical analysis of the $\log_e$ transformed primary endpoints were performed by the analysis of variance (ANOVA). The difference in least squares means (LSMeans) between Eksunbi and EU sourced Stelara, between Eksunbi and US sourced Stelara, or between EU sourced Stelara and US sourced Stelara and the corresponding 90% confidence intervals (CIs) were determined.

Back transformation provided the ratio of geometric LSMeans and 90% CIs for these ratios. Equivalence for the primary endpoints (AUC_{inf} and C_{max}) was determined as follows: For the EMA review, equivalence for the primary endpoints (AUC_{inf} and C_{max}) was determined if the 90% CI for the ratio of geometric LSMeans of Eksunbi to EU sourced Stelara is within the equivalence margin of 0.80 to 1.25.

Analysis populations

The following sets were stated for the analyses performed in the study according to the SAP:

- Enrolled Set (ENR): ENR consists of all subjects who provided informed consent for this study.
- Randomised Set (RAN): RAN consists of all subjects who received a randomisation number.
- Safety Set (SAF): SAF consists of all subjects who received Investigational Product (IP).
- Pharmacokinetic Analysis Set (PKS): PKS consists of all subjects in the SAF who had at least one PK sample analysed without any major protocol deviation that was likely to have an impact on PK assessments. Bioequivalence was based on the PK analyses set, which is supported.

The statistical analyses were conducted using ANOVA methods suitable to a parallel group design and comparisons between Test and references were made in a pairwise way (excluding non-relevant data) between the Test and relevant reference. Secondary endpoints were summarised.

Statistical methods for the primary and secondary endpoints

For the primary PK parameters, using the PK population, log transformed PK parameters (AUC_{inf}, C_{max}) Secondary PK endpoints were summarised. For summary statistics, the BLQ concentrations before IP administration were considered as zero (0.00), and other BLQ concentration were set to missing. If more than half of values are BLQ, then descriptive statistics of n, mean, median, Min and Max values were calculated only. Other statistics were not to be calculated and were reported as "NC", representing "Not Calculated". Missing values were ignored when calculating descriptive statistics.

Bioanalytical methods

PK assay: The comparative PK of ustekinumab after administration of Eksunbi or Stelara in the clinical Phase I study in healthy subjects as well as in the PK subset of the clinical Phase III study in plaque PsO patients was evaluated using an enzyme-linked immunosorbent assay (ELISA) to detect serum concentration of ustekinumab. The analytical method for determination of ustekinumab in human serum has been validated in accordance with ICH M10 with respect to specificity/interference, precision and accuracy, selectivity, dilution linearity/hook effect, and sample stability.

ADA assay

The comparative ADA incidences in response to administration of Eksunbi or Stelara were evaluated in the Phase I and Phase III studies using a bridging ligand-binding assay with an electrochemiluminescence (ECL) platform with Mesoscale Discovery (MSD). In accordance with the Guideline on Immunogenicity assessment of biotechnology-derived therapeutic proteins (EMEA/CHMP/BMWP/14327/2006 Rev.1), the presence of ADA was evaluated using the recommended

three-tiered approach: an initial screening assay to identify potentially ADA positive samples, a confirmation (specificity) assay based on competition with exogenously added ustekinumab, and a determination of the titre of ADA for confirmed positive samples. The assay was appropriately validated. The data to support the antigenic equivalence of the Eksunbi labelled critical reagents for detection of ADA against Eksunbi, EU Stelara and US Stelara is acceptable. The approach for cut-point determination is standard and acceptable. During the clinical studies, pre-dose samples were evaluated to determine whether an in-study cut-point was necessary. It was determined that the validation cut points were suitable for use during sample analysis and this is agreed.

NAb assay

The comparative NAb incidences in response to administration of Eksunbi or Stelara in the clinical Phase I study in healthy subjects as well as in the clinical Phase III study in psoriasis patients were evaluated by means of NAb detection in human serum samples using a competitive ligand-binding assay with ECL platform using MSD**.** The assay was appropriately validated and the data to support the antigenic equivalence of the Eksunbi labelled critical reagents for detection of NAb against Eksunbi, EU Stelara and US Stelara is acceptable. The positive control is anti-ustekinumab antibody and has been appropriately characterised. The cut-point for the neutralising assay is the level of response above which a sample is defined to be negative and at or below which it is defined to be positive for drug neutralising antibodies. In general, although the cut-point was not derived using patient serum pre-dose samples from SB17-1001, the statistical approach taken to determine the cut-point is standard and acceptable.

Patient flow

A total of 373 subjects were screened, of which 201 subjects (67 subjects in each Eksunbi, EU Stelara, and US Stelara) were randomised, all of whom included in the SAF and PKS. Of the randomised subjects, 186 subjects completed the study, and 15 subjects discontinued the study before completion. The most common reason for screening failure was inclusion/exclusion criteria. Subjects discontinued due to unacceptable toxicity including AEs (13 subjects; all due to COVID-19), withdrawal of informed consent (1 subject) and discretion of the Investigator (1 subject; due to subject pregnancy).

Recruitment

This study was conducted at 1 study site in France. Study initiation date: Feb 04, 2021 (first subject signed informed consent) Study completion date: Apr 01, 2022 (last subject last visit).

Conduct of the study

Protocol Deviations

A total of 34 (16.9%) subjects (10 [14.9%] patients in the Eksunbi, 14 [20.9%] subjects in the EU Stelara, and 10 [14.9%] patients in the US Stelara treatment groups) had major PD reported and the applicant outlines that no one was excluded from PKS.

Out of 34 subjects, 33 subjects reported major PD of 'blood samples for PK analysis was centrifuged in low speed'. A total of 10 subjects reported major PD of 'blood sample for immunogenicity analysis was centrifuged in low speed', and one subject reported major PD of 'the informed consent form (ICF) re-consent was not obtained at the earliest next visit after effective date of the revised informed consent obtained'. Data were not included in mean graphs as described in the PK data review document. The deviation led to the exclusion of corresponding data at the corresponding visit from descriptive

summaries, statistical analyses, PK parameter calculation and graphical representations of the mean but not to the exclusion of the subject from the PKS or SAF.

The applicant outlined that all 201 subjects were planned to be included for PK analysis. In the PK analyses populations, there were 67 subjects (EU) for each of the Test and Reference, but between n=62 and 64 were analysed.

Baseline data

The demographic characteristic for the randomised set is summarised in the below Table 3. 124 subjects (61.7%) were male, and 77 subjects (38.3%) were female in this study. The majority of subjects were White (170 [84.6%] subjects) and not Hispanic or Latino (196 [97.5%] subjects). Demographic and other baseline characteristics were generally comparable among the 3 treatments groups, with a slight lower mean value for weight and BMI in the EU sourced Stelara group.

Numbers analysed

From a possible 134 subjects **(EU analyses)** in the PK analyses set, 126 subjects were included in the PK analysis for demonstrating bioequivalence.

Table 3. Number of Subjects Analysed

Treatment	SB17	EU Stelara	US Stelara	Total
Number (%) of Subjects	n (%)	n (%)	n (%)	n (%)
Randomized Set (RAN)	67 (100.0)	67 (100.0)	67 (100.0)	201 (100.0)
Safety Set (SAF)	67 (100.0)	67 (100.0)	67 (100.0)	201 (100.0)
Pharmacokinetic Analysis Set (PKS)	67 (100.0)	67 (100.0)	67 (100.0)	201 (100.0)

n = Number of subjects in the corresponding analysis set
Randomized Set (RAN) = consisted of all subjects who received a randomization number
Safety Set (SAF) = consisted of all subjects who had received IP
Pharmacokinetic Analysis Set (PKS) = consisted of all subjects in the SAF who had had at least one PK sample analyzed without any major protocol deviation that was likely to have had an impact on PK assessments
Percentages were based on the number of randomized subjects.

Table 4. Statistical Comparison of Primary Pharmacokinetic Parameters Between SB17 and EU Stelara (Pharmacokinetic Analysis Set, Study SB17-1001)

PK Parameter	Treatment	N	n	Geometric LSMean	Ratio A/B	90% CI of Ratio
AUC_{inf} (ng·h/mL)	SB17	67	62	4958100	0.99	0.90; 1.08
	EU Stelara	67	64	5020000		
C_{max} (ng/mL)	SB17	67	62	4882	0.90	0.82; 0.98
	EU Stelara	67	64	5433		

A = SB17; B = EU Stelara
CI = confidence interval; Geometric LSMean = geometric least squares mean; N = number of subjects in Pharmacokinetic Analysis Set; n = number of subjects in the analysis; PK Parameter = pharmacokinetic parameter
Samples for PK analysis (a total of 23 PK samples from 23 subjects) were excluded due to major protocol deviation (centrifuged in low speed) from the PK parameters calculation.

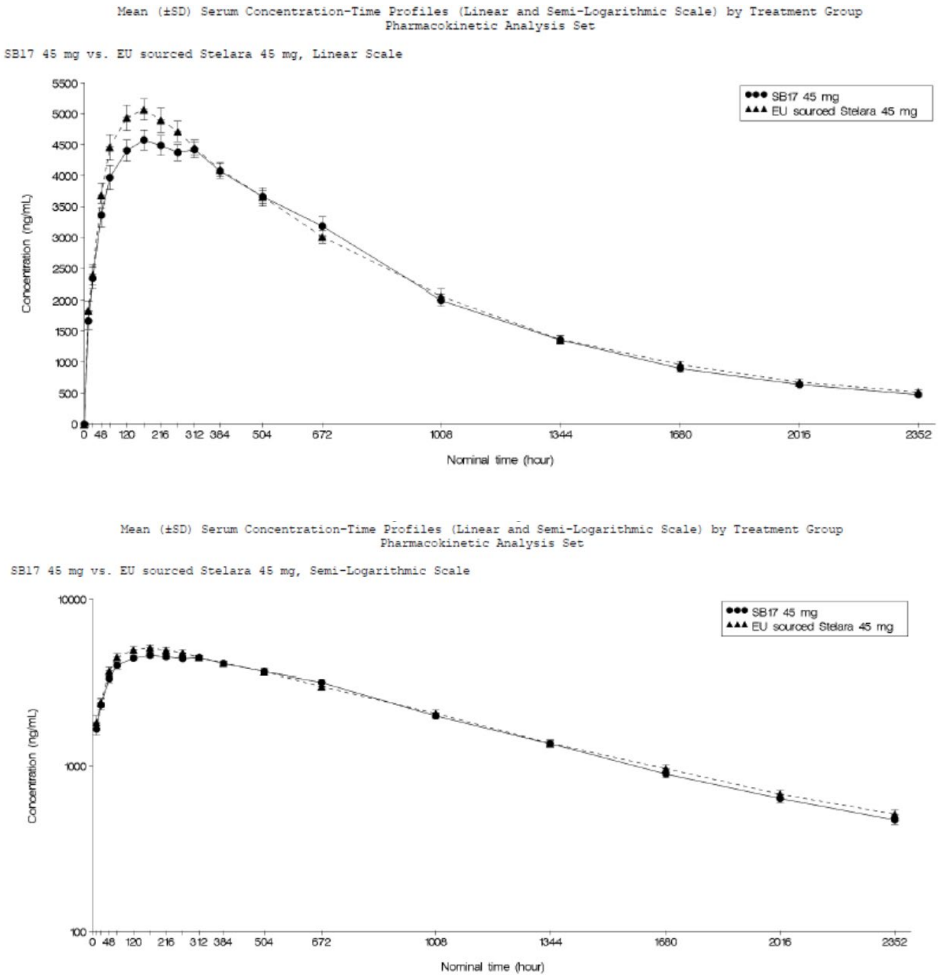
Outcomes and estimation

Ustekinumab serum concentrations

The mean serum concentration vs nominal time curves on linear and semi-logarithmic scale for the PKS are presented for pairwise comparisons of all study treatment groups comparison of Eksunbi and EU sourced Stelara, comparison of Eksunbi and US sourced Stelara, and comparison of EU sourced

Stelara and US sourced Stelara. Comparison of Eksunbi and EU Sourced Stelara will be the focus of this overview, please see the AR for full details.

Figure 3. Mean Serum Concentrations versus Nominal Times on Linear (Top Graph) and Semilogarithmic Scale (Bottom Graph) of Eksunbi and EU Sourced Stelara. Samples with low-speed centrifuge issue were excluded from the figure.



Statistical Analysis of Pharmacokinetic Similarity

The statistical analysis of the $\log_e$-transformed primary endpoints was performed by analysis of variance (ANOVA) model with treatment group as a fixed effect. The difference in least squares means (LS Means) between Eksunbi and EU sourced Stelara, between Eksunbi and US sourced Stelara, or between EU sourced Stelara and US sourced Stelara and the corresponding 90% confidence intervals (CIs) was determined.

Back transformation provided the ratio of geometric LS Means and 90% CIs for these ratios.

Equivalence for the primary endpoints (AUC_{inf} and C_{max}) was determined as follows:

For the EMA review, equivalence for the primary endpoints (AUC_{inf} and C_{max}) was determined if the 90% CI for the ratio of geometric LS Means of Eksunbi to EU sourced Stelara was within the equivalence margin of 0.80 to 1.25.

Table 5. Statistical Comparison of Primary Pharmacokinetic Parameters between Eksunbi and EU Stelara (Pharmacokinetic Analysis Set, Study SB17-1001)

PK Parameter	Treatment	N	n	Geometric LSMean	Ratio A/B	90% CI of Ratio
AUC_{inf} (ng·h/mL)	SB17	67	62	4958100	0.99	0.90; 1.08
	EU Stelara	67	64	5020000		
C_{max} (ng/mL)	SB17	67	62	4882	0.90	0.82; 0.98
	EU Stelara	67	64	5433		

A = Eksunbi; B = EU Stelara
CI = confidence interval; Geometric LSMean = geometric least squares mean; N = number of subjects in Pharmacokinetic Analysis Set; n = number of subjects in the analysis; PK Parameter = pharmacokinetic parameter
Samples for PK analysis (a total of 23 PK samples from 23 subjects) were excluded due to major protocol deviation (centrifuged in low speed) from the PK parameters calculation.

The geometric LSMean ratio (90% CI) of Eksunbi and EU sourced Stelara for AUC_{inf} and C_{max} were 0.99 (0.90 to 1.08) and 0.90 (0.82 to 0.98), respectively. These values for the 90% CIs were within the predefined equivalence margin of 0.8 to 1.25 however the geometric LS Mean ratio (90% CI) of Eksunbi and EU Stelara for C_{max} was 0.90 (0.82 to 0.98), which is within the pre-defined equivalence margin, but does not include 1.

The statistical comparison between Eksunbi and US Stelara and between EU Stelara and US Stelara showed that the corresponding 90% CIs of the geometric LS Mean ratios of the AUC_{inf} and C_{max} were within the pre-defined equivalence margin. Therefore, the PK profiles between Eksunbi and US Stelara and between EU Stelara and US Stelara were equivalent.

According to the Population-PK analyses performed in patients with PsO and PsA, patient's body weight is considered as the primary covariate affecting PK parameters of apparent clearance (CL/F), and apparent volume of distribution (V/F) of ustekinumab [Zhu et al., 2009; Zhu et al., 2010]. Generally, heavier patients tend to have lower serum ustekinumab concentrations at each dose [Lebwohl et al., 2010]. Based on the baseline comparability of demographics and baseline characteristics between the three treatment groups in Study SB17-1001, body weight was identified as a statistically different variable between the treatment groups (p-value = 0.0199).

Table 6. Baseline Comparability of Demographic and Baseline Characteristics between Main Treatment Group (Randomised Set, Study SB17-1001) (Ad-hoc Analysis)

Variables	Test	Degrees of Freedom (df)	Test Statistics	*P*-value
Age (years)	F-test	2	0.581	0.5604
Gender	Chi-squared test	2	0.042	0.9792
Height (cm)	F-test	2	0.290	0.7486
Body weight (kg)	F-test	2	3.996	0.0199
BMI (kg/m^2)	F-test	2	3.002	0.0520
Race	Fisher's exact test			0.8075
Ethnicity	Fisher's exact test			1.0000

BMI = body mass index

Accordingly, an ad-hoc analysis of covariance (ANCOVA) for the primary PK parameters with body weight as a covariate was performed after noting the 90% CI did not include 1.

Table 7. Analysis of Covariance (ANCOVA) for the Primary Pharmacokinetic Parameters with Weight as a Covariate (Pharmacokinetic Analysis Set, Study SB17-1001) (Ad-hoc Analysis)

PK Parameter	Treatment	N	n	Geo-LSMean	Ratio of SB17/Stelara		Ratio of EU Stelara /US Stelara	
					Estimate	90% CI	Estimate	90% CI
AUC_{inf} (ng·h/mL)	SB17	67	62	5015600				
	EU Stelara	67	64	4964200	1.01	0.92, 1.11		
	US Stelara	67	60	4870100	1.02	0.94, 1.12	1.00	0.92, 1.10
C_{max} (ng/mL)	SB17	67	62	4977				
	EU Stelara	67	64	5332	0.93	0.85, 1.02		
	US Stelara	67	60	5119	0.96	0.88, 1.05	1.02	0.94, 1.12

CI = confidence interval; Geo-LSMean = geometric least-square mean; N = number of subjects in the PK Analysis Set; n = number of subjects in the analysis; PK Parameter = pharmacokinetic parameter
A total of 14 subjects were excluded from the ANCOVA due to COVID-19 reported; PK parameters unreliable.
One subject was excluded from the ANCOVA due to Pregnancy reported; PK parameters unreliable.

Table 8. Summary of Pharmacokinetic Parameters (Pharmacokinetic Analysis Set, Study SB17-1001)

PK Parameter	Statistics	SB17 N = 67	EU Stelara N = 67	US Stelara N = 67
AUC_{inf} (ng·h/mL)	n	62	64	60
	Mean	5143600	5273000	5116600
	SD	1401400	1649100	1526800
	Median	4969900	5305400	4918500
	Min	2414000	2045000	2118000
	Max	8884000	10280000	10200000
C_{max} (ng/mL)	n	62	64	60
	Mean	5095	5689	5420
	SD	1498	1877	1659
	Median	5045	5480	5400
	Min	2630	2950	1590
	Max	9030	13700	11100
AUC_{last} (ng·h/mL)	n	62	64	60
	Mean	4721000	4853500	4769900
	SD	1262300	1431100	1336800
	Median	4642600	4993000	4644100
	Min	2302000	1974000	1959000
	Max	8526000	9786000	9257000
$AUC_{0\text{-}264h}$ (ng·h/mL)	n	62	64	60
	Mean	1044800	1148200	1117700
	SD	325730	365750	355820
	Median	1039000	1104500	1105300
	Min	458500	565500	291500
	Max	1780000	2820000	2042000
T_{max} (h)	n	62	64	60
	Median	168.000	168.000	168.000
	Min	48.00	12.00	48.00
	Max	672.00	504.00	1008.00
V_z/F (mL)	n	62	64	60
	Mean	7561.0	7149.3	7240.6
	SD	2312.5	1744.3	2241.5
	Median	7250.2	6945.2	6941.4
	Min	2817	2825	3207

PK Parameter	Statistics	SB17 N = 67	EU Stelara N = 67	US Stelara N = 67
	Max	12910	11560	17980
λ_z (1/h)	n	62	64	60
	Mean	0.0013891	0.0014051	0.0013624
	SD	0.00084317	0.00083473	0.00035215
	Median	0.0011864	0.0012144	0.0012921
	Min	0.0007264	0.0007386	0.0007192
	Max	0.005569	0.007060	0.002264
$t_{½}$ (h)	n	62	64	60
	Mean	582.70	563.80	541.07
	SD	171.00	161.55	134.93
	Median	584.24	571.09	536.46
	Min	124.5	98.2	306.1
	Max	954.2	938.4	963.8
CL/F (mL/h)	n	62	64	60
	Mean	9.4308	9.4592	9.6075
	SD	2.7416	3.3800	3.0698
	Median	9.0546	8.4819	9.1494
	Min	5.065	4.378	4.411
	Max	18.64	22.01	21.25
$\%AUC_{extrap}$	n	62	64	60
	Mean	7.91	7.40	6.32
	SD	5.00	3.73	3.18
	Median	6.41	6.69	5.52
	Min	1.4	1.6	2.2
	Max	30.2	18.5	14.9

N= number of subjects in the PK Analysis Set; n = number of subjects for the assessment parameter; SD = standard deviation
Min = minimum; Max = maximum; PK: pharmacokinetics.
Only the n, Min, Median, and Max were summarised for T_{max}.
14 subjects were excluded from the ANOVA due to COVD-19 reported; PK parameters unreliable.
A subject was excluded from the PK parameter summary due to subject pregnancy reported; PK parameters unreliable.
Samples with low speed centrifuge issue were excluded from PK parameters calculation.

The geometric LSMean ratios (90% CI) between Eksunbi and EU Stelara for AUC_{inf} and C_{max} were 1.01 (0.92 to 1.11) and 0.93 (0.85 to 1.02), respectively, which were within the pre-defined equivalence margin of 0.8 to 1.25 and contain 1.

In addition, the geometric LSMean ratios (90% CI) for AUC_{inf} and C_{max} between Eksunbi and US Stelara and between EU Stelara and US Stelara were all within the pre-defined equivalence margin of 0.8 to 1.25 and contain 1.

Therefore, based on the results of ad-hoc ANCOVA for the primary PK_parameters (AUC_{inf} and C_{max}) between Eksunbi and EU Stelara, between Eksunbi and US Stelara and between EU Stelara and US Stelara, the applicant concludes that bioequivalence for PK of Eksunbi, EU Stelara, and US Stelara were fully demonstrated considering individual body weight per subject.

Subgroup analysis based on immunogenicity

The subgroup analysis of the primary PK parameters (AUC_{inf}, C_{max}) by post-dose ADA status was compared among subjects in the Eksunbi, EU Stelara, and US Stelara treatment groups to comparatively evaluate the impact of ADA on PK of the product.

Blood samples for immunogenicity assessment were collected and assessed at Day 1, Day 29, Day 71, Day 99/EOS or early termination visit. NAbs and titre were assessed for ADAs where the final results were positive.

Post-dose ADA status of a subject is defined as follows:

- ADA-positive: subject reported with at least 1 ADA-positive sample value post-baseline (Day 29, Day 71, or Day 99)
- ADA-negative: subjects without any ADA-positive sample value post-baseline (Day 29, Day 71, or Day 99

Table 9. Incidence of Anti-drug Antibodies and Neutralizing Antibodies at Each Timepoint (Safety Set, 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

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′	%
		Negative	9/14	64.3	7/19	36.8	8/19	42.1	24/52	46.2

ADA = anti-drug antibody; BL = baseline; EOS = End of Study; 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; NAb = neutralizing antibody

[a] Post-dose ADA was defined 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.

Samples with low speed centrifuge issue were excluded from summary and post-dose ADA derivation.

Percentages were based on n′.

The incidence of subjects with post-dose of ADAs across timepoints was numerically lower in the Eksunbi treatment groups compared to that in the EU or US Stelara treatment group but were generally comparable.

The overall incidence of subjects with positive post-dose ADA to ustekinumab was 18/67 (26.9%), 23/67 (34.3%), and 23/67 (34.3%) of subjects in the Eksunbi, EU Stelara, and US Stelara treatment groups, respectively. There was no statistically significant difference in the incidence of post-dose ADAs to ustekinumab between Eksunbi and EU Stelara (p-value = 0.4536), Eksunbi and US Stelara (p-value = 0.4536), and EU Stelara and US Stelara (p-value = 1.0000), when comparing the incidence using Fisher's Exact Test. The incidence of ADA positive results is summarised by treatment group and titre at each timepoint in the dossier.

The incidence of subjects with NAb at each timepoint was lower in the Eksunbi treatment group compared to that in the EU or US Stelara treatment group, except at Day 29. The incidence of subject with NAb at Day 99 was 5/14 (35.7%), 12/19 (63.2%), and 11/19 (57.9%) in the Eksunbi, EU Stelara, and US Stelara treatment groups, respectively.

Immunogenicity Impact on Pharmacokinetics

It is known that ADAs in response to ustekinumab treatment have an influence on the PK profiles of ustekinumab in patients with plaque PsO and PsA [Stelara SmPC; Stelara US PI]. In PsO clinical studies, antibodies to ustekinumab were associated with reduced or undetectable serum ustekinumab concentrations and reduced efficacy.

Thus, the Analysis of Variance (ANOVA) of the primary PK parameters (AUC_{inf}, C_{max}) was performed across three treatment groups by post-dose ADA subgroup to evaluate the impact of immunogenicity on PK more precisely.

The SAP pre-specified analyses of immunogenicity in general terms and in particular, to assess the association with the treatment, Fisher's exact test was performed with the post-dose ADA status for the following: Eksunbi vs. EU sourced Stelara, Eksunbi vs. US sourced Stelara, EU sourced Stelara vs. US sourced Stelara. The evaluation of immunogenicity status in terms of PK parameters is therefore considered post hoc.

Table 10. Analysis of Variance for the Primary Pharmacokinetic Parameters by Post-dose Anti-drug Antibody (Pharmacokinetic Analysis Set, Study SB17-1001)

ADA Status	PK Parameter	Treatment	N	n	Geo-LSMean	Ratio of SB17/Stelara		Ratio of EU Stelara /US Stelara	
						Estimate	90% CI	Estimate	90% CI
Post-dose ADA positive	AUC_{inf} (ng·h/mL)	SB17	18	18	4594200				
		EU Stelara	23	22	4176400	1.10	[0.90, 1.34]		
		US Stelara	23	21	4362500	1.05	[0.90, 1.24]	0.96	[0.82, 1.12]
	C_{max} (ng/mL)	SB17	18	18	4890				
		EU Stelara	23	22	5186	0.94	[0.80, 1.12]		
		US Stelara	23	21	4715	1.04	[0.88, 1.23]	1.10	[0.95, 1.27]
Post-dose ADA negative	AUC_{inf} (ng·h/mL)	SB17	49	44	5115100				
		EU Stelara	44	42	5527800	0.93	[0.85, 1.01]		
		US Stelara	44	39	5217000	0.98	[0.89, 1.08]	1.06	[0.95, 1.18]
	C_{max} (ng/mL)	SB17	49	44	4879				
		EU Stelara	44	42	5566	0.88	[0.79, 0.97]		
		US Stelara	44	39	5431	0.90	[0.80, 1.00]	1.02	[0.91, 1.15]

CI = confidence interval; Geo-LSMean = Geometric Least-Square Mean; N = number of subjects in the Pharmacokinetic Analysis Set with the corresponding post-dose ADA result; n = number of subjects in the analysis

Post-dose ADA was defined as 'Positive', if subjects had at least one ADA positive on post-baseline and 'Negative' if subjects had no ADA positive on post-baseline.

A total of 14 subjects were excluded from the ANCOVA due to COVID-19 reported. One subject was excluded from the ANCOVA due to Pregnancy reported.

Subgroup analysis of the PK parameters by post-dose ADA status showed that the AUC_{inf} and C_{max} in the post-dose ADA positive subgroup were generally lower than those in the post-dose ADA negative subgroup.

The PK parameters were comparable across treatment groups within the subgroup. For post-dose ADA positive subgroup, the geometric LSMean ratios (90% CI) for Eksunbi and EU Stelara in AUC_{inf} and C_{max} were 1.10 (0.90 to 1.34) and 0.94 (0.80 to 1.12), respectively, and the geometric LSMean ratios (90% CI) for Eksunbi and US Stelara in AUC_{inf} and C_{max} were 1.05 (0.90 to 1.24) and 1.04 (0.88 to 1.23), respectively.

The geometric LSMeans of both AUC_{inf} and C_{max} for the post-dose ADA negative subgroups were consistent with the result of primary PK parameters for the PKS and the PK parameters were comparable across treatment groups within the subgroups. For the post-dose ADA negative subgroup, the geometric LSMean ratios (90% CI) for Eksunbi and EU Stelara in AUC_{inf} and C_{max} were 0.93 (0.85 to 1.01) and 0.88 (0.79 to 0.97), respectively, and the geometric LSMean ratios (90% CI) for Eksunbi and US Stelara in AUC_{inf} and C_{max} were 0.98 (0.89 to 1.08) and 0.90 (0.80 to 1.00), respectively.

The 90% CI for Post dose ADA Positive C_{max} Eksunbi – EU Stelara was [0.80, 1.12] Post dose ADA negative C_{max} Eksunbi – EU Stelara was [0.79, 0.97].

The comparison of pharmacokinetics in ADA-negative subjects is of greater interest as this allows direct evaluation of elimination of the substances without interference of ADAs. In ADA negative subjects, similarity was not demonstrated for both C_{max}, as the 90% CI was not within the 80%-125%.

Pharmacokinetics in target population

Phase III study

Study Title

A Phase III, Randomised, Double-blind, Multicentre Clinical Study to Evaluate the Efficacy, Safety, Tolerability, Pharmacokinetics, and Immunogenicity of Eksunbi (proposed ustekinumab biosimilar) Compared to Stelara in Subjects with Moderate to Severe Plaque Psoriasis.

Objectives

Study SB17-3001 was mainly designed to demonstrate the equivalence of Eksunbi to Stelara, in terms of the percentage change from baseline in Psoriasis Area and Severity Index (PASI) at Week 12 in patients with moderate to severe plaque PsO.

Secondary objectives of the study with respect to PK and immunogenicity profiles of Eksunbi and Stelara were as follows:

- To evaluate the PK of Eksunbi compared to Stelara in patients participating in PK evaluation.
- To evaluate the immunogenicity of Eksunbi compared to Stelara.
- To evaluate safety and immunogenicity in patients who transitioned to Eksunbi and who maintained Stelara at Week 28 for the transition period.

A total of 142 subjects participated in the PK sub-study and were included in the PKS (71 subjects who were randomised to Eksunbi treatment and 71 subjects who were randomised to Stelara treatment).

Table 11. Study Description of SB17-3001

Study ID (Country)	Study Objective	Number of Subjects	Study Design /Duration	Treatments	PK/Immunogenicity Endpoints
SB17-3001 **Phase III** (EudraCT No. 2020-006115-19) (Czech Republic, Estonia, Hungary, Latvia, Lithuania, Poland, Republic of Korea, and Ukraine)	Comparative efficacy, safety, PK, and immunogenicity	Patients with moderate to severe plaque psoriasis (PsO) Randomized Set: (SB17: 249; Stelara Overall: 254; Stelara+SB17: 122; Stelara+Stelara: 122) Safety Set 1: (SB17: 249; Stelara Overall: 254; Stelara+SB17: 122; Stelara+Stelara: 122)	Randomized, double-blind, multicenter study Total duration of treatment of approximately 56 weeks including 4 weeks of screening period. The last assessment was performed at Week 52	45 mg of SB17 or Stelara via SC injection at Week 0, 4, and then every 12 weeks up to Week 40; if a patient became > 100 kg at subsequent dosing visits, 90 mg was given in the form of two doses of 45 mg.	**PK** • Serum ustekinumab concentration at Week 0, 2, 4, 8, 12, 16, and 28. **Immunogenicity** • Incidence of anti-drug antibody (ADA) at Week 0, 4, 8, 12, 16, 28, 40, and 52. • Incidence of neutralizing antibody (NAb) at Week 0, 4, 8, 12, 16, 28, 40, and 52.

Study ID (Country)	Study Objective	Number of Subjects	Study Design /Duration	Treatments	PK/Immunogenicity Endpoints
		Safety Set 2: (SB17: 237; Stelara Overall: 244; Stelara+SB17: 122; Stelara+Stelara: 122) Pharmacokinetic Analysis Set: (SB17: 71; Stelara Overall: 71; Stelara+SB17: 34; Stelara+Stelara: 34)			

PK = pharmacokinetics; PsO = psoriasis; SC = subcutaneous

	Number (%) of Patients	N = 249 n (%)	N = 254 n (%)	N = 122 n (%)	N = 122 n (%)	N = 503 n (%)
	Randomized Set (RAN)	249 (100.0)	254 (100.0)	122 (100.0)	122 (100.0)	503 (100.0)
	Full Analysis Set (FAS)	249 (100.0)	254 (100.0)	122 (100.0)	122 (100.0)	503(100.0)
	Per-Protocol Set (PPS)	243 (97.6)	249 (98.0)	119 (97.5)	122 (100.0)	492 (97.8)
	Safety Set 1 (SAF1)	249 (100.0)	254 (100.0)	122 (100.0)	122 (100.0)	503 (100.0)
	Safety Set 2 (SAF2)	237 (95.2)	244 (96.1)	122 (100.0)	122 (100.0)	481 (95.6)
	Pharmacokinetic Analysis Set (PKS)	71 (28.5)	71 (28.0)	34 (27.9)	34 (27.9)	142 (28.2)

N = total number of patients in the Randomized Set in each treatment group; n = number of patients with available data within each category
Percentages were based on the number of subjects in the Randomized Set.
[a] Based on patients who were re-randomized at Week 28, Stelara+SB17 and Stelara+Stelara may not add up to Stelara Overall.

Study results

The PK analyses were performed for the PKS. A total of 142 patients were included in the PKS (71 patients from the Eksunbi and 71 patients from the Stelara treatment groups). The demographic characteristics and baseline characteristics were comparable for the PKS between the Eksunbi and Stelara treatment groups.

Blood samples for PK assessment were collected prior to IP administration and at the day of IP administration (Week 0, 4, 16, and 28). Blood samples for PK assessment at weeks 2, 8, and 12 were collected at any time during the period when patient was staying at investigational sites. Patients' samples were used for method development, method validation and/or investigation, only for this study.

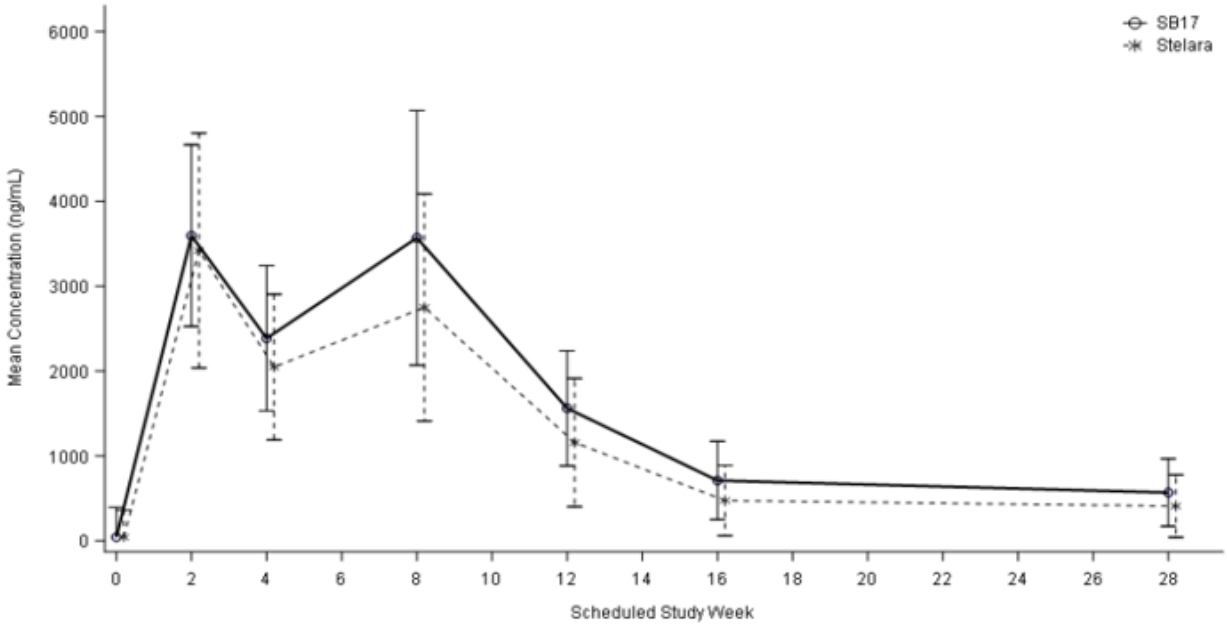
Pre-dose concentrations at Week 0 (Day 1) were below the limit of quantitation BLQ for all subjects, except for 1 subject on Eksunbi treatment (concentration of 2,919.4 ng/mL) and 2 subjects on Stelara treatment (concentrations of 2,626.0 ng/mL and 158.5 ng/mL, respectively). No protocol deviations were found to account for these quantifiable concentrations; consequently, these concentrations were retained in the PK analyses.

Pharmacokinetic Concentrations

Serum ustekinumab concentrations by visit and treatment group are summarised in the Table 15 below and mean (± SD) serum concentration-time profiles by treatment group are presented in Figure 4.

Mean serum concentrations for two treatment groups were generally comparable up to Week 28 but had a higher trend for the Eksunbi treatment group compared with Stelara treatment group around Week 8.

Figure 4. Mean (± SD) Serum Ustekinumab Concentrations for Each Treatment from Week 0 to Week 28 on Linear Scale (Pharmacokinetic Analysis Set, Study SB17-3001)



SD = standard deviation
Below the limit of quantitation concentrations (BLQ) were set to zero. The lower limit of quantitation (LLOQ) is 150 ng/mL.

This is intended to be supportive evidence of comparable mean serum ustekinumab concentration in patients with moderate to severe plaque PsO, which is considered as a representative patient population. Based on the data presented, the applicant concludes that PK similarity demonstrated in the data obtained from Studies SB17-1001 and SB17-3001 can reasonably support extrapolation of PK data to all other approved indications of Stelara in the EU. As shown in Figure 5 above, mean serum concentrations of ustekinumab were generally comparable up to week 28 between two treatment groups. A trend of higher serum concentration of ustekinumab in the Eksunbi treatment group was observed compared to the Stelara treatment group around Week 8.

Serum concentrations of ustekinumab (Eksunbi or Stelara) from Week 0 to Week 28 are summarised by treatment in the Table 12 below. As shown in the table below, mean serum concentrations of ustekinumab were generally comparable up to Week 28 between two treatment groups. A trend of higher serum concentration of ustekinumab in the Eksunbi treatment group was observed compared to the Stelara treatment group around Week 8. However, considering the large CV% and high variation range (i.e., SDs at Week 8 was 1501.002 ng/mL for the Eksunbi and 1337.157 ng/mL for the Stelara treatment groups), mean ustekinumab concentrations are generally comparable between two treatment groups.

Table 12. Summary Statistics for Serum Concentration (ng/mL) by Scheduled Time and Treatment Group (Pharmacokinetic Analysis Set, Study SB17-3001)

Scheduled Timepoints	Statistics	SB17 N = 71	Stelara N = 71
Week 0	n	69	67
	Mean	42.31	41.56
	SD	351.454	321.108
	Median	0.00	0.00
	Min, Max	0.0, 2919.4	0.0, 2626.0
	CV%	830.7	772.6
	Geo. Mean	2919.40	645.15
	Geo. SD	NA	7.280
	Geo. CV%	NA	710.4
Week 2	n	71	71
	Mean	3594.09	3419.94
	SD	1070.174	1383.325
	Median	3385.80	3269.60
	Min, Max	1244.8, 6214.9	340.8, 7361.7
	CV%	29.8	40.4
	Geo. Mean	3422.24	3104.98
	Geo. SD	1.388	1.623
	Geo. CV%	33.7	51.4
Week 4	n	70	71
	Mean	2385.14	2046.84
	SD	857.081	858.841
	Median	2396.70	2003.90
	Min, Max	875.2, 4470.9	0.0, 4092.8
	CV%	35.9	42.0
	Geo. Mean	2226.21	1893.42
	Geo. SD	1.470	1.581
	Geo. CV%	40.0	48.3
Week 8	n	68	69
	Mean	3569.38	2749.02
	SD	1501.002	1337.157
	Median	3360.15	2764.10
	Min, Max	935.5, 7248.6	409.7, 6376.0
	CV%	42.1	48.6
	Geo. Mean	3245.38	2374.06
	Geo. SD	1.579	1.817

Scheduled Timepoints	Statistics	SB17 N = 71	Stelara N = 71
	Geo. CV%	48.1	65.4
Week 12	n	70	70
	Mean	1560.17	1156.77
	SD	678.492	756.516
	Median	1490.35	1112.40
	Min, Max	246.3, 4149.0	0.0, 3138.5
	CV%	43.5	65.4
	Geo. Mean	1403.66	1000.82
	Geo. SD	1.643	2.025
	Geo. CV%	52.9	80.3
Week 16	n	70	69
	Mean	710.11	473.02
	SD	462.479	413.745
	Median	665.85	440.20
	Min, Max	0.0, 2579.7	0.0, 1612.5
	CV%	65.1	87.5
	Geo. Mean	644.15	517.03
	Geo. SD	1.773	1.842
	Geo. CV%	62.3	67.3
Week 28	n	69	68
	Mean	567.22	408.49
	SD	397.049	367.912
	Median	497.20	344.80
	Min, Max	0.0, 2050.2	0.0, 1353.6
	CV%	70.0	90.1
	Geo. Mean	514.81	504.56
	Geo. SD	1.814	1.719
	Geo. CV%	65.2	58.4

CV% = coefficient of variation; Geo. CV% = geometric coefficient of variation; Geo. Mean = geometric mean; Geo. SD = geometric standard deviation; Max = maximum; Min = minimum; n = total number of patients with available data; NA = not applicable
Below the limit of quantitation (BLQ) concentrations were set to zero. The lower limit of quantitation (LLOQ) is 150 ng/mL

Study Conclusion

Systemic exposure of Eksunbi and Stelara across all timepoints up to Week 28 was evaluated by the applicant in the clinical Phase III study (SB17-3001) in patients with moderate to severe plaque PsO. The mean serum concentrations of ustekinumab were generally comparable between the Eksunbi and

Stelara treatment groups up to Week 28.

Other Subgroup Analysis of Pharmacokinetics

Serum ustekinumab concentrations by visit, treatment group and overall, ADA status (up to Week 28) are summarised in Table 13. The incidence of overall ADA positive status was lower for Eksunbi (8/69; 11.6%) than for Stelara (32/71; 45.1%) treatment group.

For subjects with overall ADA negative up to Week 28, mean concentrations were comparable up to Week 28 between the treatment groups.

For subjects with overall ADA positive up to Week 28, mean concentrations were comparable up to Week 28 between the treatment groups, although there was a higher trend for the Eksunbi treatment group than Stelara treatment group around Week 8.

Table 13. Summary of Concentration by Scheduled Time, Treatment Group, and Overall Anti-drug Antibody Status up to Week 28 (Pharmacokinetic 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	NA	NA	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

CV%: coefficient Variation; N: N's for each ADA subgroup (Positive, Negative, or Inconclusive) within each treatment n: Number of subjects in each treatment group and ADA subgroup; Negative: Negative overall ADA status; Positive: Positive overall ADA status; SD: Standard deviation

Subjects with inconclusive/no overall ADA status (i.e., subjects missing baseline ADA result or subjects with no ADA result after first treatment administration at Week 0) are excluded from this summary.

Pharmacokinetic Conclusions (phase III study)

• Mean serum concentrations for the two treatment groups were generally comparable up to Week 28, but there was a higher trend for the Eksunbi treatment group compared with the Stelara treatment group around Week 8.

• In the overall ADA negative subgroup, mean serum concentrations were comparable up to Week 28 between the Eksunbi and Stelara treatment groups. In the overall ADA positive subgroup, mean serum concentrations were comparable up to Week 28 between the treatment groups, although there was a higher trend for Eksunbi treatment group than Stelara treatment group around Week 8.

A number of points for clarification were raised in relation to the PK analysis in the target population and these points have been discussed satisfactorily by the applicant as part of the responses.

Special populations

No PK data has been provided for subjects with impaired renal or hepatic function. No PK data are available for children.

In study (SB17-3001) only a limited number of patients with PsO ≥65 years of age were included in the study. The mean age was 44.2 years with an age range of 18-77 years.

No separate analysis for elderly patients was presented.

Pharmacokinetic interaction studies

Not applicable

Pharmacokinetics using human biomaterials

Not applicable

2.6.2.2. Pharmacodynamics

Mechanism of action

Eksunbi has been developed as a proposed biosimilar to the reference product Stelara (approved in 2009 in the EU).

Eksunbi is a recombinant, fully human immunoglobulin (Ig) G1 kappa monoclonal antibody (mAb) directed against interleukin IL-12 and IL-23, which are cytokines that are involved in immune and inflammatory responses. Binding of the antigen binding fragment (Fab) domain of ustekinumab 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 signalling pathways.

Primary and secondary pharmacology

No data on PD has been provided. Since this is a biosimilar application, the secondary pharmacology does not have to be characterised again.

2.6.3. Discussion on clinical pharmacology

Comparative PK data of Eksunbi was generated in one PK study in healthy volunteers (SB17-1001) following a single subcutaneous (SC) injection. Additionally, steady-state PK characteristics after repeat SC administration were evaluated in a phase 3 confirmatory study in adult patients with moderate to severe chronic plaque-type psoriasis (SB17-3001).

PK study SB17-1001

Phase I study SB17-1001 is the pivotal study investigating PK similarity. This was a randomised, double-blind, parallel group, single dose, 3-arm study in healthy subjects to demonstrate similarity in PK, safety, tolerability and immunogenicity between Eksunbi, EU-Stelara and US-Stelara. The total study duration was approximately 18 weeks (including the 4-week Screening period). Study SB17-1001 was conducted entirely within the EU in France. The primary comparison planned to be Eksunbi against EU Stelara. For the clinical Phase I study (SB17-1001), a single-dose parallel group study rather than a single-dose cross-over study was designed to obtain information necessary for evaluation of biosimilarity considering a long $t_{1/2}$ of ustekinumab (approximately 21 days) and adequate period to assess the potential influence of immunogenicity, which is in line with the EMA guideline [EMA/CHMP/BMWP/403543/2010]. Overall, the design of the Phase I study (SB17-1001) is in accordance with the "Guideline on similar biological medicinal products containing monoclonal antibodies - non-clinical and clinical issues" (EMA/CHMP/BMWP/403543/2010) and generally in agreement with previous Scientific Advice received from the EMA during the EMA SA and follow-up SA [EMA/CHMP/SAWP/791150/2017; EMA/CHMP/SAWP/493969/2019]. Specific design aspects that were not followed or were changed during subsequent protocol amendments are discussed in the respective sections below.

It is noted that eligibility criteria are wider than those presented in the request for scientific advice, where the applicant proposed to include healthy male volunteers aged 18 to 55 years (body weight 60–85.5 kg and BMI 20-28 kg/m^2). In the original EMA SA [EMA/CHMP/SAWP/791150/2017; the applicant proposed a single dose (90 mg SC PFS), parallel group phase I study in healthy male volunteers, but this approach was amended and the selection of healthy subjects as the target population and the single dose of 45 mg for SC injection as the dosing regimen was endorsed by the EMA during follow-up SA [EMA/CHMP/SAWP/493969/2019]; this is acceptable to the CHMP.

In the study, sex criterion was extended to also include female subjects with a body weight of 60.0-90.0 kg and a body mass index (BMI) 19.0-29.9 kg/m^2 (inclusive) and this is in line with the protocol. A more homogenous population is preferred for a biosimilar study, as it would represent a more sensitive model to demonstrate, or exclude, differences between the treatment arms, if such exist. Overall, despite the aspects discussed above, eligibility criteria are acceptable to the CHMP. As regards the inclusion criteria for body weight/BMI, restricting body weight and BMI is endorsed, considering that pharmacokinetic modelling in psoriasis subjects revealed lower exposure of ustekinumab in subjects >100 kg (EPAR Stelara, EMEA/CHMP/29255/2009). However, in order to ensure that treatment arms are balanced with regard to body weight, stratification according to body weight was advised in the EMA SA (Please see below the discussion on ad hoc ANCOVA analysis for the primary PK parameters with body weight as a covariate).

The applicant used a 45mg dose instead of the originally planned 90 mg dose for this phase 1 PK study. The selection of healthy subjects as the target population and the single dose of 45 mg for SC injection as the dosing regimen was endorsed by the EMA during SA and follow-up SA [EMA/CHMP/SAWP/791150/2017; EMA/CHMP/SAWP/493969/2019]

As suggested by the EMA guideline [EMEA/CHMP/BMWP/42832/2005 Rev. 1] a single-dose study with the lowest therapeutic dose was selected to characterise the full PK profile of ustekinumab, including

the late elimination phase which provides essential information on biosimilarity. According to the SmPC of Stelara, ustekinumab has been shown to exhibit dose-proportional increases in exposure (C_{max} and AUC) following a single SC administration at doses ranging from approx. 24 – 240 mg in PsO patients. The lowest therapeutic dose of Stelara is 45 mg for adult PsO patients with a body weight ≤ 100 kg or 90 mg for those with body weight > 100 kg. Based on the information, a dose of single SC injection of 45 mg ustekinumab for healthy subjects was deemed acceptable to the CHMP to show PK similarity between Eksunbi and Stelara.

The primary objective of the study was to demonstrate PK similarity of Eksunbi to both EU-Stelara and US-Stelara; as well as to demonstrate similarity between EU-Stelara and US-Stelara, in terms of C_{max} and $AUC_{0\text{-}inf}$. For an EU MA, the comparison between Eksunbi and EU-Stelara is of primary importance, while other comparisons are considered supportive.

Secondary objectives comprised additional PK parameters to support similarity, comparison of safety, tolerability and immunogenicity between Eksunbi and reference products.

The assessment of biosimilarity in terms of PK was based on 90% confidence intervals (CIs) for the ratio of the geometric means (Eksunbi/EU-Stelara) for C_{max} and $AUC_{0\text{-}inf}$ of the ustekinumab concentrations which had to be contained within the bioequivalence limits of 80-125%. The equivalence margins used in the study are in line with conventionally used margins for biosimilar products. Study objectives are overall adequate for the purpose of PK biosimilarity exercise.

The primary endpoints were C_{max} and $AUC_{0\text{-}inf}$. This is in line with relevant EMA guideline (EMA/CHMP/BMWP/403543/2010) for a single dose study with subcutaneous administration and with the SA advice: EMA/CHMP/SAWP/791150/2017. The secondary PK endpoints comprised (AUC_{last}), ($AUC_{0\text{-}264h}$), (T_{max}), (V_z/F), (λ_z), ($t_{1/2}$), (CL/F), (T_{last}) to (%AUC_{extrap}). The secondary PK endpoints are considered adequate to the CHMP.

In the PK study, both treatments were administrated subcutaneously. The applicant applied for the SC presentations and for an intravenous presentation 130mg IV. It was advised during the EMA SA that additional PK parameters, such as partial AUCs, should be incorporated into the study protocols of the proposed clinical phase I and III studies and that especially the late partial AUCs should be comparable to support similar elimination between the proposed biosimilar and the originator product. This is considered important to support extrapolation of the SC data to the IV administration route, and consequently, to waive a clinical study using the IV presentation. Neither the EMA SA nor the relevant guideline were followed and no data on partial AUCs were provided with the initial submission. Therefore, comparability in absorption and elimination could not be established for the SC route of administration at that time nor extrapolation of the SC data to the IV administration route. As requested by the CHMP, the applicant provided with their responses partial AUC analyses with several varying time points, justifying the selection thereof and have adequately demonstrated the robustness of the study results as outlined below.

The analysis of variance (ANOVA) of partial AUC for Eksunbi and EU Stelara for the similarity assessment with various timepoints in elimination phase was assessed to demonstrate the robustness of the clinical Phase I study results. The 90% confidence intervals (CIs) of the geometric least squares mean (LSMean) ratios of partial AUC for the comparison of Eksunbi and EU Stelara were within the pre-defined equivalence margin of 0.8 to 1.25 and contained unity regardless of any given timepoints between 504 h to 2352 h. The ad-hoc analyses of partial AUC for Eksunbi and EU Stelara with various timepoints further support the robustness of the demonstrated similarity in the primary PK endpoints of Study SB17-1001 between Eksunbi and EU Stelara in normal healthy subjects, which is considered the most sensitive population to detect potential differences in PK between products if there are any. Therefore, these results further support the similarity in subcutaneous (SC) route of administration

between Eksunbi and EU Stelara as well as the extrapolation of the SC data to the intravenous (IV) administration route of Eksunbi.

After a single-dose injection, subjects were followed for 99 days of PK, safety, and immunogenicity assessments. Blood samples for PK analysis were collected at various timepoints during 99 days of the PK sampling period.

The sampling schedule changed from the time of EMA SA. Intensive daily sampling was carried out from Day 1 to Day 4, then every second day to day 14. It had been advised during the EMA SA that the sampling time-points should be selected sufficiently tight to provide a reliable estimate of peak exposure and to adequately characterise the whole PK profile, especially time-points around T_{max}. The range of T_{max} values is noted to be large in the study results. The applicant was requested to provide a justification that the sampling time–points around T_{max} were sufficiently tight to ensure reliable estimates of C_{max} were obtained. In their responses the applicant has explained that a few outliers in each treatment group caused a dispersion of T_{max} values and large T_{max} range. The CHMP considered the sampling schedule of Study SB17-1001 was adequate to obtain reliable estimates of maximum serum concentration (C_{max}).

The statistical methods for the primary and secondary endpoints methods for analyses are considered acceptable.

373 subjects were screened of whom 201 subjects were randomised. Of the subjects who were randomised, 186 completed the study and 15 subjects discontinued the study. The most common reason for screening failure was inclusion/exclusion criteria. Subjects discontinued due to unacceptable toxicity including AEs (13 subjects; all due to COVID-19), withdrawal of informed consent (1 subject) and discretion of the Investigator (1 subject; due to subject pregnancy).

The applicant was requested to provide a listing of the PK values (parameter values) for 33 subjects who reported major PD of 'blood samples for PK analysis was centrifuged in low speed'. The current definition of the PK populations described in the SAP, does not appear to warrant exclusion of these subjects from PK analyses, unless it can be shown that the observed PK parameter values were 'unreliable'. Consequently, the applicant was requested to strengthen its claim and show how the primary PK parameter values from these subjects would be unreliable, so as to warrant exclusion from the statistical analysis. In addition, the demographic characteristics of these exclusions were summarised alongside those included in the analyses. There appeared to be 'unreliable' PK parameters due to either COVID-19, sampling or pregnancy based on the applicant 's responses. The definition of why some particular parameters are more unreliable than others was provided as requested and is acceptable to the CHMP.

The applicant outlines that all 201 subjects were included for PK analysis. In the PK analyses populations, there were 67 subjects (EU) for each of the Test and Reference, but between n=62 and 64 were analysed. Regarding these 8 subjects excluded from the statistical analysis for bioequivalence: 5 subjects excluded from Eksunbi and 3 subjects from EU Stelara and given that the lower 90% CI for C_{max} is close to the lower acceptable limit of 0.80. The applicant has provided analyses of the primary PK endpoints (AUC_{inf} and C_{max}) including the PK parameters from the 8 excluded subjects and these results are in line with the primary analyses where these subjects were excluded. The CHMP acknowledged that there was no change to the bioequivalence conclusion.

In Study SB17-1001, 124 (61.7%) subjects were male, and 77 (38.3%) subjects were female. The majority of subjects were White (170 [84.6%] subjects) and not Hispanic or Latino (196 [97.5%] subjects). The demographic characteristics (average age, height, weight, and body mass index [BMI]) and other baseline characteristics of the subject were comparable among the three treatment groups

for both Randomised Set (RAN) and PKS, with a slight lower mean value for weight and BMI in the EU Stelara treatment group. The provided data on baseline characteristics did not give rise to concern.

PK parameters from 15 subjects were considered unreliable due to either COVID-19 infection or subject's pregnancy. After PK data review between Sponsor and CRO, it was determined that the PK parameters (i.e., AUC_{inf}, C_{max}, AUC_{last}, AUC_{0-264h}, T_{max}, V_z/F, λ_z, $t_{1/2}$, CL/F, and $\%AUC_{extrap}$) for these subjects were not to be included in the summary statistics and ANOVA for PK parameters. The applicant was requested to provide the full subject listing of the PK values for all those eligible for the PK population. In their responses, the applicant stated that the reliability of the PK results for those excluded was questionable although they belong to the PK population. The explanation provided was not considered satisfactory, since these subjects seem to belong to the PK population and the precise impact of COVID-19 in these could not be known. Subsequently the applicant provided a statistical analysis with data from the excluded 15 subjects, where available. The geometric least squares mean (LSMean) ratio (90% confidence interval [CI]) of Eksunbi and EU Stelara for AUC_{inf} and C_{max} were within the pre-defined equivalence margin of 0.80 to 1.25.

Following a single SC dose of 45 mg/0.5 mL, the mean serum ustekinumab concentration-time profiles for Eksunbi, EU-Stelara and US-Stelara were overall similar.

The geometric LSMean ratio (90% CI) of Eksunbi and EU sourced Stelara for AUC_{inf} and C_{max} were 0.99 (0.90 to 1.08) and 0.90 (0.82 to 0.98), respectively. These values for the 90% CIs were within the predefined equivalence margin of 0.8 to 1.25; however, the geometric LSMean ratio (90% CI) of Eksunbi and EU Stelara for C_{max} was 0.90 (0.82 to 0.98), which is within the pre-defined equivalence margin, but does not include 1. Accordingly, an ad-hoc analysis of covariance (ANCOVA) for the primary PK parameters with body weight as a covariate was performed, showing the geometric LSMean ratios (90% CI) between Eksunbi and EU Stelara for AUC_{inf} and C_{max} were 1.01 (0.92 to 1.11) and 0.93 (0.85 to 1.02), respectively, which were within the pre-defined equivalence margin of 0.8 to 1.25 and contains 1.

The applicant compared weight using a general ANOVA approach in a post hoc way which uses combined data (mean weight) across 3 groups to generate a p-value showing weight can be used as a covariate. However, the p-value of interest is one which compares mean weights between the Test and the EU reference only (excluding data from the US reference). Moreover, the justification for a weight adjusted analysis (with a p-value of 0.0199) should be based on a comparison of weights between the relevant Test and EU reference formulations. The applicant was requested to provide the p-value for this analysis, only keeping in relevant data for the EU submission. The ad hoc analysis supported no statistical difference in mean weights between Eksunbi and EU Stelara.

The impact of post-dose ADA status on the PK parameters is considered by the CHMP a post-hoc analysis. For the ADA negative group, C_{max} was considerably outside the 90% BE limits for Test vs EU reference, while for C_{max} positive, AUC positive and AUC negative status, the 90% CIs were within 0.80 to 1.25. Consequently, it was not clear to the CHMP that sample size alone is the reason for C_{max} results outside the 0.80 to 1.25 limits. The applicant was requested to explain the impact of the C_{max} results in the post ADA negative status given that the 90% CI for the Test vs Ref are outside the 0.80 to 1.25 range and also do not include 1 in the interval. The CHMP considers that comparison of pharmacokinetics in ADA-negative subjects is of greater interest as this allows direct evaluation of elimination of the substances without interference of ADAs. In ADA negative subjects, similarity was not demonstrated for both C_{max} as the 90% CI was not within the 80% -125%. The applicant was requested to discuss the results of the subgroup analysis of the PK parameters by post dose ADA status with particular focus on ADA negative subjects. The PK parameters based on the ANCOVA by post-dose ADA status with body weight as a covariate indicate that body weight is an attributing factor to C_{max} in ADA-negative subjects being outside the 0.80 to 1.25 and not including 1, which is aligned

with a fact that body weight is a predisposing factor to affect PK of ustekinumab. This was agreed by the CHMP.

Phase III study SB17-3001

Systemic exposure of Eksunbi and Stelara in the target population was evaluated across all timepoints up to Week 28 in a clinical Phase III study (SB17-3001) in patients with moderate to severe plaque PsO. This study was a randomised, double-blind, multicentre, active control clinical study to compare the efficacy, safety, and immunogenicity of Eksunbi compared with Stelara in patients with moderate to severe chronic PsO. Data through Week 28 were presented by the applicant in support of PK similarity in the target population.

A secondary objective of this study was the comparison of steady-state PK of Eksunbi and Stelara. In this context, serum trough concentrations (C_{trough}) of ustekinumab were determined in all patients at Week 1/Day 1 (pre-dose), and pre-dose at Weeks 4, 8, 16, 28 (40, and 52).

While the mean serum concentrations of ustekinumab were generally comparable between the Eksunbi and Stelara treatment groups up to Week 28, exposure to Eksunbi was slightly higher throughout the available timepoints presented and most notably higher at the week 8 timepoint.

For the Phase 3 study (Study SB17-3001) partial AUCs covering up to Week 28 of dosing were also derived. Several had 90% CI outside the margin of 0.8 to 1.25 which was identified to be caused by formation of ADAs, which was not similar between the two products. Eksunbi treatment resulted in a lower ADA incidence than EU Stelara. When evaluating similarity based on the ADA negative population, all 90% CI were within the 0.8 and 1.25 margin, this is acceptable to the CHMP.

Specifically, while the applicant states that the mean serum concentrations of ustekinumab were generally comparable between the Eksunbi and Stelara treatment groups up to Week 28, it was highlighted that exposure to Eksunbi was slightly higher throughout and was notably higher at the week 8 timepoint when compared to Stelara. The applicant therefore provided a further detailed discussion in relation to these apparent differences in exposure and their possible clinical relevance as requested. A statistical comparison of various partial AUCs of Eksunbi and EU Stelara in Study 1001 showed that the 90% confidence intervals (CIs) of the geometric least squares mean (LSMean) ratios of partial AUC for the comparison of SB17 and EU Stelara were all within the pre-defined equivalence margin of 0.8 to 1.25 and contained unity, regardless of any given timepoints between 504 h to 2352 h. For further details on clinical relevance please refer to the discussion on efficacy and safety.

It was also noted that pre-dose concentrations at Week 0 (Day 1) were below the limit of quantitation BLQ for all subjects, except for 1 subject on Eksunbi treatment (concentration of 2,919.4 ng/mL) and 2 subjects on Stelara treatment (concentrations of 2,626.0 ng/mL and 158.5 ng/mL, respectively). The applicant outlined that no protocol deviations were observed which would account for these quantifiable concentrations, therefore the applicant included these concentrations in the PK analyses.

The applicant provided a discussion on the overall PK conclusions based on the totality of the data, including a discussion on any differences observed between healthy volunteers in the Phase I study and variability in the target population.

The applicant provided a detailed discussion of the phase III PK data which comprehensively addresses the recommendations of the CHMP SA, as follows:

The approach for PK assessment in the phase III study is outlined as measuring C_{trough} in a sub-set of patients (n=80) for PK. According to the EMA Guideline EMA/CHMP/BMWP/403543/2010 (May 2012), a full characterisation of the PK profile is not inevitably required for the patient population during Phase III, but any additional PK parameter to C_{trough} (C_{max}, T_{max}, volume of distribution, half-life after the first dose as well as partial AUCs) will ease the evaluation of PK similarity also for the PsO patient

population. Thus, the evaluation concerning similarity of these parameters after the initial treatment in PsO patients is recommended by the Agency.

In study (SB17-3001) only a limited number of patients with PsO ≥65 years of age were included in the study. The mean age was 44.2 years with an age range of 18-77 years. A separate analysis for elderly patients has been presented. Based on the *ad hoc* analyses results, considering the small number of elderly patients and large % coefficient of variation (CV) as well as high variation range, mean ustekinumab concentrations for elderly patients in the PKS are generally comparable between the two treatment groups. Therefore, as the PK profile among elderly patients does not appear to differ from the total patient population, the applicant believes that relevant wording for elderly patient is not necessary at this time for the Summary of Product Characteristic (SmPC) of Eksunbi and the CHMP agrees.

2.6.4. Conclusions on clinical pharmacology

The PK bioequivalence has been demonstrated between Eksunbi and EU Stelara in Study SB17-1001, which was performed in the most sensitive and homogeneous population of healthy subjects. PK data assessed in psoriasis patients from Study SB17-3001 were provided as supportive data only. Taken together, the similarity in partial AUCs between Eksunbi and EU Stelara specifically in the elimination phase in Study SB17-1001 along with the results from Study SB17-3001 provides the evidence for extrapolation of the SC data to the IV administration route.

2.6.5. Clinical efficacy

2.6.5.1. Dose-response studies

No dose response studies were performed and are not deemed necessary in the biosimilarity setting.

2.6.5.2. Main study

Title of Study - Study SB17-3001

Study SB17-3001 was a randomised, double-blind, multicentre study to evaluate the efficacy, safety, tolerability, PK and immunogenicity of Eksunbi compared to Stelara in patients with moderate to severe plaque PsO.

This study was conducted in total of 45 study centres: 6 centres in the Czech Republic, 2 centres in Estonia, 1 centre in Hungary, 4 centres in the Republic of Korea, 2 centres in Latvia, 3 centres in Lithuania, 13 centres in Poland, and 14 centres in Ukraine.

The primary objective of Study SB17-3001 was to demonstrate the equivalence of Eksunbi to Stelara, in terms of the percent change from baseline in PASI at Week 12 in patients with moderate to severe plaque PsO.

The secondary objective was to evaluate the efficacy of Eksunbi compared to Stelara in terms of percent change from baseline in PASI other than Week 12, Physician's Global Assessment (PGA), PASI50, PASI75, PASI90, and PASI100 response rate, and change from baseline in Dermatology Life Quality Index (DLQI). Overall, the study objectives, design, and methodology were agreed by the EMA during SA and follow-up SA [EMA/CHMP/SAWP/791150/2017; EMA/CHMP/SAWP/493969/2019]. The inclusion and exclusion criteria are in line with those in the clinical trials performed with Stelara in patients with PsO [Stelara SmPC; Stelara US PI] (for more details see below).

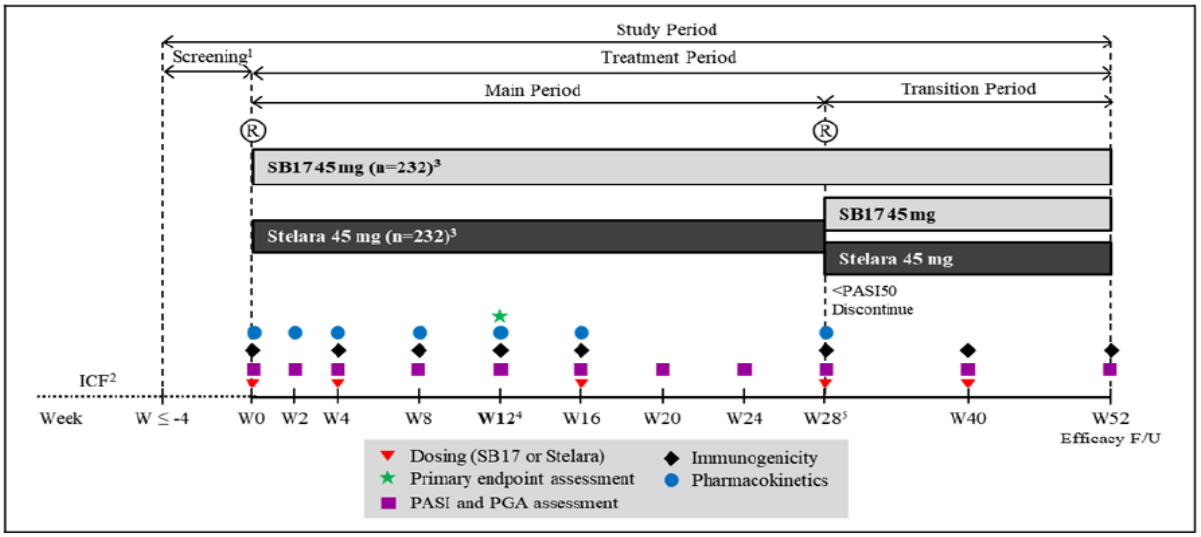
The applicant initially provided a clinical study report (CSR) containing interim data collected up to data cut-off date of Sep 15 2022, containing a full set of 40-week data and a subset of 52-week data of approximately 103 patients from the Phase III Study SB17-3001, with a commitment to submit the final CSR with full 52-week data of the Phase III study during the procedure. The study was completed on December 08, 2022 as the final CSR was in development at the time of initial MAA. The final CSR was provided by the applicant with the responses to the List of questions.

Methods

For Study SB17-3001, eligible patients were randomised in a 1:1 ratio to receive either Eksunbi or Stelara via SC injection. Investigational products (IPs; Eksunbi or Stelara) were administered at Week 0, 4, and then every 12 weeks up to Week 40, and the last assessment was performed at Week 52. At Week 28, patients who achieved PASI50 response and were considered eligible entered into the transition period. In the transition period, patients that received Stelara were randomised again in a 1:1 ratio to either continue on Stelara (Stelara to Stelara) or were transitioned to Eksunbi (Stelara to Eksunbi), until Week 40. Patients that received Eksunbi continued to receive Eksunbi until Week 40, but they followed the randomisation procedure in order to maintain blinding.

The graphical study design of the Study SB17-3001 is presented below:

Figure 5. Study design



Study Participants

Main inclusion criteria

Inclusion Criteria for Main Period:

Subjects had to meet all of the following criteria to be eligible for the study:

1. Aged 18 years or older at Screening (defined as the time of signing the informed consent form [ICF]).

2. Had plaque psoriasis diagnosed at least 6 months prior to Screening, with or without psoriatic arthritis.

3. Had plaque psoriasis at Screening and Randomisation with the involvement and severity defined as the following:

a. Total affected BSA ≥ 10%.

b. PASI score of ≥ 12.

c. PGA score of ≥ 3 (moderate).

4. Considered to be a candidate for phototherapy or systemic therapy for psoriasis at Screening.

5. Were less than 95 kg of body weight at Screening and at Randomisation.

6. Had adequate haematological function at Screening defined as the following by central lab:

a. White blood cell count ≥ 3.5×10^3 cells/μL (≥ 3.5×10^9 cells/L).

b. Neutrophil count ≥ 1.5×10^3 cells/μL (≥ 1.5×10^9 cells/L).

c. Haemoglobin ≥ 10 g/dL.

d. Platelet count ≥ 125,000/mm^3 (≥ 125×10^9/L).

7. Had adequate renal and hepatic function at Screening defined as the following by central lab:

a. Serum creatinine < 1.5 × upper limit of normal (ULN).

b. Serum alanine transaminase (ALT) and aspartate transaminase (AST) < 2 × ULN.

8. Non-childbearing potential female.

9. Had provided informed consent and was able to, in the opinion of the Investigator, understand the implications of taking part in the study and were willing to follow the study requirements.

Informed consent had to be obtained prior to any study related procedures.

Medical history included menopausal status, clinically significant diseases, surgical procedures, and lifestyle measures (smoking and alcohol).

Completed physical examination at Screening visit; abbreviated physical examination at subsequent visits (the abbreviated physical examination had to include general appearance, cardiovascular, respiratory systems, and abdomen; other body systems to be examined at the discretion of the Investigator). The result for physical examinations had to be confirmed by the Investigator. Body weight had to be measured at Screening and at every visit (recommended to be done after overnight fasting state) but height had to be measured only at Screening. Vital signs included blood pressure (BP), pulse rate, and body temperature. If TB was suspected at any point during the study, a chest X-ray and QuantiFERON-Gold Plus test had to be performed and the Sponsor had to be informed.

Previous and concomitant medication or therapy at Screening and concomitant medication or therapy only at visits until Week 52 or ET (visit or safety follow-up phone call, if done). Medications before randomisation had to be reported as much to ensure eligibility. All ongoing medications at Randomisation had to be reported.

AEs were collected from the time of signing the informed consent (even if this is prior to IP administration) until Week 52 or ET (visit or safety follow-up phone call, if done).

Virology screening was performed at Screening only. HBV (HBsAg, HBcAb), HCV (HCV antibody [HCV Ab]), and HIV (HIV antibody [HIV Ab]) will be tested. Those who were HCV Ab positive had to be

tested for HCV RNA. Subjects who were HIV Ab positive had to do a confirmatory HIV RNA test. If the QuantiFERON-Gold Plus test was indeterminate, one retest had to be done. If the follow-up test was still indeterminate, the subject was indicated as screen failed. Retests were not allowed for positive tests.

Serum pregnancy test had to be performed at Screening for women of childbearing potential. For women with amenorrhea of at least 12 months without an alternative medical cause, serum FSH test was performed at Screening. From Randomisation, a urine pregnancy test was performed and had to be negative before each IP administration. Additional pregnancy test(s) had to be performed besides the scheduled after Randomisation at the Investigator's discretion.

Blood and urine samples for clinical laboratory test were collected at Screening, Week 12 and 52 (or ET visit), and prior to IP administration at Week 0, 4, 16, 28, and 40.

• Haematology: Haemoglobin, haematocrit, platelet count, white blood cell count (total and differential);

• Chemistry: Sodium, potassium, calcium, phosphorus, creatinine, glucose, total bilirubin, albumin, ALT, AST, alkaline phosphatase (ALP), C-reactive protein (CRP);

• Urinalysis (dipstick): Protein, blood, leucocytes, nitrite, glucose, ketone, pH, specific gravity, bilirubin, urobilinogen

For PK subgroup only (approximately 140 subjects), blood samples for PK analysis were collected at Week 2, 8, and 12, and prior to IP administration at Week 0, 4, 16, and 28.

Blood samples for immunogenicity were collected at Week 8, 12, and 52 (or ET visit) and prior to IP administration at Week 0, 4, 16, 28, and 40.

At Week 28, subjects who achieved PASI50 response and were considered eligible entered the transition period. Subjects who received Stelara were re-randomised in a 1:1 ratio to either continue to receive Stelara or were transitioned to Eksunbi. Subjects who received Eksunbi continued to receive Eksunbi up to Week 40, but they also followed the randomisation procedure in order to maintain blinding.

Subjects who prematurely discontinued from the study at any time post 1st IP administration were required to have an ET visit. ET visit was performed at 12 weeks from the last IP administration. If ET visit happened before 11 weeks, a phone call for safety follow-up was performed at 12 weeks (± 7 days) from the last IP administration.

Inclusion Criteria for Transition Period:

1. Achieved a PASI50 response on Week 28 visit assessment.

2. Was willing to participate in the extended study period and were able to follow the study procedure with the opinion of the Investigator.

Main exclusion criteria

Subjects who met any of the following criteria were not eligible for the study:

1. Had non-plaque forms of psoriasis, including erythrodermic, pustular, guttate, or drug-induced psoriasis at Screening.

2. Had other skin disease other than psoriasis that:

a. Required topical or systemic corticosteroid or other immunosuppressive therapy at Screening.

b. That would confound the efficacy evaluation per Investigator discretion at Screening.

3. Had used biologics (any therapeutic monoclonal antibody or fusion receptor protein) such as;

a. Any tumour necrosis factor (TNF) inhibitors within the previous 6 months prior to Randomisation.

b. Any interleukin (IL)-12 or IL-23 inhibitor biologics (including ustekinumab/ustekinumab biosimilars, guselkumab, tildrakizumab, or rizankizumab), IL-17 inhibitor (including secukinumab, ixekizumab, or brodalumab), rituximab, or integrin inhibitor biologics at any time prior to Randomisation.

c. Other biologics within the longer of either 5 half-lives or 3 months prior to Randomisation.

4. Had known allergic reactions or hypersensitivity to ustekinumab or to any ingredients of Stelara or Eksunbi at Screening.

5. Had a history of any systemic allergic reaction or hypersensitivity to prior biologic therapies at Screening.

6. Had any history of asthma that:

a. Required intubation at any time prior to Screening.

b. Required hospitalisation or 14 days or more of oral corticosteroids use (cumulatively) within 6 months prior to Randomisation.

c. Required oral corticosteroids or considered to be corticosteroid-dependent in the opinion of the Investigator at Randomisation.

7. Had any history of exfoliative dermatitis, reversible posterior leukoencephalopathy syndrome (RPLS), facial palsy, allergic alveolitis, or non-infectious pneumonia including interstitial pneumonia, cryptogenic organising pneumonia, or eosinophilic pneumonia, etc. at Screening.

8. Had received phototherapy (including ultraviolet B [UVB], psoralen and ultraviolet A [PUVA], or sunbaths/tanning beds, etc.) or conventional systemic therapy (including corticosteroids, methotrexate [MTX], calcineurin inhibitors, retinoids, vitamin D analogues, fumaric acid esters, apremilast, 6-thioguanine, hydroxyurea, etc.) for psoriasis within 4 weeks prior to Randomisation.

9. Had received topical therapy for psoriasis (including corticosteroids, vitamin D analogues, retinoids, calcineurin inhibitors, coal tar, anthralin, urea, alpha-hydroxy acid, or salicylic acid, etc.) within 2 weeks prior to Randomisation.

10. Had received any disease-modifying anti-rheumatic drugs (DMARDs), any systemic immunosuppressants (including those mentioned above in systemic psoriasis therapy, antimalarials, sulfasalazine, Janus kinase [JAK] inhibitors, gold, minocycline, azathioprine, 6-mercaptopurine, mycophenolate mofetil, etc.) or any other injectable or enema corticosteroids, within 4 weeks prior to Randomisation (except for leflunomide: within 12 weeks from Randomisation).

11. Had received a non-biologic IP from another study within 5 half-lives of that product prior to Randomisation or used an investigational device prior to Randomisation.

12. Women who were pregnant or nursing at Screening, or men and women that were planning pregnancy during the study period and until 15 weeks after the last dose of IP.

13. Had received a live or live attenuated viral vaccine or a live bacterial vaccine (except Bacille Calmette-Guerin [BCG] vaccination) within 4 weeks prior to Randomisation or had planned to do so within 15 weeks after the last dose of IP. For BCG vaccination, subjects who had received BCG within 12 months prior to Randomisation or planned to do so within 12 months after the last dose of IP.

14. Had active or latent tuberculosis (TB) at Screening, by known history or any of the following:

a. Positive QuantiFERON-Gold Plus test.

b. Positive chest X-ray findings (radiographs taken within 3 months prior to Randomisation with radiologist confirmation will be accepted) determined by a qualified physician such as radiologist or pulmonologist, including active TB, untreated or inadequately treated old, inactive or healed TB.

c. By any other positive findings determined by TB specialist, including suggestive signs or symptoms of TB or recent close contact with active TB patients.

15. Had a history of ongoing infection or a positive test of hepatitis B virus (HBV, defined as hepatitis B surface antigen [HBsAg] positive or HBsAg negative and hepatitis B core antibody [HBcAb] positive), hepatitis C virus (HCV; for subjects who had previously received anti-HCV treatment must have had a sustained virologic response [SVR] for at least 24 weeks post-treatment and there were no evidence of significant liver fibrosis [i.e., must be METAVIR F0 or F1] in addition to negative HCV-ribonucleic acid (RNA) at Screening to be eligible), or human immunodeficiency virus (HIV) infection, or any history of primary immunodeficiency at Screening.

16. Had a history of sepsis (defined as a life-threatening organ dysfunction caused by infection), chronic or recurrent infection, conditions that require regular antibiotic prophylaxis (such as rheumatic heart disease), opportunistic, granulomatous (for TB, please see above), or invasive fungal infection at Screening.

17. History of other bacterial, fungal, viral, parasitic, or helminthic infection that required oral antimicrobial within 2 weeks prior to Randomisation or had a serious infection (a bacterial, fungal, viral, parasitic, or helminthic infection that required hospitalisation or treatment with parenteral antimicrobials) within 8 weeks prior to Randomisation. Other mild infections were resolved before Randomisation. For Coronavirus Disease 2019 (COVID-19), please see Exclusion Criteria #29 below.

18. Had history of lymphoproliferative disease or leukaemia at Screening.

19. Had history of malignancy (except for squamous or basal cell carcinoma of the skin that had been treated and had not recurred within 3 months prior to screening, or was surgically treated cervical carcinoma in situ), within the last 5 years prior to Screening.

20. Had history of myocardial infarction, New York Heart Association (NYHA) III/IV congestive heart failure, or stroke within 12 months prior to Randomisation.

21. Had uncontrolled hypertension (defined as systolic blood pressure [SBP] ≥ 160 mmHg or diastolic blood pressure [DBP] ≥ 100 mmHg confirmed after repeat measurement) at Screening.

22. Had uncontrolled diabetes mellitus (defined as having history of diabetic peripheral neuropathy or diabetic foot, or otherwise considered uncontrolled in the opinion of the Investigator) at Screening.

23. Had history of organ transplantation at Screening.

24. Any evidence of alcohol or substance abuse within the last 12 months prior to Screening.

25. Had history of a major surgery in the opinion of the Investigator within the 12 weeks prior to Randomisation or had a plan to do so during the study period.

26. Had psychiatric disease at Screening defined as:

a. Current uncontrolled mental disorder (including depression) in the opinion of the Investigator.

b. History of suicidal attempts or ideation.

c. Considered to be at risk of suicide in the opinion of the Investigator.

27. Had other major organ dysfunction or failure such as liver cirrhosis, dialysis-dependent renal failure, any cardiopulmonary disease with functional disability of NYHA III/IV equivalent, aplastic

anaemia or any other transfusion-dependent/stimulating factor dependent haematological disorders, or dementia at Screening.

28. Were considered to be at risk of progressive weight gain or widely fluctuating body weight, in the opinion of the Investigator, at Screening.

29. Had history of COVID-19 as:

a. History of asymptomatic, mild or moderate COVID-19 within 8 weeks prior to Randomisation.

b. Any history of severe or critical COVID-19, or hospitalisation due to COVID-19 at Randomisation.

c. Any history of COVID-19 complications or sequalae including lung fibrosis, thromboembolism, cardiac, gastrointestinal, neuropsychiatric, 'long COVID', or dermatologic manifestations, etc. at Randomisation.

Note: COVID-19 severity grade was assessed according to World Health Organization (WHO) COVID-19 disease severity classification. Subjects who had suggestive signs or symptoms of COVID-19 were evaluated and determined to be COVID-19 negative per local regulations before Screening.

30. Had any other disease or disorder, that put the subject at risk if they were enrolled, in the opinion of the Investigator, at Screening.

31. Had poor venous access or were unwilling to undergo multiple venepuncture and blood sampling at Screening.

Exclusion Criteria for Transition Period:

1. Subject was considered to be of increased risk when entered in the Transition Period, in the opinion of the Investigator.

Treatments

Table 14. Schedule of activities

Assessment	Screening	Treatment Period										
Visit	0	1	2	3	4	5	6	7	8	9	10	11 or ET[16]
Day (± Visit Window)	−28 to −1	1	15 (±3)	29 (±3)	57 (±3)	85 (±3)	113 (±5)	141 (±5)	169 (±5)	197 (± 5)	281 (±7)	365 (±7)
Week	−4 to 0	0	2	4	8	12	16	20	24	28	40	52
Written informed consent[1]	✓											
Demographic information	✓											
Medical and surgical history[2]	✓											
Psoriasis BSA involvement (%)	✓	✓										
Physical examination[3]	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓
Height and weight[4]	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓
12-lead ECG	✓											
Vital signs[5]	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓
Chest X-ray	✓											
TB evaluation[6]	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓
Assessment of eligibility	✓	✓								✓		
Randomisation		✓								✓[15]		
IP administration		✓		✓			✓			✓	✓	
Previous and concomitant medications[7]	Continuously											
AE monitoring[8]	Continuously											
EFFICACY ASSESSMENTS												
PASI	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓
PGA	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓
DLQI		✓		✓		✓	✓			✓	✓	✓
LABORATORY ASSESSMENTS												
Virology screen[9]	✓											
QuantiFERON-Gold Plus test[10]	✓											
Pregnancy test and FSH test[11]	✓	✓		✓			✓			✓	✓	✓
Clinical laboratory test[12]	✓	✓		✓		✓	✓			✓	✓	✓
PK assessment[13]		✓	✓	✓	✓	✓	✓			✓		
Immunogenicity assessment[14]		✓		✓	✓	✓	✓			✓	✓	✓

AE = Adverse event; BSA = Body surface area; DLQI = Dermatology Life Quality Index; ECG = Electrocardiogram; ET = Early termination; FSH = Follicle stimulating hormone; IP = Investigational product; PASI = Psoriasis Area and Severity Index; PGA = Physician's Global Assessment; PK = Pharmacokinetic(s); TB = Tuberculosis

Subjects were administered Eksunbi or Stelara 45 mg at Week 0, Week 4, followed by every 12 weeks up to Week 40. By eligibility criteria, all subjects received 45 mg at Week 0 (Randomisation). 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). Each injection was applied at different sites.

No visit window was allowed at Week 0 for the first IP administration. The visit window for dosing visit except for Week 0 was allowed as follows:

- ± 3 days for Week 4
- ± 5 days for Week 16 and Week 28
- ± 7 days for Week 40

IP administration delay was to be avoided as much as possible. If IP dose delay that required out-of-window administration was necessary due to AE, etc., administration of the IP was performed as soon as possible. IP dose delay was possible up to 4 weeks from the scheduled dosing date. If 4 weeks was exceeded, the IP administration was to be skipped. Subsequent visit schedules were not to be changed due to administration delay or be skipped. However, if the last scheduled IP (Week 40) could not be given even after a 4-week delay, an ET visit was made. Even if IP administration was not skipped, out-of-window administration was still considered a protocol deviation (PD).

Test Product, Dose and Mode of Administration, Batch Number	
Test Product:	SB17
Presentation:	0.5 mL of 90 mg/mL solution of ustekinumab in a pre-filled syringe (PFS)
Mode of Administration:	Subcutaneous injection

Dose:	45 mg at Week 0, 4, and then every 12 weeks up to Week 40. If the subject becomes > 100 kg at subsequent dosing visits the subject will receive 90 mg in the form of two doses of 45 mg.
Reference Product, Dose and Mode of Administration, Batch Number	
Reference Product:	Stelara (EU-sourced)
Presentation:	0.5 mL of 90 mg/mL solution of ustekinumab in a PFS
Mode of Administration:	Subcutaneous injection
Dose:	45 mg at Week 0, 4, and then every 12 weeks up to Week 40. If the subject becomes > 100 kg at subsequent dosing visits the subject will receive 90 mg in the form of two doses of 45 mg.
Duration of Treatment: 52 weeks (Last IP injection was at Week 40)	

Objectives

Primary Study Objective

To demonstrate the equivalence of Eksunbi to Stelara, in terms of the percent change from baseline in Psoriasis Area and Severity Index (PASI) at Week 12 in patients with moderate to severe plaque psoriasis.

Secondary Study Objectives

To evaluate the efficacy of Eksunbi compared to Stelara by

− Percent change from baseline in PASI other than Week 12

− Physician's Global Assessment (PGA)

− PASI50, PASI75, PASI90, and PASI100 response rate

− Change from baseline in Dermatology Life Quality Index (DLQI)

• To evaluate the safety and tolerability of Eksunbi compared to Stelara

• To evaluate the PK of Eksunbi compared to Stelara in patients participating in PK evaluation

• To evaluate the immunogenicity of Eksunbi compared to Stelara

• To evaluate safety and immunogenicity in patients who transitioned to Eksunbi and who maintained Stelara at Week 28 for the transition period

Outcomes/endpoints

The primary efficacy endpoint is percent change from baseline in PASI at Week 12 in patients with moderate to severe plaque PsO.

The secondary efficacy endpoints included the following:

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

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

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

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

Sample size

To calculate equivalence margin and sample size, the percent change from baseline in PASI at Week 12 were referred from five randomised controlled studies of ustekinumab.

A fixed-effect meta-analysis of the above five studies estimates a risk difference of 70.96% with a 95% confidence interval (CI) [68.12%, 73.80%]. Although an equivalence limit of 34% is statistically calculated to preserve 50% of the effect of ustekinumab over and above placebo, a clinical equivalence margin [−15%, 15%] was set for the comparison with the 95% CI of the mean difference in the percent change from baseline in PASI at Week 12 (Table 15 below).

Table 15. Percent Change from Baseline in PASI at Week 12 from Clinical Studies with Ustekinumab

	Ustekinumab		Placebo	
Study	**N**	**Mean (SD)**	**N**	**Mean (SD)**
PHOENIX 1 [Leonardi et al., 2008]	255	75.6% (27.04)	253	7.0% (30.77)
PHOENIX 2 [Papp et al., 2008]	405	77.0% (25.78)	404	4.9% (34.78)
PEARL [Tsai et al., 2011]	59	78.5% (27.2)	60	3.1% (43.0)
LOTUS [Zhu et al., 2013]	158	86.8% (19.7)	160	12.9% (45.3)
Igarashi et al [Igarashi et al., 2012]	62	73.1% (29.6)	30	10.9% (31.7)
Meta-analysis for risk difference with 95% CI	**70.96% [68.12%, 73.80%]**			

CI = confidence interval; SD = standard deviation
Source: Section 2.7.3, Table 1

Based on this equivalence margin, a sample size of 192 patients per treatment group was calculated with the assumptions of common standard deviation (SD) of 31.33, 10% loss from the primary analysis and approximately 100 remainders per treatment group after transition at Week 28 at the overall 5% significance level, providing over 90% power. Overall, 464 patients (232 patients per treatment group) were randomised into the study to determine equivalence of percent change from baseline in PASI at Week 12.

The nQuery Advisor option two one-sided equivalence tests (TOST) for two-group design gives the following statement to estimate the n per group to show the equivalence: "When the sample size in each group is 232, a two group design will have 99.86% power to reject both the null hypothesis that the test mean minus the standard mean is below −15 and the null hypothesis that the test mean minus the standard mean is above 15 i.e., that the test and standard are not equivalent, in favour of the alternative hypothesis that the means of the two groups are equivalent, assuming that the expected difference in means is 0, the common standard deviation is 31.33 and that each test is made at the 2.5% level."

The equivalence margin for the comparison with the 90% CI of the difference in the percent change from baseline in PASI at Week 12 was set to [−10%, 10%] by the Agency's recommendation. Based on the equivalence margin, a sample size of 169 patients per treatment group was calculated with the assumption of the common SD of 31.33 at the overall 10% significance level, providing 80% power. Overall, 338 patients (169 patients per treatment group) were randomised into the study to determine equivalence of percent change from baseline in PASI at Week 12.

The nQuery Advisor option TOST for two-group design gives the following statement to estimate the n per group to show the equivalence: "When the sample size in each group is 169, a two group design will have 80% power to reject both the null hypothesis that the test mean minus the standard mean is below −10 and the null hypothesis that the test mean minus the standard mean is above 10 i.e., that the test and standard are not equivalent, in favour of the alternative hypothesis that the means of the two groups are equivalent, assuming that the expected difference in means is 0, the common standard deviation is 31.33 and that each test is made at the 5% level."

Therefore, the sample size of 464 allowed enough power to detect the equivalence in the 95% CI or 90% CI of the difference in the percent change from baseline in PASI at Week 12.

Randomisation and blinding (masking)

Subjects were randomised in a 1:1 ratio to receive either Eksunbi or Stelara via subcutaneous injection.

Investigative products (IPs; Eksunbi or 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.

A unique subject number was assigned to subjects at Screening. The subject number was used to register the subject using the Interactive Web Response System (IWRS) and the subject was then randomised (in a ratio of 1:1) to either Eksunbi or Stelara.

Selection of Doses in the Study

The approved dose of Stelara for psoriasis is 45 mg for subjects less than 100 kg and 90 mg for patients more than 100 kg, administered via subcutaneous injection initially and 4 weeks later, followed by 45 mg or 90 mg every 12 weeks. For a biosimilar study, the study dose generally follows the approved dose, which is the case for this SB17-3001 study. Per-protocol, all randomised eligible subjects received a 45 mg dose at Week 0 and Week 4, and every 12 weeks up to Week 40. A dose of 90 mg (in the form of 2 doses of 45 mg) was used in subjects with a body weight that was greater than 100 kg during the study. The primary analysis was done with subjects ≤ 100 kg who received only 45 mg doses, according to EMA recommendations. Therefore, it was highly recommended that subjects maintain a body weight of ≤ 100 kg.

Blinding

This study was double-blinded. Subjects, Investigators, and other study personnel were unaware of the treatment group assignments throughout the study treatment period after randomisation.

Emergency unblinding procedures are described in Section 8.5 of the study protocol.

To ensure the blinding of the treatment group assignment, blinding cap was applied to IP (Eksunbi or Stelara). The carton and IP pre-filled syringe (PFS) were packed and labelled in identical appearance.

Statistical methods

A statistical analysis plan (SAP) was submitted. The final version of the document was approved on November 11, 2022 and included 6 amendments. Versions 0.3 and 0.4 included adding in sections on estimands. The final outputs were generated with a date stamp of 07/12/2022, one day before the study completion date (08/12/2022) as given on page 2 of the CSR. The data cut-off date was 15/09/2022.

Analysis Sets

Several analyses sets were defined, in particular, of relevance for a conclusion on equivalence are:

- Full Analysis Set (FAS) consisted of all subjects who were randomised. Following the intent-to-treat principle, subjects were analysed according to the treatment group that they were assigned to at Randomisation. However, subjects who did not have any efficacy assessment result after randomisation or did not receive IP during the study period were excluded from FAS.
- Per-Protocol Set (PPS) consisted of all FAS subjects who weighed ≤ 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 PDs that had impact on the primary efficacy assessment. Major PDs that led to exclusion from this set were pre-defined prior to unblinding the treatment group assignment for analyses.

Analysed:	Treatment	SB17	Stelara			Total
			Overall	SB17	Stelara	
	Number (%) of Subjects	N=249 n (%)	N=254 n (%)	N=122 n (%)	N=122 n (%)	N=503 n (%)
	Randomised Set	249 (100.0)	254 (100.0)	122 (100.0)	122 (100.0)	503 (100.0)
	Full Analysis Set	249 (100.0)	254 (100.0)	122 (100.0)	122 (100.0)	503 (100.0)
	Per-protocol Set	243 (97.6)	249 (98.0)	119 (97.5)	122 (100.0)	492 (97.8)
	Safety Analysis Set 1	249 (100.0)	254 (100.0)	122 (100.0)	122 (100.0)	503 (100.0)
	Safety Analysis Set 2	237 (95.2)	244 (95.1)	122 (100.0)	122 (100.0)	481 (95.6)
	PK Population	71 (28.5)	71 (28.0)	34 (27.9)	34 (27.9)	142 (28.2)

Estimands Approach

The applicant proposes the principal stratum, with supportive sensitivity analyses using a hypothetical estimand approach. The main IEs were proposed as discontinuations due to the war in Ukraine.

Handling of Dropouts or Missing Data

Missing efficacy data was handled as stated below:

For the supportive and sensitivity analysis to the primary efficacy analysis based on FAS, missing data for PASI score was imputed for subjects who dropped out of the study prior to the primary analysis time-point or missed the assessment at Week 12. A MAR approach assumed that subjects who withdraw from a study or missed the assessment had missing values similar to similar subjects who completed the study in that treatment group. This approach ensures that evidence of lack of equivalence is not diluted when there are missing data.

The missing value was imputed by multiple imputation method with the assumption of monotone missing pattern and regression method. Multiple imputation was conducted based on change from baseline values.

Missing secondary efficacy endpoints, safety, and PK data were not imputed.

Interim Analyses and Data Monitoring

An interim analysis to analyse the efficacy, safety, PK, and immunogenicity data was performed when all subjects completed the procedures at Week 28 and approximately 100 subjects (which ended up as 103 subjects) completed Week 52.

Multiple Comparisons/Multiplicity

No multiple comparison adjustments for type I error were used for the primary endpoint.

Active-control Studies Intended to Show Equivalence

This was an active control study to demonstrate equivalence in terms of percent change from baseline in PASI at Week 12 between Eksunbi and Stelara based on a pre-specified equivalence margin. The null hypothesis tested for the primary efficacy analysis was that either (1) Eksunbi is inferior to Stelara or (2) Eksunbi is superior to Stelara.

The equivalence between the two treatment groups was declared if the two-sided 95% CI of the LSMeans difference of percent change from baseline in PASI at Week 12 is entirely contained within the pre-defined equivalence margin of [−15%, 15%]. Primary efficacy analysis was performed for the PPS. Similar analysis was performed for the FAS to support the primary analysis.

Additionally, the two-sided 90% CI of the LSMeans difference between the two treatment groups was estimated for both the PPS and FAS with a narrower pre-defined equivalence margin of [−10%, 10%] as a sensitivity analysis.

Protocol Amendments

One global amendment (Amendment 1 dated Feb 15, 2021) and two country-specific amendments (Amendments 1.1, Czech Republic dated Apr 28, 2021 and Ukraine dated Jul 26, 2022) were made to the original protocol (dated Dec 30, 2020).

The key features of each amendment are as follows:

Global Protocol Amendment 1 (Version 2.0), Feb 15, 2021

• To clarify the reviewer for X-ray finding and ECG assessments

- Section 4.3. Exclusion Criteria for Main Period

- Section 6.2.4. Twelve-lead Electrocardiogram

- Section 6.2.6. Chest X-ray

Country-specific Protocol Amendment 1.1 - Czech Republic (Version 2.1), Apr 28, 2021

• To clarify the contraception methods and prohibited corticosteroids as per Czech Republic regulatory authority request

- Section 4.5. Lifestyle Considerations

- Section 5.3.2. Prohibited Concomitant Medication or Treatment

Country-specific Protocol Amendment 1.1 - Ukraine (Version 2.1), Jul 26, 2022

• To update study process in order to minimise the risk of procedural disruptions due to the Ukraine-Russian War

- Section 6.2.2. Clinical Laboratory Evaluations

- Section 7.1. Study Flow and Visit Schedule

• Further details on the Ukraine-Russian War such as the background, risks and mitigations, impact on this study, and the related documents are provided in the dossier.

Results

Participant flow

A total of 658 subjects were screened in the study, out of which 503 subjects were randomised and 155 subjects were screen failed. The most common reason for screening failure was not meeting the eligibility criteria.

Of the 503 subjects who were randomised, 481 (95.6%) subjects completed 28 weeks of the study and 103 (21.4%) subjects completed 52 weeks of the study. The completion rate at Week 28 was comparable between the two treatment groups, Eksunbi: 237 (95.2%) subjects vs Stelara Overall: 244 (96.1%) subjects. Prior to Week 28, 22 (4.4%) subjects discontinued treatment; Eksunbi: 12 (4.8%) subjects vs Stelara Overall: 10 (3.9%) subjects. The most common reason for discontinuation from IP before Week 28 was 'Other' and all related to war in Ukraine.

At Week 28, subjects who achieved a PASI50 response and were considered eligible entered into the transition period. The 237 subjects in the Eksunbi treatment group continued to receive Eksunbi until Week 40. The 244 subjects in the Stelara treatment group were further randomised into 2 treatment groups: continue Stelara treatment (Stelara+Stelara: 122 subjects) or transition to receive Eksunbi (Stelara+Eksunbi: 122 subjects) until Week 40.

The completion rate at Week 52 was comparable between the two treatment groups (233 [98.3%] patients in the Eksunbi and 233 [95.5%] patients in the Stelara Overall treatment groups, respectively). From the 244 patients in the Stelara Overall treatment group who entered the transition period, 117 (95.9%) patients from the Stelara+Eksunbi treatment group and 116 (95.1%) patients from the Stelara+Stelara treatment group completed the study.

The randomised allocation to treatment by subject is presented in the dossier.

Table 16. Subject Disposition by Treatment Group (Enrolled Set)

Number of Subjects	SB17 n (%)	Stelara Overall n (%)	Stelara+ SB17[a] n (%)	Stelara+ Stelara[a] n (%)	Total n (%)
Screened					658
Screening Failures					155
Reasons for Screening Failures					
Does not meet eligibility criteria					138 (89.0)
Consent Withdrawal					8 (5.2)
Lost to follow-up					1 (0.6)
Other					8 (5.2)
Main Period					
Randomised at Week 0[a]	249 (100.0)	254 (100.0)			503 (100.0)
Completed Week 28[a]	237 (95.2)	244 (96.1)			481 (95.6)

Number of Subjects	SB17 n (%)	Stelara Overall n (%)	Stelara+ SB17[a] n (%)	Stelara+ Stelara[a] n (%)	Total n (%)
Patient discontinuation from IP on or before Week 28 (Main period)[a,b]	12 (4.8)	10 (3.9)			22 (4.4)
Primary reason for discontinuation[a]					
Consent withdrawal by subject	2 (0.8)	4 (1.6)			6 (1.2)
Patient lost to follow-up	0 (0.0)	1 (0.4)			1 (0.2)
Protocol violation	1 (0.4)	0 (0.0)			1 (0.2)
Lack of Efficacy[c]	1 (0.4)	0 (0.0)			1 (0.2)
Other	8 (3.2)	5 (2.0)			13 (2.6)
Patient discontinuation from IP on or before Week 28 (Main period) related to COVID-19[a]	0 (0.0)	0 (0.0)			0 (0.0)
Patient discontinuation from IP on or before Week 28 (Main period) related to war in Ukraine[a]	8 (3.2)	5 (2.0)			13 (2.6)
Transition Period					
Randomised at Week 28[d]	237 (100.0)	244 (100.0)	122 (100.0)	122 (100.0)	481 (100.0)
Completed Week 52[d]	233 (98.3)	233 (95.5)	117 (95.9)	116 (95.1)	466 (96.9)
Patient discontinuation from IP after Week 28 (Transition period)[d]	4 (1.7)	11 (4.5)	5 (4.1)	6 (4.9)	15 (3.1)
Primary reason for discontinuation[d]					
Adverse Events	0 (0.0)	2 (0.8)	0 (0.0)	2 (1.6)	2 (0.4)
Consent withdrawal by patient	0 (0.0)	2 (0.8)	2 (1.6)	0 (0.0)	2 (0.4)
Patient lost to follow-up	1 (0.4)	1 (0.4)	1 (0.8)	0 (0.0)	2 (0.4)
Other	3 (1.3)	6 (2.5)	2 (1.6)	4 (3.3)	9 (1.9)
Patient discontinuation from IP after Week 28 (Transition period) related to COVID-19[d]	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
Patient discontinuation from IP after Week 28 (Transition period) related to war in Ukraine[d]	3 (1.3)	5 (2.0)	1 (0.8)	4 (3.3)	8 (1.7)

COVID-19 = Coronavirus Disease 2019; n = number of patients with available data within each category
[a] Percentages were based on the number of randomised patients at Week 0.
[b] Includes patients that completed Week 28 but discontinued before starting transition period.
[c] Lack of efficacy other than failure to achieve PASI50 response on Week 28 visit.
[d] Percentages were based on the number of randomised patients at Week 28.
Percentages of screening failure reasons were based on number of screening failures.

Data Sets Analysed

The number of subjects in each analysis set is summarised in Table 17 below.

Of the 503 subjects randomised, all subjects were included in the FAS and SAF1, 492 (97.8%) subjects satisfied the criteria for the PPS, 481 (95.6%) subjects satisfied the criteria for the SAF2, and 142 (28.2%) subjects were included in the PKS.

Table 17. Number of subjects in the Analysis Sets by Treatment Group (Randomised Set)

Number of subjects	SB17 N=249 n (%)	Stelara Overall N=254 n (%)	Stelara+ SB17[a] N=122 n (%)	Stelara+ Stelara[a] N=122 n (%)	Total N=503 n (%)
Randomised Set	249 (100.0)	254 (100.0)	122 (100.0)	122 (100.0)	503(100.0)
Full Analysis Set	249 (100.0)	254 (100.0)	122 (100.0)	122 (100.0)	503(100.0)
Per-Protocol Set	243 (97.6)	249 (98.0)	119 (97.5)	122 (100.0)	492 (97.8)
Safety Set 1	249 (100.0)	254 (100.0)	122 (100.0)	122 (100.0)	503 (100.0)
Safety Set 2	237 (95.2)	244 (96.1)	122 (100.0)	122 (100.0)	481 (95.6)
Pharmacokinetic Analysis Set	71 (28.5)	71 (28.0)	34 (27.9)	34 (27.9)	142 (28.2)

N: Total number of subjects in the Randomised Set in each treatment group; n: Number of subjects with available data within each category

Percentages were based on the number of subjects in the Randomised Set.

a. Based on subjects who were re-randomised at Week 28, Stelara+SB17 and Stelara+Stelara may not add up to Stelara Overall.

Recruitment

A total of 658 subjects were screened in the study, out of which 503 subjects were randomised and 155 subjects were screen failed. The most common reason for screening failure was not meeting the eligibility criteria.

Of the 503 subjects who were randomised, 481 (95.6%) subjects completed 28 weeks of the study and 446 (96.9%) subjects completed 52 weeks of the study. The completion rate at Week 28 was comparable between the two treatment groups, Eksunbi: 237 (95.2%) subjects vs Stelara Overall: 244 (96.1%) subjects.

Prior to Week 28, 22 (4.4%) subjects discontinued treatment; Eksunbi: 12 (4.8%) subjects vs Stelara Overall: 10 (3.9%) subjects. The most common reason for discontinuation from IP before Week 28 was 'Other' and all related to war in Ukraine.

At Week 28, subjects who achieved a PASI50 response and were considered eligible entered into the transition period. The 237 subjects in the Eksunbi treatment group continued to receive Eksunbi until Week 40. The 244 subjects in the Stelara treatment group were further randomised into 2 treatment groups: continue Stelara treatment (Stelara+Stelara: 122 subjects) or transition to receive Eksunbi (Stelara+Eksunbi: 122 subjects) until Week 40.

At the time of data cut-off for the main CSR (Sep 15, 2022), all of the randomised subjects had either completed the Week 40 visit or discontinued; 103 (21.4%) subjects had completed the study; Eksunbi: 53 (22.4%) subjects vs Stelara Overall: 50 (20.5%) subjects. From the 50 subjects in the Stelara Overall treatment group, 26 (21.3%) subjects had transitioned to Eksunbi treatment; and 24 (19.7%) subjects had continued Stelara treatment. Eight (1.7%) subjects discontinued treatment after Week 28; Eksunbi: 2 (0.8%) subjects vs Stelara Overall: 6 (2.5%) subjects. The most common reason for discontinuation from IP after Week 28 was 'Other' and all were related to the war in Ukraine.

The final updated information on discontinuation rates up to Week 52 per treatment group in Study SB17-3001 is presented in Table 18.

Up to the data cut-off date for the main CSR, all randomised patients had either completed the Week 40 visit of the study or discontinued from the study. Thus, there is no update on final CSR in discontinuation rates on/before Week 28, as provided in Table 19. As presented in Table 20, a total of 22 (4.4%) patients (12 [4.8%] patients in the Eksunbi and 10 [3.9%] patients in the Stelara Overall treatment groups) discontinued from IP on or before Week 28, and primary reasons for discontinuation are listed in Table 21. All patients of category "other" belong to war-related discontinuation (13 [2.6%] patients: 8 [3.2%] patients in the Eksunbi and 5 [2.0%] patients in the Stelara Overall treatment groups) for the main period.

For the final result of patient discontinuation from IP after Week 28 (transition period), a total of 15 (3.1%) patients (4 [1.7%] patients in the Eksunbi+Eksunbi, 11 [4.5%] patients in the Stelara Overall, 5 [4.1%] patients in the Stelara+Eksunbi, 6 [4.9%] patients in the Stelara+Stelara treatment groups) discontinued the study after Week 28. All patients of category "other" belong to war-related discontinuation (8 [1.7%] patients: 3 [1.3%] patients in the Eksunbi+Eksunbi, 5 [2.0%] patients in the Stelara Overall, 1 [0.8%] patient in the Stelara+Eksunbi, and 4 [2.3%] patients in the Stelara+Stelara treatment groups) for the transition period, except for 1 patient in the Stelara+Eksunbi treatment group.

Table 18. Disposition of Patients (Enrolled Set, Study SB17-3001)

Number of Patients	**SB17** n (%)	**Stelara Overall** n (%)	**Stelara +SB17[a]** n (%)	**Stelara +Stelara[a]** n (%)	**Total** n (%)
Screened					658
Screening Failures					155
Reasons for Screening Failures					
Does not meet eligibility criteria					138 (89.0)
Consent Withdrawal					8 (5.2)
Lost to follow-up					1 (0.6)
Other					8 (5.2)
Main Period					
Randomized at Week 0[a]	249 (100.0)	254 (100.0)			503 (100.0)
Completed Week 28[a]	237 (95.2)	244 (96.1)			481 (95.6)

Number of Patients	SB17 n (%)	Stelara Overall n (%)	Stelara +SB17[a] n (%)	Stelara +Stelara[a] n (%)	Total n (%)
Patient discontinuation from IP on or before Week 28 (Main period)[a,b]	12 (4.8)	10 (3.9)			22 (4.4)
Primary reason for discontinuation[a]					
Consent withdrawal by subject	2 (0.8)	4 (1.6)			6 (1.2)
Patient lost to follow-up	0 (0.0)	1 (0.4)			1 (0.2)
Protocol violation	1 (0.4)	0 (0.0)			1 (0.2)
Lack of Efficacy[c]	1 (0.4)	0 (0.0)			1 (0.2)
Other	8 (3.2)	5 (2.0)			13 (2.6)
Patient discontinuation from IP on or before Week 28 (Main period) related to COVID-19[a]	0 (0.0)	0 (0.0)			0 (0.0)
Patient discontinuation from IP on or before Week 28 (Main period) related to war in Ukraine[a]	8 (3.2)	5 (2.0)			13 (2.6)
Transition Period					
Randomized at Week 28[d]	237 (100.0)	244 (100.0)	122 (100.0)	122 (100.0)	481 (100.0)
Completed Week 52[d]	233 (98.3)	233 (95.5)	117 (95.9)	116 (95.1)	466 (96.9)
Patient discontinuation from IP after Week 28 (Transition period)[d]	4 (1.7)	11 (4.5)	5 (4.1)	6 (4.9)	15 (3.1)
Primary reason for discontinuation[d]					
Adverse Events	0 (0.0)	2 (0.8)	0 (0.0)	2 (1.6)	2 (0.4)
Consent withdrawal by patient	0 (0.0)	2 (0.8)	2 (1.6)	0 (0.0)	2 (0.4)
Patient lost to follow-up	1 (0.4)	1 (0.4)	1 (0.8)	0 (0.0)	2 (0.4)
Other	3 (1.3)	6 (2.5)	2 (1.6)	4 (3.3)	9 (1.9)
Patient discontinuation from IP after Week 28 (Transition period) related to COVID-19[d]	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
Patient discontinuation from IP after Week 28 (Transition period) related to war in Ukraine[d]	3 (1.3)	5 (2.0)	1 (0.8)	4 (3.3)	8 (1.7)

COVID-19 = Coronavirus Disease 2019; n = number of patients with available data within each category
[a] Percentages were based on the number of randomized patients at Week 0.
[b] Includes patients that completed Week 28 but discontinued before starting transition period.
[c] Lack of efficacy other than failure to achieve PASI50 response on Week 28 visit.
[d] Percentages were based on the number of randomized patients at Week 28.
Percentages of screening failure reasons were based on number of screening failures.

After the data cut-off, 3 more patients discontinued the study due to the war in Ukraine during the transition period: 1 patient from the Eksunbi+Eksunbi, 2 patients from the Stelara+Stelara treatment groups. As a result, a total of 13 (2.6%) patients (8 [3.2%] patients in the Eksunbi, 5 [2.0%] patients in the Stelara treatment groups) in the main period and 8 (1.7%) patients (3 [1.3%] patients in the Eksunbi+Eksunbi, 5 [2.0%] patients in the Stelara Overall, 1 [0.8%] patient in the Stelara+Eksunbi, 4 [3.3%] patients in the Stelara+Stelara treatment groups) in the transition period discontinued from the study due to war in Ukraine (final CSR).

Overall, the number of patients discontinued IP during transition period (after Week 28) is low and no difference noted by primary reason for discontinuation between treatment groups. Out of 22 patients, 13 patients discontinued IP before Week 28 due to war in Ukraine, and out of 15 patients, 8 patients discontinued IP after Week 28 due to war in Ukraine.

Overall, discontinuation rates in the main clinical study were low and generally balanced between Eksunbi and Stelara treatment groups. Based on the final CSR, discontinuation rates in the both the main study period and the transition period (after Week 28) were mainly related to disruption arising from the war in Ukraine and were reported in similar numbers across patients treated with Eksunbi and Stelara.

Table 19. Subject Disposition by Treatment Group Enrolled Set

Number of subjects	SB17 n (%)	Stelara Overall n (%)	Stelara+SB17 n (%)	Stelara+Stelara n (%)	Total n (%)
Screened					658
Screening failures					155
Reasons for screening failures					
Does not meet eligibility criteria					138 (89.0)
Consent withdrawal					8 (5.2)
Lost to follow-up					1 (0.6)
Other					8 (5.2)
Main Period					
Randomised at Week 0*	249 (100.0)	254 (100.0)			503 (100.0)
Completed Week 28*	237 (95.2)	244 (96.1)			481 (95.6)
Subject discontinuation from IP on or before Week 28(Main period)*#	12 (4.8)	10 (3.9)			22 (4.4)

Source: Listing 16.2.1-1.1

Conduct of the study

Protocol Deviations

A summary including the number and proportion of subjects with PDs and number of subjects for each PD by treatment group is presented in Table 20 below.

PDs related to COVID-19 by treatment group and those related to war in Ukraine by treatment group are also presented separately by the Applicant.

A complete list of PDs by subject is provided in the submission and in the responses.

A total of 262 (52.1%) subjects had PDs and 253 (50.3%) subjects had at least one major PD; Eksunbi: 123 (49.4%) subjects vs Stelara Overall: 130 (51.2%) subjects.

The most common major PDs which led to exclusion from PPS were related to study procedures in 6 (1.2%) subjects, followed by exclusion criteria in 4 (0.8%) subjects. The frequency and pattern of PDs were comparable between the two treatment groups.

Table 20. Major Protocol Deviations by Treatment Group (Randomised Set)

Table 10-2 Major Protocol Deviations by Treatment Group (Randomised Set)

Number of Subjects	SB17 N=249 n (%)	Stelara N=254 n (%)	Total N=503 n (%)
Any PDs	126 (50.6)	136 (53.5)	262 (52.1)
With at least one major PD	123 (49.4)	130 (51.2)	253 (50.3)
Excluded from Per-Protocol Set	5 (2.0)	5 (2.0)	10 (2.0)
Study procedures criteria	3 (1.2)	3 (1.2)	6 (1.2)
Exclusion criteria	2 (0.8)	2 (0.8)	4 (0.8)
Others	123 (49.4)	130 (51.2)	253 (50.3)
Study procedures criteria	92 (36.9)	85 (33.5)	177 (35.2)
IP compliance	62 (24.9)	63 (24.8)	125 (24.9)
Exclusion criteria	8 (3.2)	13 (5.1)	21 (4.2)
Concomitant medication criteria	2 (0.8)	1 (0.4)	3 (0.6)
Inclusion criteria	2 (0.8)	1 (0.4)	3 (0.6)

IP: Investigational product; N: Total number of subjects in the Randomised Set in each treatment group; n: Number of subjects with available data within each category; PDs = Protocol deviations.
Percentages were based on the number of subjects in the Randomised Set.
Subjects with multiple PDs within the same category are counted only once under that category.
Source: Table 14.1-1.4

Table 21. Summary of Protocol Deviations Related to War in Ukraine by Treatment Group

Randomised Set

Table 14.1-1.7
Summary of Protocol Deviation Related to War in Ukraine by Treatment Group
Randomised Set

Number of subjects	SB17 N=249 n (%)	Stelara N=254 n (%)	Total N=503 n (%)
Any protocol deviations	47 (18.9)	45 (17.7)	92 (18.3)
With at least one major protocol deviation	46 (18.5)	44 (17.3)	90 (17.9)
- Excluded from Per-protocol set	0 (0.0)	0 (0.0)	0 (0.0)
- Others	46 (18.5)	44 (17.3)	90 (17.9)
IP Compliance	36 (14.5)	33 (13.0)	69 (13.7)
Out-of-window administration of IP	25 (10.0)	22 (8.7)	47 (9.3)
IP administration was skipped	11 (4.4)	12 (4.7)	23 (4.6)
Study Procedures Criteria	36 (14.5)	30 (11.8)	66 (13.1)
Body weight was not measured at scheduled visit	20 (8.0)	19 (7.5)	39 (7.8)
PASI assessment was not done at scheduled visit	20 (8.0)	19 (7.5)	39 (7.8)
Psoriasis PGA was not completed at scheduled visit	20 (8.0)	19 (7.5)	39 (7.8)
Tuberculosis evaluation was not performed at scheduled visit	20 (8.0)	19 (7.5)	39 (7.8)
Out of visit window for non-dosing visit	17 (6.8)	11 (4.3)	28 (5.6)
Blood sample for immunogenicity was not collected at scheduled visit	16 (6.4)	13 (5.1)	29 (5.8)
Blood or urine samples for clinical laboratory test (Haematology, Chemistry, and Urinalysis) were not collected at scheduled visit	12 (4.8)	11 (4.3)	23 (4.6)
DLQI assessment was not completed at scheduled visit	11 (4.4)	11 (4.3)	22 (4.4)
Urine pregnancy test was not performed at scheduled visit	3 (1.2)	1 (0.4)	4 (0.8)
Blood sample for PK was not collected at scheduled visit	0 (0.0)	1 (0.4)	1 (0.2)
With at least one minor protocol deviation	21 (8.4)	20 (7.9)	41 (8.2)
IP Compliance	1 (0.4)	0 (0.0)	1 (0.2)
IP was not administered at a different anatomic location than the previous location	1 (0.4)	0 (0.0)	1 (0.2)
Study Procedures Criteria	20 (8.0)	20 (7.9)	40 (8.0)
Physical examination or vital sign measurement were not performed at scheduled visit	20 (8.0)	19 (7.5)	39 (7.8)
Early termination visit was not performed	11 (4.4)	11 (4.3)	22 (4.4)

Source: Listing 16.2.2-1.1
- N: Total number of subjects in the Randomised Set in each treatment group.
- n: Number of subjects with available data within each category.
- Percentages were based on the number of subjects in the Randomised Set.
- Subjects with multiple protocol deviations within the same category are counted only once under that category.

Following the EMA guidance on the war in Ukraine, estimands framework has been applied to deal with events impacting the analysis of the primary efficacy endpoint. Early discontinuation from study on or before Week 12 and missed assessment at Week 12 due to reasons including war in Ukraine were considered as Intercurrent Events (IEs). These IEs were handled using the principal stratum strategy by taking the population to the principal stratum in which the IEs would not occur and using the hypothetical strategy with a Missing at Random (MAR) approach in which the missing values were replaced using multiple imputation method. Also, as a result of this consideration, a sensitivity analysis

of the primary efficacy endpoint excluding subjects affected by the war in Ukraine was additionally performed.

Baseline data

Subject demographics and baseline characteristics were summarised by country and each treatment group for the RAN and PKS. Continuous variables (e.g., age, height, weight, BMI) were summarised by treatment group with descriptive statistics (n, mean, standard deviation [SD], median, minimum, and maximum). Qualitative variables (e.g., gender, childbearing potential for Female subjects, race, ethnicity, and country) were summarised by treatment group with frequency and percentages. The summary of subject demographics and baseline characteristics were also provided by country and treatment group.

By-subject listings of demographic and other baseline characteristics were provided.

Demographic Characteristics

The demographic characteristics were comparable between the Eksunbi and Stelara Overall treatment groups and there were no statistically significant differences between treatment groups. Overall, the mean age was 44.2 years (range: 18-77 years) and the majority of subjects were white (98.8%) and male (62.0%).

The demographic characteristics were also comparable between the 2 further treatment groups (Stelara+Eksunbi and Stelara+Stelara) for the RAN, refer to Table 22 below.

Table 22. Demographic Characteristics by Treatment Group (Randomised Set)

Characteristics	SB17 N=249	Stelara Overall N=254	Stelara+SB17* N=122	Stelara+Stelara* N=122	Total N=503
Age (years)					
n	249	254	122	122	503
Mean	44.0	44.3	45.3	43.2	44.2
SD	13.21	12.42	12.80	11.93	12.81
Median	43.0	44.0	44.0	43.0	43.0
Min, Max	19, 77	18, 76	18, 74	19, 76	18, 77
Gender, n (%)					
Male	150 (60.2)	162 (63.8)	80 (65.6)	79 (64.8)	312 (62.0)
Female	99 (39.8)	92 (36.2)	42 (34.4)	43 (35.2)	191 (38.0)
Childbearing Potential, n (%)					
Yes	57 (22.9)	59 (23.2)	27 (22.1)	30 (24.6)	116 (23.1)
No	42 (16.9)	33 (13.0)	15 (12.3)	13 (10.7)	75 (14.9)
Not Applicable (Male)	150 (60.2)	162 (63.8)	80 (65.6)	79 (64.8)	312 (62.0)
Race, n (%)					
American Indian or Alaska Native	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
Asian	2 (0.8)	4 (1.6)	2 (1.6)	2 (1.6)	6 (1.2)
Black or African American	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
Native Hawaiian or Other Pacific Islander	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
White	247 (99.2)	250 (98.4)	120 (98.4)	120 (98.4)	497 (98.8)
Other	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)

Characteristics	SB17 N=249	Stelara Overall N=254	Stelara+SB17* N=122	Stelara+Stelara* N=122	Total N=503
Country, n (%)					
Czech Republic	26 (10.4)	25 (9.8)	13 (10.7)	12 (9.8)	51 (10.1)
Estonia	10 (4.0)	12 (4.7)	6 (4.9)	6 (4.9)	22 (4.4)
Hungary	2 (0.8)	3 (1.2)	1 (0.8)	2 (1.6)	5 (1.0)
Korea	2 (0.8)	4 (1.6)	2 (1.6)	2 (1.6)	6 (1.2)
Lithuania	14 (5.6)	14 (5.5)	6 (4.9)	8 (6.6)	28 (5.6)
Latvia	0 (0.0)	2 (0.8)	2 (1.6)	0 (0.0)	2 (0.4)
Poland	122 (49.0)	121 (47.6)	58 (47.5)	58 (47.5)	243 (48.3)
Ukraine	73 (29.3)	73 (28.7)	34 (27.9)	34 (27.9)	146 (29.0)
Ethnicity, n (%)					
Hispanic or Latino	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
Indian (Indian Subcontinent)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
Chinese	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
Japanese	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
Korean	2 (0.8)	4 (1.6)	2 (1.6)	2 (1.6)	6 (1.2)
Mixed Ethnicity	0 (0.0)	1 (0.4)	1 (0.8)	0 (0.0)	1 (0.2)
Other	247 (99.2)	249 (98.0)	119 (97.5)	120 (98.4)	496 (98.6)
Height (cm)					
n	249	254	122	122	503
Mean	172.32	172.82	173.11	173.20	172.57
SD	9.435	9.429	8.095	10.474	9.426
Median	173.00	173.00	174.00	173.00	173.00
Min, Max	150.0, 192.0	149.7, 197.0	156.0, 192.0	149.7, 197.0	149.7, 197.0

Characteristics	SB17 N=249	Stelara Overall N=254	Stelara+SB17* N=122	Stelara+Stelara* N=122	Total N=503
Weight (kg)					
n	249	254	122	122	503
Mean	80.72	79.91	80.21	79.90	80.31
SD	11.784	12.019	11.745	12.272	11.898
Median	83.00	82.10	81.90	82.65	82.20
Min, Max	46.7, 95.0	46.7, 95.0	46.7, 95.0	50.9, 94.9	46.7, 95.0
BMI (kg/m^2)					
n	249	254	122	122	503
Mean	27.24	26.76	26.76	26.65	27.00
SD	3.943	3.664	3.578	3.702	3.808
Median	27.30	27.20	27.45	26.55	27.20
Min, Max	16.8, 39.1	16.7, 35.5	16.7, 34.2	18.5, 35.5	16.7, 39.1

Source: Listing 16.2.4-1.1
- SD: Standard Deviation; Min: Minimum; Max: Maximum.
- Country: CZE = Czech Republic; EST = Estonia; HUN = Hungary; KOR = Korea; LTU = Lithuania; LVA = Latvia; POL = Poland; UKR = Ukraine.
- Percentages were based on the number of subjects in the Randomised Set.
- *: Based on subjects who were re-randomised at Week 28, Stelara+SB17 and Stelara+Stelara may not add up to Stelara Overall.
- Body mass index (BMI; kg/m^2) was calculated using weight at baseline and height at screening.

The baseline characteristics were well-balanced between the Eksunbi and Stelara Overall treatment groups and there were no statistically significant differences between the treatment groups.

Table 23. Baseline Characteristics by Treatment Group (Randomised Set)

Characteristics	SB17 N=249	Stelara Overall N=254	Total N=503
Duration of psoriasis (years)			
Mean	15.03	16.13	15.59
SD	11.383	11.881	11.639
Total psoriasis BSA involvement (%)			
Mean	27.31	26.66	26.98
SD	13.486	13.772	13.621
PASI at baseline			
Mean	22.52	22.07	22.29
SD	7.819	7.690	7.749
PGA Score of ≥ 4 (Marked or Severe) at baseline, n (%)	92 (36.9)	94 (37.0)	186 (37.0)
DLQI at baseline			
Mean	13.4	13.2	13.3
SD	7.24	6.96	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 conventional systemic treatment for psoriasis, n (%)			
Yes	117 (47.0)	132 (52.0)	249 (49.5)
No	132 (53.0)	122 (48.0)	254 (50.5)
Use of prior phototherapy, n (%)			
Yes	114 (45.8)	128 (50.4)	242 (48.1)
No	135 (54.2)	126 (49.6)	261 (51.9)
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)
Smoking status, n (%)			
Current smoker	62 (24.9)	74 (29.1)	136 (27.0)
Past smoker	27 (10.8)	38 (15.0)	65 (12.9)
Non-smoker	160 (64.3)	142 (55.9)	302 (60.0)
Alcohol status, n (%)			
Current drinker	107 (43.0)	112 (44.1)	219 (43.5)
Past drinker	13 (5.2)	17 (6.7)	30 (6.0)
Non-drinker	129 (51.8)	125 (49.2)	254 (50.5)

BSA: Body surface area; DLQI: Dermatology Life Quality Index; PASI: Psoriasis Area and Severity Index; PGA: Physician's Global Assessment; SD: Standard deviation

Percentages were based on the number of subjects in the Randomised Set.

Duration of psoriasis (years) – calculated as difference between date of informed consent and diagnosed date of plaque psoriasis.

Prior Medication

A similar proportion of subjects in the Eksunbi and Stelara Overall treatment groups (248 [99.6%] subjects and 250 [98.4%] subjects, respectively) had taken prior medications which started and ended prior to the study (i.e., first dose of IP) .The most commonly reported prior medication by PT was clobetasol propionate (Eksunbi: 109 [43.8%] subjects; Stelara Overall: 109 [42.9%] subjects), followed by COVID-19 vaccine (Eksunbi: 94 [37.8%] subjects; Stelara Overall: 94 [37.0%] subjects), mometasone furoate (Eksunbi: 86 [34.5%] subjects; Stelara Overall: 80 [31.5%] subjects), methotrexate (Eksunbi: 78 [31.3%] subjects; Stelara Overall: 86 [33.9%] subjects) and betamethasone/calcipotriol (Eksunbi: 79 [31.7%] subjects; Stelara Overall: 84 [33.1%] subjects).

Concomitant Medication

A similar proportion of subjects in the Eksunbi and Stelara Overall treatment groups (118 [47.4%] subjects and 117 [46.1%] subjects, respectively) had received any concomitant medication during the main period. The most commonly reported concomitant medications by PT during the main period was COVID-19 vaccine (Eksunbi: 42 [16.9%] subjects; Stelara: 47 [18.5%] subjects), followed by paracetamol (Eksunbi: 11 [4.4%] subjects; Stelara: 15 [5.9%] subjects), ibuprofen (Eksunbi: 10 [4.0%] subjects; Stelara: 10 [3.9%] subjects), and azithromycin (Eksunbi: 6 [2.4%] subjects; Stelara: 7 [2.8%] subjects).

A similar proportion of subjects in the Eksunbi and Stelara Overall treatment groups (33 [13.9%] subjects and 35 [14.3%] subjects, respectively) had received any concomitant medication during the transition period. Paracetamol was the most commonly reported concomitant medication by PT during the transition period (Eksunbi: 4 [1.7%] subjects; Stelara Overall:4 [1.6%] subjects).

A similar proportion of subjects in the Eksunbi and Stelara Overall treatment groups (189 [75.9%] subjects and 187 [73.6%] subjects, respectively) had received any concomitant medication during the overall period. The most commonly reported concomitant medications by PT during the overall period was COVID-19 vaccine (Eksunbi: 42 [16.9%] subjects; Stelara Overall: 49 [19.3%] subjects), followed by paracetamol (Eksunbi: 13 [5.2%] subjects; Stelara Overall: 20 [7.9%] subjects), ibuprofen (Eksunbi: 11 [4.4%] subjects; Stelara Overall: 13 [5.1%] subjects), metformin hydrochloride (Eksunbi: 10 [4.0%] subjects; Stelara Overall: 12 [4.7%] subjects), other emollients and protectives (Eksunbi: 15 [6.0%] subjects; Stelara Overall: 6 [2.4%] subjects), drospirenone/ethinylestradiol (Eksunbi: 12 [4.8%] subjects; Stelara Overall: 9 [3.5%] subjects), and levothyroxine sodium (Eksunbi: 8 [3.2%] subjects; Stelara Overall: 13 [5.1%] subjects).

Prohibited Medication

Prohibited medications were reported for 3 (0.6%) subjects total during the main period. In the Eksunbi treatment group, 1 (0.4%) subject was reported with use of clobetasol; and in the Stelara treatment group, 1 (0.4%) subject was reported with use of clobetasol propionate.

No prohibited medications were reported during the transition period.

Prohibited medications were reported for 7 (1.4%) subjects total during the overall period (Eksunbi: 4 (1.6%) subjects; Stelara Overall: 3 (1.2%) subjects). In the Eksunbi treatment group, use of clobetasol products and methylprednisolone was reported for 1 (0.4%) subject each; in the Stelara Overall treatment group, use of carbamide products, clobetasol propionate, and methotrexate was reported for 1 (0.4%) subject each.

There were 3 cases of prohibited medication that were not included in either of the tables and listings in 2 subjects (2 cases of efalizumab; hydrocortisone); this was due to an error linking the PD and the corresponding concomitant medications. The PD itself was captured and reported in this CSR. These findings were properly reported by the applicant as prohibited medications in the final CSR.

Rescue medication was not provided to subjects in this study. If the subject could not continue the study without prohibited medications due to lack of efficacy or for other reasons, discontinuation of IP had to be considered.

Any other medications and treatments (except for prohibited concomitant medications or treatments) that were considered necessary for the subject's welfare, and that were not expected to interfere with the evaluation of the IP could be given at the Investigator's discretion.

Corticosteroid nasal spray, eye drops, ear drops, and inhalers were permitted.

Emollients, moisturisers, or shampoos that do not contain ingredients that are prohibited are allowed except within 24 hours before the time of PASI/PGA evaluation.

A list of medications prohibited during the study is presented and corticosteroids are described in more detail in Table 24 below.

Table 24. Prohibited Medications prior to Randomisation and throughout the Study

Medication	Time Prohibited prior to Randomisation
Phototherapy (including UVB, PUVA, or sunbaths/ tanning beds, etc.) or systemic therapy for psoriasis (including oral/injectable corticosteroids, MTX, calcineurin inhibitors, retinoids, vitamin D analogues, fumaric acid esters, apremilast, 6-thioguanine, hydroxyurea, etc.)[a]	4 weeks
Topical therapy for psoriasis (including corticosteroids, vitamin D analogues, retinoids, calcineurin inhibitors, coal tar, anthralin, urea, alpha-hydroxy acid, or salicylic acid, etc.)	2 weeks
DMARDs/systemic immunosuppressant (including those mentioned above in systemic psoriasis therapy, antimalarials, sulfasalazine, JAK inhibitors, gold, minocycline, azathioprine, 6-mercaptopurine, mycophenolate mofetil, etc.)	4 weeks
Leflunomide	12 weeks
TNF inhibitors	6 months
IL-12, IL-23, IL-17, integrin inhibitors, rituximab	At any time
Any other therapeutic monoclonal antibodies or fusion receptor protein	5 half-lives of that product or 3 months, whichever is longer
Non-biologic IP from another study	5 half-lives of that product
Live or live attenuated viral vaccine or a live bacterial vaccine	4 weeks (until 15 weeks after last IP)
BCG vaccination	12 months (until 12 months after last IP)

Phototherapy

Almost half of all subjects (242 [48.1%] subjects) had prior phototherapy; the frequency was comparable between treatment groups (Eksunbi: 114 [45.8%] subjects; Stelara Overall: 128 [50.4%] subjects), comparable across phototherapy categories such as UVB or PUVA. Prior phototherapy was comparable between the treatment groups in therapy type and frequency of events.

There was no case of phototherapy after enrolment in the study.

Treatment Compliance

Compliance was assessed by the subject's source documents and electronic case report form (eCRF).

All dosing information including the exact date and time of IP administration was recorded in the source document and eCRF.

The Investigator or designee maintained the documents of IP accountability and record the IP kit number administered to subjects. IP accountability and dispensing records were kept and contained the following information:

- The identification of the subjects to whom the drug was dispensed.
- The date(s) and quantity of the drug dispensed and exact package to the subject.
- The dispensing and inventory logs that must be available for review.

The used IP was destroyed at the investigational site according to local regulation after drug accountability was done. All unused IPs was returned to the Sponsor or designated vendor unless local destruction at site was approved by the Sponsor. If destruction was authorised at the investigational site, the Investigator had to ensure that the materials were destroyed in compliance with all applicable environmental regulations, institutional policies, and any instructions provided by the Sponsor. Destruction of the IP was adequately documented.

Numbers analysed

Table 25. Number of subjects analysed

Number of subjects	SB17 N=249 n (%)	Stelara Overall N=254 n (%)	Stelara+ SB17[a] N=122 n (%)	Stelara+ Stelara[a] N=122 n (%)	Total N=503 n (%)
Randomised Set	249 (100.0)	254 (100.0)	122 (100.0)	122 (100.0)	503(100.0)
Full Analysis Set	249 (100.0)	254 (100.0)	122 (100.0)	122 (100.0)	503(100.0)
Per-Protocol Set	243 (97.6)	249 (98.0)	119 (97.5)	122 (100.0)	492 (97.8)
Safety Set 1	249 (100.0)	254 (100.0)	122 (100.0)	122 (100.0)	503 (100.0)
Safety Set 2	237 (95.2)	244 (96.1)	122 (100.0)	122 (100.0)	481 (95.6)
Pharmacokinetic Analysis Set	71 (28.5)	71 (28.0)	34 (27.9)	34 (27.9)	142 (28.2)

N: Total number of subjects in the Randomised Set in each treatment group; n: Number of subjects with available data within each category
Percentages were based on the number of subjects in the Randomised Set.
a. Based on subjects who were re-randomised at Week 28, Stelara+SB17 and Stelara+Stelara may not add up to Stelara Overall.

Outcomes and estimation

Primary Efficacy Results

The primary efficacy analysis was performed for the PPS with percent change from baseline in PASI at Week 12 between the Eksunbi and Stelara treatment groups. The 95% CI of the LSMeans difference between the two treatment groups in relation to the percent change from baseline in PASI was estimated for PPS; the results are summarised in Table 26 below.

The percent change from baseline in PASI at Week 12 was equivalent between the Eksunbi and Stelara treatment groups in the PPS. The adjusted difference in LSMeans at Week 12 was −0.6 (SE: 1.62) and the 95% CI of the adjusted treatment difference was [−3.780 to 2.579] which was entirely contained within the pre-defined equivalence margin of [−15%, 15%].

Table 26. Equivalence Analysis of Percent Change from Baseline in PASI at Week 12 (Per-Protocol Set)

				Difference (SB17 - Stelara)	
Timepoint	**Treatment**	**n**	**LSM (SE)**	**LSM (SE)**	**95% CI**
Week 12	SB17 (N=243)	243	85.7 (2.53)	−0.6 (1.62)	[−3.780, 2.579]
	Stelara (N=249)	249	86.3 (2.41)		

CI: confidence interval; LSM: Least Squares Means; N: total number of subjects in the Per-Protocol Set in each treatment group; n: number of subjects with available data at Week 12; PASI: Psoriasis Area and Severity Index; SE: standard error
Inferential statistics for percent change from baseline in PASI at Week 12 were based on analysis of covariance model with the baseline value of PASI as a covariate and pooled centres (country) and treatment groups as factors.
Therapeutic equivalence is declared if the two-sided 95% CI of the difference of LSMeans of percent changes from baseline at Week 12 between SB17 and Stelara lies within the pre-defined equivalence margin of [−15%, 15%].
Source: Table 14.2-2.1.1

Equivalence, based on reported results is demonstrated for the primary efficacy endpoint of percent change from baseline in PASI at week 12 using the +/- 15% equivalence margins stipulated.

Supportive Analysis for Primary Efficacy Analysis

To support the primary efficacy analysis, the supportive analysis for the primary efficacy analysis was also performed for both available cases (subjects with non-missing primary endpoint) and multiple imputation (for missing values) under the FAS. The 95% CI of the LSMeans difference between the two treatment groups in relation to the percent change from baseline in PASI for the FAS are presented in Table 27 below (based on available case and using multiple imputation, respectively).

The percent change from baseline in PASI at Week 12 was equivalent between the Eksunbi and Stelara treatment groups based on available case under the FAS. The adjusted difference rate in LSMeans at Week 12 was −0.7 (SE: 1.60) and the 95% CI of the adjusted treatment difference was [−3.836 to 2.456] which was also entirely contained within the pre-defined equivalence margin of [−15%, 15%]. This finding was replicated in the FAS multiple imputation analysis, LSMeans −0.7 (SE: 1.60) and 95% CI [−3.849, 2.439].

Table 27. Equivalence Analysis of Percent Change from Baseline in PASI at Week 12 Based on available Case (Full Analysis Set)

				Difference (SB17 - Stelara)	
Timepoint	**Treatment**	**n**	**LSM (SE)**	**LSM (SE)**	**95% CI**
Week 12	SB17 (N=249)	246	85.7 (2.42)	−0.7 (1.60)	[−3.836, 2.456]
	Stelara (N=254)	252	86.3 (2.31)		

CI: confidence interval; LSM: Least Squares Means; N: total number of subjects in the Full Analysis Set in each treatment group; n: number of subjects with available data at Week 12; PASI: Psoriasis Area and Severity Index; SE: standard error
Inferential statistics for percent change from baseline in PASI at Week 12 were based on analysis of covariance model with the baseline value of PASI as a covariate and pooled centres (country) and treatment groups as factors.
Therapeutic equivalence is declared if the two-sided 95% Confidence Interval of the difference of LSMeans changes from baseline at Week 12 between SB17 and Stelara lies within the pre-defined equivalence margin of [−15%, 15%].

Sensitivity Analysis of Primary Efficacy Variable

The several sensitivity analyses of primary efficacy endpoint were performed with a narrower predefined equivalence margin of [−10%, 10%] but with a 90% CI instead of a 95% CI. The 90% CI of the LSMeans difference between the two treatment groups in relation to the percent change from baseline in PASI for the PPS at Week 12 is presented, and for the FAS are presented in Table 28 below (based on available case and using multiple imputation, respectively).

The LSMeans for the PPS is −0.6 (SE: 1.62, 90% CI [−3.267, 2.066]), the FAS available cases is −0.7 (SE: 1.60, 90% CI [−3.329, 1.948]), and FAS multiple imputation is −0.7 (SE: 1.60, 90% CI [−3.343,

1.933]), all within the pre-specified margin of [−10%, 10%].

Table 28. Sensitivity Analysis of Percent Change from Baseline in PASI at Week 12 using Multiple Imputation (Full Analysis Set)

				Difference (SB17 - Stelara)	
Timepoint	**Treatment**	**n**	**LSM (SE)**	**LSM (SE)**	**90% CI**
Week 12	SB17 (N=249)	249	85.7 (2.43)	−0.7 (1.60)	[−3.343, 1.933]
	Stelara (N=254)	254	86.4 (2.32)		

CI: Confidence interval; LSM: Least Squares Means; N: Total number of subjects in the Full Analysis Set in each treatment group; n: Number of subjects with available data at Week 12; PASI: Psoriasis Area and Severity Index; SE: Standard error
Inferential statistics for percent change from baseline in PASI at Week 12 were based on analysis of covariance model with the baseline value of PASI as a covariate and pooled centres (country) and treatment groups as factors.
Change from baseline in PASI scores have been imputed by multiple imputation method under the assumption of missing at random.

To assess the impact of the war in Ukraine, another sensitivity analysis was performed for the FAS using multiple imputation by excluding subjects that were affected by the war with pre-defined equivalence margin of [−15%, 15%]. The 95% CI of the LSMeans difference between the two treatment groups in relation to the percent change from baseline in PASI for FAS at Week 12 are presented in the table below. Since the War occurred after all Ukrainian subjects have completed the Week 12 visit, there was no impact on primary efficacy analysis.

Table 29. Sensitivity analysis of percent change from baseline in PASI at week 12 (FAS)

				Difference (SB17 - Stelara)	
Timepoint	Treatment	n	LSM (SE)	LSM (SE)	95% CI
Week 12	SB17 (N=249)	249	85.7 (2.43)	-0.7 (1.60)	[-3.849, 2.439]
	Stelara (N=254)	254	86.4 (2.32)		

Source: Listing 16.2.6-1.1
- PASI: Psoriasis Area and Severity Index; LSM: Least Squares Means; SE: Standard Error; CI: Confidence Interval.
- N: Total number of subjects in the Full Analysis Set in each treatment group.
- n: Number of subjects with available data at Week 12.
- Inferential statistics for percent change from baseline in PASI at Week 12 is based on analysis of covariance model with the baseline value of PASI as a covariate and pooled centres(country) and treatment groups as factors.
- Change from baseline in PASI scores have been imputed by Multiple Imputation (MI) method under the assumption of missing at random.
- Analysis was conducted excluding subjects who does not have assessment result at Week 12 due to the war in Ukraine.
- No subjects were excluded as there were no subjects with missing assessment result at Week 12 due to the war in Ukraine.

Subgroup Analysis of Primary Efficacy Variable

The subgroup analysis of the percent change from baseline in PASI at Week 12 by age groups, gender, overall, ADA up to Week 52, prior biologic use and history of psoriatic arthritis is summarised in Table 30 below. Generally, within each subgroup the percent change from baseline in PASI was similar between treatment groups.

Table 30. Subgroup Analysis of Percent Change from Baseline in PASI at Week 12 (Per-Protocol Set)

Subgroup	Treatment	n	LSM (SE)	Difference (SB17 - Stelara) LSM (SE)	95% CI
Age					
< 65 years	SB17 (N=229)	229	85.3 (3.02)	0.04 (1.67)	[−3.234, 3.313]
	Stelara (N=230)	230	85.3 (2.94)		
≥ 65 years	SB17 (N=14)	14	82.0 (7.39)	−7.4 (6.51)	[−20.837, 6.017]
	Stelara (N=19)	19	89.5 (5.55)		
Gender					
Male	SB17 (N=146)	146	81.8 (2.99)	−2.4 (1.99)	[−6.369, 1.472]
	Stelara (N=160)	160	84.3 (2.84)		
Female	SB17 (N=97)	97	89.1 (3.44)	3.0 (2.80)	[−2.536, 8.500]
	Stelara (N=89)	89	86.1 (3.30)		
Overall ADA (up to 52 weeks)[a]					
Positive	SB17 (N=36)	36	85.1 (4.15)	2.2 (3.32)	[−4.329, 8.808]
	Stelara (N=102)	102	82.9 (3.28)		
Negative	SB17 (N=202)	202	86.4 (3.56)	−2.2 (2.01)	[−6.148, 1.747]
	Stelara (N=146)	146	88.6 (3.56)		
Prior Biologic Use					
Yes	SB17 (N=16)	16	87.0 (4.02)	−2.4 (4.44)	[−11.545, 6.661]
	Stelara (N=19)	19	89.5 (4.15)		
No	SB17 (N=227)	227	85.8 (2.61)	−0.3 (1.71)	[−3.639, 3.069]
	Stelara (N=230)	230	86.1 (2.48)		
History of Psoriatic arthritis					
Yes	SB17 (N=61)	61	83.5 (3.53)	−0.4 (2.91)	[−6.129, 5.411]
	Stelara (N=54)	54	83.8 (3.76)		
No	SB17 (N=182)	182	86.0 (2.83)	−0.5 (1.93)	[−4.295, 3.314]
	Stelara (N=195)	195	86.5 (2.63)		

CI: Confidence interval; LSM: Least Squares Means; N: Total number of subjects in the Per-Protocol Set in each treatment group and subgroup; n: Number of subjects with available data at Week 12; PASI: Psoriasis Area and Severity Index; SE: Standard error.
Inferential statistics for percent change from baseline in PASI at Week 12 were based on analysis of covariance model with the baseline value of PASI as a covariate and pooled centres (countries) and treatment groups as factors.
a. Subjects with inconclusive ADA status (SB17: 5 subjects, Stelara: 1 subject) are not included in this table.

Subgroup analyses (pre-specified in the SAP) are not powered and not controlled for any inflation of type I error. However, most 95% CI contain zero suggesting no statistical difference between Eksunbi and Stelara for these subgroups.

Secondary Efficacy Results

Secondary efficacy endpoints include percent change from baseline of PASI score other than Week 12, PASI50, PASI75, PASI90, and PASI100 response rate, PGA scores, and DLQI scores.

Percent Change from Baseline in PASI other than Week 12

The summary of PASI score by visit and treatment for the FAS is presented below.

The mean PASI score was similar at baseline with 22.5 and 22.1 in the Eksunbi and Stelara Overall treatment groups, respectively.

At Week 2, the mean PASI scores of two treatment groups were similar (Eksunbi: 17.8; Stelara Overall: 17.2).

By Week 4, the mean PASI score had dropped to approximately half the baseline mean values, indicating an improvement in the subjects' condition.

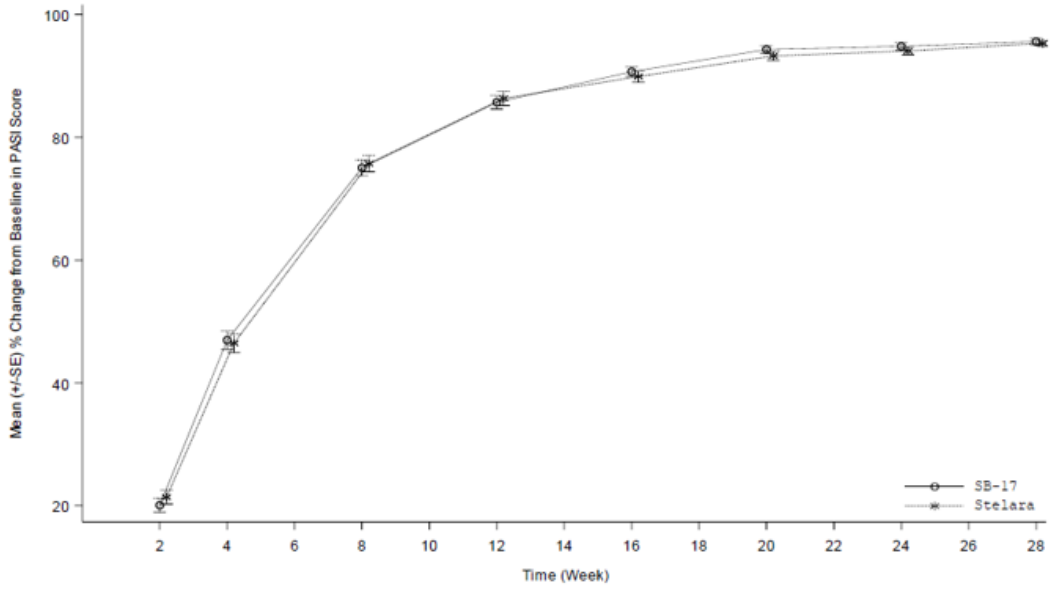
At Week 40, the mean PASI scores of the Eksunbi and Stelara Overall treatment groups fell to 0.8 and 0.9, respectively; at this timepoint the percent change from baseline of two treatment groups was 96.3% and 95.9%, respectively.

At Week 52, 233 (100%) patients in the Eksunbi treatment group and 243 (99.6%) patients in the Stelara Overall treatment group achieved a PASI50 response; 221 (94.8%) and 223 (94.9%) patients achieved a PASI75 response in the Eksunbi and Stelara Overall treatment groups, respectively; 201 (86.3%) and 198 (84.3%) patients achieved a PASI90 response in the Eksunbi and Stelara Overall treatment groups, respectively; 121 (51.9%) and 120 (51.1%) patients achieved a PASI100 response in the Eksunbi and Stelara Overall treatment groups, respectively. Thus, efficacy was similar between the treatment groups, which maintained up to Week 52.

The individual PASI score profiles for each subject are listed in the submission.

The percent change from baseline up to Week 28 in PASI score for the FAS and the PPS is presented below. The time response curve is similar between the treatment groups supporting the robustness of the primary efficacy analysis.

Figure 6. Percent Change from Baseline in PASI up to Week 28 (Full Analysis Set)



PASI: Psoriasis Area and Severity Index; SE: Standard error
% change from baseline in PASI score at Week X = [(PASI score at baseline – PASI score at Week X)/PASI score at baseline] × 100.
The symbol and error bar represent the mean and standard error at each timepoint.

PASI Response Rate

The summary of PASI response rate by visit and treatment group for the FAS is presented below.

At Week 12, 234 (95.1%) subjects in the Eksunbi treatment group and 243 (96.4%) subjects in the Stelara treatment group achieved a PASI50 response; 201 (81.7%) and 204 (81.0%) subjects achieved a PASI75 response in the Eksunbi and Stelara treatment groups, respectively; 132 (53.7%) and 145 (57.5%) subjects achieved a PASI90 response in the Eksunbi and Stelara treatment groups, respectively; and 49 (19.9%) and 57 (22.6%) subjects achieved a PASI100 response in the Eksunbi and Stelara treatment groups, respectively.

Table 31. Summary of Psoriasis Area Severity Index Response Rate by Visit and Treatment Group (Full Analysis Set, Study SB17-3001)

Responder Category	SB17 N = 249		Stelara Overall N = 254		Stelara+SB17[a] N = 122		Stelara+Stelara[a] N = 122	
Timepoint	n/n'	%	n/n'	%	n/n'	%	n/n'	%
PASI50								
Week 2	17/249	6.8	24/254	9.4				
Week 4	116/249	46.6	116/254	45.7				
Week 8	214/248	86.3	225/253	88.9				
Week 12	234/246	95.1	243/252	96.4				
Week 16	240/244	98.4	242/249	97.2				
Week 20	229/231	99.1	239/242	98.8				
Week 24	232/235	98.7	242/244	99.2				
Week 28	237/238	99.6	245/245	100.0	122/122	100.0	122/122	100.0
Week 40	235/235	100.0	240/240	100.0	120/120	100.0	120/120	100.0
Week 52	233/233	100.0	234/235	99.6	117/117	100.0	117/118	99.2
PASI75								
Week 2	2/249	0.8	1/254	0.4				
Week 4	30/249	12.0	34/254	13.4				
Week 8	137/248	55.2	149/253	58.9				
Week 12	201/246	81.7	204/252	81.0				
Week 16	219/244	89.8	221/249	88.8				
Week 20	221/231	95.7	228/242	94.2				
Week 24	229/235	97.4	232/244	95.1				
Week 28	234/238	98.3	240/245	98.0	120/122	98.4	119/122	97.5
Week 40	231/235	98.3	233/240	97.1	116/120	96.7	117/120	97.5
Week 52	221/233	94.8	223/235	94.9	111/117	94.9	112/118	94.9
PASI90								
Week 2	0/249	0.0	0/254	0.0				
Week 4	11/249	4.4	5/254	2.0				
Week 8	67/248	27.0	78/253	30.8				
Week 12	132/246	53.7	145/252	57.5				
Week 16	160/244	65.6	166/249	66.7				
Week 20	181/231	78.4	189/242	78.1				
Week 24	192/235	81.7	190/244	77.9				
Week 28	202/238	84.9	204/245	83.3	104/122	85.2	99/122	81.1
Week 40	204/235	86.8	205/240	85.4	105/120	87.5	100/120	83.3
Week 52	201/233	86.3	198/235	84.3	101/117	86.3	97/118	82.2
PASI100								

Responder Category	SB17 N = 249		Stelara Overall N = 254		Stelara+SB17[a] N = 122		Stelara+Stelara[a] N = 122	
Timepoint	n/n′	%	n/n′	%	n/n′	%	n/n′	%
Week 2	0/249	0.0	0/254	0.0				
Week 4	2/249	0.8	2/254	0.8				
Week 8	28/248	11.3	30/253	11.9				
Week 12	49/246	19.9	57/252	22.6				
Week 16	70/244	28.7	67/249	26.9				
Week 20	100/231	43.3	107/242	44.2				
Week 24	104/235	44.3	114/244	46.7				
Week 28	109/238	45.8	110/245	44.9	58/122	47.5	52/122	42.6
Week 40	117/235	49.8	129/240	53.8	65/120	54.2	64/120	53.3
Week 52	121/233	51.9	120/235	51.1	67/117	57.3	53/118	44.9

N = total number of patients in the Full Analysis Set in each treatment group; n = total number of patients with each PASI response at each assessment visit; n′ = number of patients with available data at each assessment visit.
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.
Percentages were based on n′.
[a] Based on patients in the Full Analysis Set who were re-randomised at Week 28, Stelara+SB17 and Stelara+Stelara may not add up to Stelara Overall.

Physician's Global Assessment

The summary of PGA score by visit and treatment group for the PPS is presented in Table 32 below.

At baseline, the majority of subjects had a 'moderate' PGA score 157 (63.1%) subjects and 160 (63.0%) subjects in the Eksunbi and Stelara treatment groups, respectively.

Sixty-eight (27.3%) subjects and 75 (29.5%) subjects had 'marked' classification, and 24 (9.6%) and 19 (7.5%) subjects had a 'severe' PGA classification in the Eksunbi and Stelara treatment groups, respectively. Neither treatment group had any subjects classified as 'mild', 'minimal', or 'cleared' at baseline, due to eligibility criteria.

The proportion of subjects with a PGA response of 'cleared' or 'minimal' (i.e., PGA 0 or 1) by visit and treatment group for PPS and FAS is summarised below.

The proportion of subjects with PGA responses 'cleared' or 'minimal' were similar between the Eksunbi and Stelara Overall treatment groups up until Week 52.

At Week 12, 209 (85.0%) patients for the Eksunbi and 220 (87.3%) patients for the Stelara treatment group had a PGA response of 'cleared' or 'minimal'; at Week 28, 223 (93.7%) patients for the Eksunbi and 226 (92.2%) patients for the Stelara Overall treatment groups, respectively; at Week 52, 210 (90.1%) patients for the Eksunbi and 205 (87.2%) patients for the Stelara Overall treatment groups, respectively.

Table 32. Proportion of Patients with a Physician's Global Assessment Response of Cleared or Minimal by Visit and Treatment Group (Full Analysis Set, Study SB17-3001)

	SB17 N = 249		Stelara Overall N = 254		Stelara+SB17[a] N = 122		Stelara+Stelara[a] N = 122	
Timepoint	**n/n′**	**%**	**n/n′**	**%**	**n/n′**	**%**	**n/n′**	**%**
Baseline	0/249	0.0	0/254	0.0	0/122	0.0	0/122	0.0
Week 2	5/249	2.0	4/254	1.6				
Week 4	47/249	18.9	48/254	18.9				
Week 8	167/248	67.3	173/253	68.4				
Week 12	209/246	85.0	220/252	87.3				
Week 16	214/244	87.7	216/249	86.7				
Week 20	213/231	92.2	226/242	93.4				
Week 24	218/235	92.8	226/244	92.6				
Week 28	223/238	93.7	226/245	92.2	113/122	92.6	112/122	91.8
Week 40	216/235	91.9	224/240	93.3	112/120	93.3	112/120	93.3
Week 52	210/233	90.1	205/235	87.2	102/117	87.2	103/118	87.3

N = total number of patients in the Full Analysis Set in each treatment group; n = total number of patients with each PGA response at each assessment visit; n′ = number of patients with available data at each assessment visit; PGA = Physician's Global Assessment

Percentages were based on n′.

[a] Based on patients in the Full Analysis Set who were re-randomized at Week 28, Stelara+SB17 and Stelara+Stelara may not add up to Stelara Overall.

PGA response: 0 = Cleared, 1 = Minimal

Change from Baseline in Dermatology Life Quality Index (DLQI)

The DLQI is a dermatology-specific quality of life instrument designed to measure the health-related quality of life of adult patients suffering from a skin disease [Finlay AY and Khan GK, 1994]. The DLQI consists of 10 questions concerning patients' perception of the impact of skin diseases on different aspects of their health-related quality of life over the last week. The DLQI assessment was performed by the Investigator at the timepoints as described.

A summary of DLQI score by visit and treatment group is presented. The mean DLQI score was similar at baseline at 13.4 and 13.2 in both treatment groups, respectively.

The general DLQI response across time was similar between the two treatment groups; the mean DLQI score at Week 52 had reduced to 1.9 in both the Eksunbi and Stelara Overall treatment groups (Stelara+Eksunbi: 1.8; Stelara+Stelara: 2.0, all for the FAS). A summary of DLQI score by visit and treatment group is presented in Table 33 below.

The DLQI score by visit and treatment group for each subject is provided in the listings.

Table 33. Summary of DLQI by Visit and Treatment Group (Full analysis Set)

	SB17 N = 249		Stelara Overall N = 254		Stelara+SB17[a] N = 122		Stelara+Stelara[a] N = 122	
Timepoint	Mean Value (SD)	CFB Mean (SD)	Mean Value (SD)	CFB Mean (SD)	Mean Value (SD)	CFB Mean (SD)	Mean Value (SD)	CFB Mean (SD)
Baseline	13.4 (7.24)		13.2 (6.96)		12.9 (7.07)		13.5 (6.97)	
Week 4	7.6 (5.62)	5.9 (5.79)	7.8 (6.01)	5.4 (5.18)				
Week 12	3.5 (4.12)	9.9 (6.79)	3.4 (4.11)	9.7 (6.55)				
Week 16	3.1 (4.19)	10.3 (7.40)	3.4 (4.39)	9.8 (6.90)				
Week 28	2.5 (3.54)	11.0 (7.48)	2.5 (3.73)	10.7 (6.91)	2.4 (3.53)	10.5 (6.63)	2.4 (3.85)	11.1 (7.21)
Week 40	1.9 (3.35)	11.5 (7.48)	1.8 (3.10)	11.3 (6.86)	1.9 (3.10)	10.8 (6.61)	1.8 (3.11)	11.7 (7.11)
Week 52	1.9 (3.35)	11.5 (7.31)	1.9 (3.29)	11.2 (7.06)	1.8 (3.64)	10.9 (6.81)	2.0 (2.91)	11.5 (7.32)

CFB = change from baseline; DLQI = Dermatology Life Quality Index; N = total number of patients in the Full Analysis Set in each treatment group; SD = standard deviation

[a] Based on patients in the Full Analysis Set who were re-randomized at Week 28, Stelara+SB17 and Stelara+Stelara may not add up to Stelara Overall.

Change from Baseline for DLQI score at Week X = DLQI score at baseline – DLQI score at Week X. The numbers actually mean decrease from baseline, although described in positive numbers.

Impact of war in Ukraine on the Secondary Endpoints

During the war, all of the patients completed the Week 16 visit, except for 6 subjects who could not visit the site due to the war. Thus, it is believed that up to Week 16 the impact of the war would be considered as relatively minimal. Thereafter, gradually study conduct disruption occurred, resulting in increased study discontinuations or missed/delayed visits. The discontinuation or visit miss/delay pattern was balanced between the treatment groups, so it is expected that the impact on other secondary efficacy endpoints was evenly distributed on each treatment group, lessening the possibility of bias impacting the results of the study.

Ancillary analyses

As outlined above, a sensitivity analysis was conducted using multiple imputation by excluding any subject that was impacted due to Ukraine war at Week 12 to assess the impact of war on Primary analysis.

It is highlighted that the Final CSR of Study SB17-3001 with complete data of 52 weeks of study was provided with an update on the impact of the war in Ukraine provided as part of the responses also.

The discontinuation or visit miss/delay pattern remained generally comparable between the two treatment groups in the Final CSR.

A total of 13 (2.6%) patients (8 [3.2%] patients in the Eksunbi, 5 [2.0%] patients in the Stelara treatment groups) in the main period and 8 (1.7%) patients (3 [1.3%] patients in the Eksunbi+Eksunbi, 5 [2.0%] patients in the Stelara Overall, 1 [0.8%] patient in the Stelara+Eksunbi, 4 [3.3%] patients in the Stelara+Stelara treatment groups) in the transition period discontinued from the study due to the war in Ukraine.

The incidence of protocol deviations (PDs) related to the war for the Randomised Set (RAN) also remained comparable between the Eksunbi and Stelara treatment groups (Eksunbi: 47 [18.9%] patients, Stelara: 45 [17.7%] patients), as well as by category, including out-of-window administration of investigational product (IP) (Eksunbi: 25 [10.0%] patients, Stelara: 22 [8.7%] patients), skip of IP administration (Eksunbi: 11 [4.4%] patients, Stelara: 12 [4.7%] patients), and out of visit window for non-dosing visit (Eksunbi: 17 [6.8%] patients, Stelara: 11 [4.3%] patients), in the Final CSR. Among patients who skipped IP administration, all randomised patients (4 patients) from Site 1207 skipped Week 28 IP due to delay of IP delivery due to the war and were re-randomised afterwards.

Immunogenicity

Product-Related Risk Factors of Eksunbi

Regarding immunogenicity, several product quality attributes (e.g. aggregates, fragments) are particularly important, although the exact mechanisms of these quality attributes of immune response induction are not known. Due to the different use of host cell lines manufacturing Eksunbi or Stelara, some quality attributes of Eksunbi are different from those of Stelara (e.g. N-glyconeuraminic acid [NGNA] forms, galactose-α-1,3-galactose [α-gal]), which are closely associated with adverse immune reaction. Other than these, a minor difference was observed in some quality attributes [45 mg PFS, 90 mg PFS] and [130 mg vial]) discussed in the Quality part of the AR further.

The purpose of immunogenicity testing in the Eksunbi clinical studies (SB17-1001 and SB17-3001) was to determine whether ADAs and NAbs against Eksunbi or Stelara occurred in similar rates and have similar impact on the safety or efficacy between two products. For this purpose, a fully validated sensitive immunogenicity assay (ADA or NAb assay) was developed to fit its intended use.

Following the guidelines, a three-tiered approach for ADA assay (a bridging-ligand binding assay [Eksunbi]: Electrochemiluminescence (ECL)-based immunoassay with Meso Scale Discovery [MSD] platform) was applied for Study SB17-1001 and Study SB17-3001.

The comparative ADA incidences in response to administration of Eksunbi or Stelara in the clinical Phase I study in healthy subjects as well as in the clinical Phase III study in plaque PsO patients were evaluated by means of ADA detection in human serum samples using a validated bridging ligand-binding assay with ECL platform with MSD. ADAs against ustekinumab in human serum are detected and confirmed using a multi-tiered approach in an ECL assay.

Study SB17-3001

In Study SB17-3001, sampling schedules were designed to distinguish patients being transiently positive from patients developing a persistent antibody response. Given the ADA development, drug tolerance and ustekinumab's median half-life (approximately 3 weeks) in patients with PsO, blood samples for immunogenicity assessment were collected prior to IP administration and at the day of IP administration (Week 0, 4, 16, 28, and 40). To assess the impact of immunogenicity on safety, PK, and efficacy, immunogenicity sampling was performed before administration of the drug during the treatment period and incorporated into the PK schedule concomitantly. In addition, blood samples for immunogenicity assessment at Week 8, 12, and 52/early termination (ET) visit was also collected at any time during the period when the patient was staying at investigational sites.

Immunogenicity results

Up to Week 52, a total of 146 (29.0%) patients (41 [16.5%] patients in the Eksunbi, 105 [41.3%] patients in the Stelara, 48 [39.3%] patients in the Stelara+Eksunbi, and 53 [43.4%] patients in the Stelara+Stelara treatment groups) had overall ADA positive results in the overall period. The incidence of ADA and NAb tended to be lower in Eksunbi than Stelara by visit and overall status. The titre distribution for ADA tended to be more comparable between treatment groups. The incidence of ADA occurring after transition was comparable between treatment groups (ADA from Week 28 to 52; 5.6% for Eksunbi+Eksunbi, 5.1% for Stelara+Eksunbi and 6.7% for Stelara+Stelara).

Table 34. Incidence of overall Anti-Drug Antibody by Visit and Treatment Group (Safety Set 1)

Table 14.3-4.3
Incidence of Overall Anti-Drug Antibody (ADA) by Visit and Treatment Group
Safety Set 1

Timepoint	Assessment	SB17 N=249 n/n' (%)	Stelara Overall N=254 n/n' (%)	Stelara+SB17* N=122 n/n' (%)	Stelara+Stelara* N=122 n/n' (%)	Total N=503 n/n' (%)
Week 12 Overall	Positive	19/249 (7.6)	80/254 (31.5)	38/122 (31.1)	38/122 (31.1)	99/503 (19.7)
	Negative	222/249 (89.2)	173/254 (68.1)	83/122 (68.0)	84/122 (68.9)	395/503 (78.5)
	Inconclusive	8/249 (3.2)	1/254 (0.4)	1/122 (0.8)	0/122 (0.0)	9/503 (1.8)
Week 28 Overall	Positive	33/249 (13.3)	100/254 (39.4)	46/122 (37.7)	50/122 (41.0)	133/503 (26.4)
	Negative	210/249 (84.3)	153/254 (60.2)	75/122 (61.5)	72/122 (59.0)	363/503 (72.2)
	Inconclusive	6/249 (2.4)	1/254 (0.4)	1/122 (0.8)	0/122 (0.0)	7/503 (1.4)
Week 52 Overall	Positive	41/249 (16.5)	105/254 (41.3)	48/122 (39.3)	53/122 (43.4)	146/503 (29.0)
	Negative	203/249 (81.5)	148/254 (58.3)	73/122 (59.8)	69/122 (56.6)	351/503 (69.8)
	Inconclusive	5/249 (2.0)	1/254 (0.4)	1/122 (0.8)	0/122 (0.0)	6/503 (1.2)

Source: Listing 16.2.9.1.8
- N: Total number of subjects in the Safety Set 1 in each treatment group.
- n: Number of subjects with available data within each category.
- n': number of subjects with available assessment results at each visit; Percentages were based on n'.
- *: Based on subjects in the Safety Set 2, Stelara+SB17 and Stelara+Stelara may not add up to Stelara Overall.

Up to Week 52, a total of 351 (69.8%) patients (203 [81.5%] patients in the Eksunbi, 148 [58.3%] patients in the Stelara, 73 [59.8%] patients in the Stelara+Eksunbi, and 69 [56.6%] patients in the Stelara+Stelara treatment groups) had overall ADA negative results in the overall period. The incidence of ADAs tended to be lower in the Eksunbi than the Stelara treatment group by visit and overall status.

Efficacy

The subgroup analysis of the percent change from baseline in PASI at Week 12 (primary efficacy endpoint) by overall ADA up to Week 52 (Table 35 below). In general, within each subgroup, the percent change from baseline in PASI at Week 12 was similar between the two treatment groups.

Table 35. Subgroup Analysis of Percent Change from Baseline in Psoriasis Area and Severity Index at Week 12 by Overall ADA Status (Per-protocol Set, Study SB17-3001)

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; n′ = number of patients with available data at each assessment visit; NE = not estimable; PASI = Psoriasis Area and Severity Index; SE = standard error
Overall ADA 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 indicates at least one positive result with higher titre level compared to baseline after first IP administration at Week 0 for patients with positive ADA at baseline.
Overall ADA 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 up to Week 52 was defined inconclusive for a patient with positive ADA at baseline and without positive result with higher titre level observed post-baseline by Week 52.
Inferential statistics for percent change from baseline in PASI at Week 12 is based on analysis of covariance model with the baseline value of PASI as a covariate and country and treatment groups as factors.

In addition, other than the primary efficacy endpoint of the percent change from baseline in PASI score at Week 12, the ad-hoc analysis of percent change from baseline in PASI score by overall ADA status up to Week 52 was performed to assess the impact of ADA on efficacy between the Eksunbi and Stelara treatment groups. As shown below, within each subgroup per overall ADA positive or negative results, the PASI score up to Week 52 are comparable between the Eksunbi and Stelara treatment groups. Therefore, the ADA impact on efficacy between the Eksunbi and Stelara treatment groups appears to be comparable.

Table 36. Summary of PASI Score by Overall Anti-drug Antibody Positive Results up to Week 52, Visit and Treatment Group (Full Analysis Set, Study SB17-3001) (Ad-hoc Analysis)

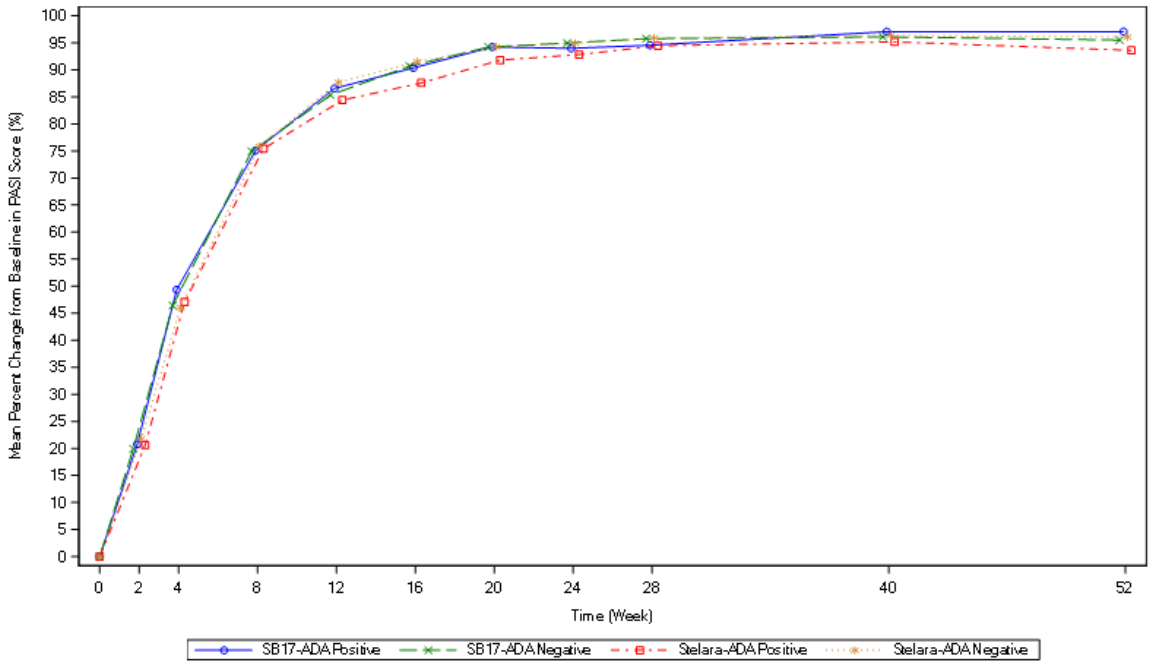
		SB17	**Stelara Overall**	**Stelara+ SB17[a]**	**Stelara+ Stelara[a]**	**Total**
		N = 41	**N = 105**	**N = 48**	**N = 53**	**N = 146**
Timepoint	**Statistics**	**%CFB**	**%CFB**	**%CFB**	**%CFB**	**%CFB**
Week 2	n	41	105			146
	Mean	20.76	20.58			20.63
	SD	17.034	17.476			17.295
	Median	19.1	17.96			18.33
	Min	−8.2	−0.3			−8.2
	Max	77.3	80.3			80.3
Week 4	n	41	105			146
	Mean	49.35	47.07			47.71
	SD	24.286	23.5			23.662
	Median	48.86	46.03			47.18
	Min	0.0	0.0			0.0
	Max	98.2	100.0			100.0
Week 8	n	41	105			146
	Mean	75.09	75.43			75.33
	SD	20.784	19.637			19.894
	Median	79.07	79.37			79.22
	Min	27.8	13.2			13.2
	Max	100.0	100.0			100.0
Week 12	n	41	105			146
	Mean	86.58	84.42			85.02
	SD	12.554	18.284			16.858
	Median	89.53	90			89.9
	Min	58.7	-12.2			-12.2
	Max	100.0	100.0			100.0
Week 16	n	41	103			144
	Mean	90.37	87.58			88.37

Timepoint	Statistics	SB17 N = 41 %CFB	Stelara Overall N = 105 %CFB	Stelara+ SB17[a] N = 48 %CFB	Stelara+ Stelara[a] N = 53 %CFB	Total N = 146 %CFB
	SD	11.029	14.756			13.818
	Median	93.94	92.78			93.49
	Min	58.7	27.5			27.5
	Max	100.0	100.0			100.0
Week 20	n	38	99			137
	Mean	94.24	91.81			92.48
	SD	9.457	11.017			10.629
	Median	98.26	96.3			96.97
	Min	52.1	48.9			48.9
	Max	100.0	100.0			100.0
Week 24	n	40	100			140
	Mean	93.99	92.83			93.16
	SD	12.193	9.793			10.502
	Median	98.07	97.3			97.59
	Min	26.9	41.1			26.9
	Max	100.0	100.0			100.0
Week 28	n	41	101	48	53	142
	Mean	94.56	94.46	94.23	94.68	94.49
	SD	12.662	7.269	7.854	6.766	9.108
	Median	98.63	97.35	97.48	97.18	97.63
	Min	21.6	62.1	62.1	70.2	21.6
	Max	100.0	100.0	100.0	100.0	100.0
Week 40	n	39	100	47	53	139
	Mean	97.07	95.18	94.75	95.56	95.71
	SD	4.955	7.596	8.864	6.326	6.991
	Median	100	98.23	98.2	98.94	99.28
	Min	77.7	55.5	55.5	70.2	55.5
	Max	100.0	100.0	100.0	100.0	100.0
Week 52	n	38	99	46	53	137
	Mean	97.08	93.6	93.55	93.65	94.57
	SD	5.279	10.255	9.618	10.869	9.263
	Median	100	97.93	97.84	97.93	98.7
	Min	74.1	47.4	61.3	47.4	47.4
	Max	100.0	100.0	100.0	100.0	100.0

% CFB = percent change from baseline; Min = minimum; Max = maximum; N = total number of patients in the Full Analysis Set in each treatment group; n = number of patients with available data within each category;
SD = Standard Deviation

Percent change from baseline of PASI score (%) at Week X = [(PASI score at baseline - PASI score at Week X)/ PASI score at baseline]×100.
[a] Based on patients in the Full Analysis Set who were re-randomised at Week 28, Stelara+SB17 and Stelara+Stelara may not add up to Stelara Overall.

Figure 7. Percent Change from Baseline in Psoriasis Area and Severity Index by Overall ADA Status up to Week 52 (Full Analysis Set, Study SB17-3001) (Ad-hoc Analysis)



Furthermore, in order to support biosimilarity in presence of lower immunogenicity of Eksunbi, the applicant provided an updated analyses of the effect of Eksunbi versus Stelara on % change in PASI in which the focus was on ADA negative and nAB negative patients.

Considering lower immunogenicity (i.e., lower incidence of anti-drug antibodies [ADA]) of Eksunbi, the subgroup analyses of the efficacy endpoints were performed by overall ADA status (both overall ADA-positive and negative) up to Week 52. The percent change from baseline in PASI at Week 12 was equivalent between the Eksunbi and Stelara treatment groups for the overall ADA negative subgroup in the PPS. The adjusted difference in least square means (LSMeans) at Week 12 was −2.2 and the 95% CI of the adjusted treatment difference was [−6.194, 1.805], which was entirely contained within the pre-defined equivalence margin of [−15%, 15%]. In addition, the PASI score up to Week 52 are comparable between the Eksunbi and Stelara treatment groups in the overall ADA negative subgroup. The results analysed in patients who did not mount an ADA response complement the primary efficacy analysis.

The subgroup analysis was performed for the percent change from baseline in PASI (primary efficacy endpoint; Table 37) and percent change from baseline in PASI up to Week 52 by overall neutralizing antibody (NAb) negative status up to Week 52 (Table 40). As the definition of overall NAb was not pre-defined in the study protocol, definition of overall NAb status was established for subgroup analysis. The overall NAb is defined as positive if there is at least one positive NAb measurement at any time during the period (including baseline). If there is no positive NAb measurement during the period, then the overall NAb status is defined as negative. The incidence of overall NAb by visit and treatment group for the Safety Set 1 (SAF1) is provided in Table 39. The incidence of overall NAb was lower in

the Eksunbi compared to the Stelara treatment groups (Stelara Overall, Stelara+Eksunbi, and Stelara+Stelara) treatment groups at all timepoints, with a similar degree to the incidence of overall ADA.

Table 37. Incidence of Overall Neutralizing Antibody by Visit and Treatment Group (Study SB17-3001, Safety Set 1) (Ad-hoc Analyses)

Timepoint	Result	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' (%)	Total N=503 n/n' (%)
Week 12 Overall	Positive	20/249 (8.0)	76/254 (29.9)	37/122 (30.3)	35/122 (28.7)	96/503 (19.1)
	Negative	229/249 (92.0)	178/254 (70.1)	85/122 (69.7)	87/122 (71.3)	407/503 (80.9)
Week 28 Overall	Positive	34/249 (13.7)	90/254 (35.4)	41/122 (33.6)	45/122 (36.9)	124/503 (24.7)
	Negative	215/249 (86.3)	164/254 (64.6)	81/122 (66.4)	77/122 (63.1)	379/503 (75.3)
Week 52 Overall	Positive	36/249 (14.5)	94/254 (37.0)	42/122 (34.4)	48/122 (39.3)	130/503 (25.8)
	Negative	213/249 (85.5)	160/254 (63.0)	80/122 (65.6)	74/122 (60.7)	373/503 (74.2)

N = total number of patients in the Safety Set 1 in each treatment group; n = number of patients with available data within 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.
Percentages were based on n'.
Overall NAb is positive if there is at least one positive NAb measurement at any time during the period (including baseline).
If there is no positive NAb measurement during the period, then the overall NAb status is negative.
In case of samples with determined as 'Inconclusive', these samples were also tested with NAb assay since these samples were determined as ADA positive (but neither treatment induced or boosted ADAs). If these 'Inconclusive' ADA samples from patients were determined as NAb positive by NAb assay, it would be included as NAb positive and thereby counted for overall NAb positive.

As seen in Table 38, the percent change from baseline in PASI at Week 12 was equivalent between the Eksunbi and Stelara treatment groups for the overall NAb negative subgroup in the Per-protocol Set. The adjusted difference in LSMeans at Week 12 was −2.3 and the 95% CI of the adjusted treatment difference was [−6.121, 1.424], which was entirely contained within the pre-defined equivalence margin of [−15%, 15%].

Table 38. Equivalence Analysis of Percent Change from Baseline in Psoriasis Area and Severity Index at Week 12 for Patients with Overall Neutralizing Antibody Negative Results up to Week 52 (Per-Protocol Set, Study SB17-3001) (Ad-hoc Analysis)

Timepoint	Treatment	N	n	LSMean (SE)	Difference (SB17 – EU Stelara)	
					Estimate	95% CI
Week 12	SB17	209	209	86.2 (3.49)	–2.3	[–6.121, 1.424]
	EU Stelara	156	156	88.6 (3.48)		

CI = confidence interval; LSM = least squares mean; N = total number of patients in the Per-Protocol Set in each treatment group and subgroup; n = number of patients with available data at Week 12; NAb = neutralizing antibody; SE = standard error
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 pooled centers (country) and treatment groups as factors.
Therapeutic equivalence is declared if the two-sided 95% Confidence Interval of the difference of Least Squares means (LS means) changes from baseline at Week 12 between SB17 and Stelara lies within the pre-defined equivalence margin of [−15%, 15%].
NAb positive and NAb negative is the overall NAb status up to Week 52.
Overall NAb is positive if there is at least one positive NAb measurement at any time during the period (including baseline). If there is no positive NAb measurement during the period, then the overall NAb status is negative.

In the overall NAb negative subgroup, the percent change from baseline in PASI (Table 39) is similar up to Week 52 across the treatment groups (Eksunbi, Stelara, Eksunbi+Eksunbi, Stelara+Eksunbi, Stelara+Stelara treatment groups), complementing the primary efficacy analysis.

Table 39. Summary of Percent Change from Baseline in Psoriasis Area and Severity Index for Patients with Overall Neutralizing Antibody Negative Results up to Week 52 (Per-Protocol Set, Study SB17-3001) (Ad-hoc Analysis)

Timepoint	Statistics	SB17 N=209 n/n' (%) %CFB	Stelara Overall N=254 n/n' (%) %CFB	Stelara +SB17[a] N=122 n/n' (%) %CFB	Stelara +Stelara[a] N=122 n/n' (%) %CFB	Total N=503 n/n' (%) %CFB
Week 2	n	209	156			365
	Mean	19.53	21.39			20.32
	SD	17.590	18.571			18.014
	Median	16.92	19.07			18.18
	Min	−23.7	−25.6			−25.6
	Max	72.2	70.9			72.2
Week 4	n	209	156			365
	Mean	46.66	45.98			46.37
	SD	23.642	24.424			23.948
	Median	48.58	46.28			47.71
	Min	−2.0	−25.6			−25.6
	Max	100.0	100.0			100.0
Week 8	n	209	155			364
	Mean	74.92	75.71			75.26
	SD	20.251	22.052			21.011
	Median	78.57	81.22			79.37
	Min	1.3	−25.6			−25.6
	Max	100.0	100.0			100.0

Week 12	n	209	156			365
	Mean	85.35	87.69			86.35
	SD	18.208	18.187			18.211
	Median	91.99	92.38			92.16
	Min	1.3	−25.6			−25.6
	Max	100.0	100.0			100.0
Week 16	n	205	154			359
	Mean	90.71	91.42			91.01
	SD	12.807	14.239			13.425
	Median	96.00	96.41			96.14
	Min	14.5	−25.6			−25.6
	Max	100.0	100.0			100.0
Week 20	n	194	151			345
	Mean	94.22	94.41			94.30
	SD	9.424	11.193			10.221

Timepoint	**Statistics**	**SB17 N=209 n/n' (%)**	**Stelara Overall N=254 n/n' (%)**	**Stelara +SB17[a] N=122 n/n' (%)**	**Stelara +Stelara[a] N=122 n/n' (%)**	**Total N=503 n/n' (%)**
		%CFB	**%CFB**	**%CFB**	**%CFB**	**%CFB**
	Median	98.17	99.01			98.74
	Min	40.5	20.9			20.9
	Max	100.0	100.0			100.0
Week 24	n	197	152			349
	Mean	94.90	95.07			94.97
	SD	9.254	9.685			9.431
	Median	98.21	100.00			98.89
	Min	27.3	20.9			20.9
	Max	100.0	100.0			100.0
Week 28	n	199	153	78	74	352
	Mean	95.79	95.87	96.36	95.33	95.82
	SD	6.460	6.685	5.716	7.616	6.549
	Median	98.46	98.91	100.00	98.80	98.72
	Min	65.2	56.5	73.3	56.5	56.5
	Max	100.0	100.0	100.0	100.0	100.0

Week 40	n	198	149	77	72	347
	Mean	96.15	96.52	96.89	96.12	96.31
	SD	6.593	6.943	6.400	7.505	6.738
	Median	99.28	100.00	100.00	100.00	100.00
	Min	62.8	56.8	56.8	62.1	56.8
	Max	100.0	100.0	100.0	100.0	100.0
Week 52	n	196	145	75	70	341
	Mean	95.53	96.20	96.99	95.37	95.82
	SD	8.252	8.059	7.185	8.878	8.165
	Median	99.57	100.00	100.00	100.00	100.00
	Min	56.5	50.0	56.8	50.0	50.0
	Max	100.0	100.0	100.0	100.0	100.0

%CFB = percent change from baseline; Max = maximum; Min = minimum; N = total number of patients in the Per-Protocol Set in each treatment group and subgroup; n = number of patients with available data within each category; NAb = neutralizing antibody; SD = standard deviation
Percent change from baseline in PASI score (%) at Week X = [(PASI score at baseline - PASI score at Week X)/ PASI score at baseline]×100.
NAb positive and NAb negative is the overall NAb status up to Week 52.
Overall NAb is positive if there is at least one positive NAb measurement at any time during the period (including baseline). If there is no positive NAb measurement during the period, then the overall NAb status is negative.
[a] Based on patients in the Per-Protocol Set who were re-randomized at Week 28, Stelara+SB17 and Stelara+Stelara may not add up to Stelara Overall.

In conclusion, the percent change from baseline in PASI at Week 12 was equivalent between the Eksunbi and Stelara treatment groups without ADAs. LSMeans at Week 12 was −2.2 [−6.194, 1.805], which was within the pre-defined equivalence margin of [−15%, 15%]. In addition, the PASI score up to Week 52 are comparable between treatment groups in ADA negative subgroup.

Overall NAb was defined as positive if there was at least one positive NAb measurement at any time during the period (including baseline). The incidence of overall NAb was lower in the Eksunbi compared to the Stelara treatment groups. The percent change from baseline in PASI at Week 12 was equivalent between the Eksunbi and Stelara treatment groups for the overall NAb negative subgroup in the Per-protocol Set. The adjusted difference in LSMeans at Week 12 was −2.3 and the 95% CI of the adjusted treatment difference was [−6.121, 1.424]. In addition, the PASI score up to Week 52 are comparable between treatment groups in NAb negative subgroup.

Summary of main efficacy results

The following Table 40 summarise the efficacy results from the main studies supporting the present application. These summaries should be read in conjunction with the discussion on clinical efficacy as well as the biosimilarity assessment (see later sections).

Table 40. Summary of efficacy for trial SB17-3001

Title: A Phase III, Randomised, Double-blind, Multicentre Clinical Study to Evaluate the Efficacy, Safety, Tolerability, Pharmacokinetics, and Immunogenicity of Eksunbi (proposed ustekinumab biosimilar) Compared to Stelara in Subjects with Moderate to Severe Plaque Psoriasis		
Study identifier	SB17-3001 EudraCT Number: 2020-006115-19	
Design	randomised, double-blind, parallel, 2-arm, 2 stage, active control, multicentre	
	Duration of main phase: Duration of Run-in phase: Duration of Extension phase:	Start Jul 06, 2021 (first subject signed informed consent)- Dec 08, 2022 (last subject's last activity) Not applicable Not applicable
Hypothesis	Equivalence	
Treatments groups	Eksunbi (N=249 randomised)	Patients were randomised to receive Eksunbi via subcutaneous injection to be administered at Week 0, 4, and then every 12 weeks up to Week 40. At Week 28, patients who achieved a PASI50 response and were considered eligible entered into the transition period. In the transition period, patients who received Stelara were randomised again in 1:1 ratio to either continue on Stelara or transition to SB17 until Week 40. Patients who received SB17 continued to receive SB17 until Week 40 but they followed the randomisation procedure in order to maintain blinding.
	Stelara Overall (N=254 randomised)	Patients were randomised to receive Stelara via subcutaneous injection to be administered at Week 0, 4, and then every 12 weeks up to Week 40. At Week 28, patients who achieved a PASI50 response and were considered eligible entered into the transition period. In the transition period, patients who received Stelara were randomised again in 1:1 ratio to either continue on Stelara or transition to SB17 until Week 40.
	Stelara+Eksunbi (N=122 randomised)	At Week 28, patients who achieved a PASI50 response and were considered eligible entered into the transition period. In the transition period, half of the patients who received Stelara were randomised to transition to Eksunbi until Week 40.
	Stelara+Stelara (N=122 randomised)	At Week 28, patients who achieved a PASI50 response and were considered eligible entered into the transition period. In the transition period, half of the patients who received Stelara were randomised to continue on Stelara until Week 40.

Endpoints and definitions	Primary endpoint	Percent improvement in PASI score from baseline to Week 12.	Percent improvement in Psoriasis Area and Severity Index (PASI) score from Baseline to Week 12 in subjects with moderate to severe plaque psoriasis. Clinical equivalence is demonstrated if the 95% CI for the adjusted mean difference in percentage PASI improvement between test and reference groups is contained within the equivalence margin range of [-15%, 15%]
	Secondary endpoint	PASI50, PASI75, PASI90, PASI100	PASI50, PASI75, PASI90, and PASI100 response rates at Week 2, 4, 8, 12, 16, 20, 24, 28, 40, and 52
		Percent improvement in PASI	Percent change from baseline in PASI at Week 2, 4, 8, 16, 20, 24, 28, 40, and 52
	Secondary endpoint	PGA responses	Patients achieving Physician's Global Assessment (PGA) response at Week 2, 4, 8, 12, 16, 20, 24, 28, 40, and 52
	Secondary endpoint	Change in DLQI scores	Change from baseline in Dermatology Life Quality Index (DLQI) scores at Week 4, 12, 16, 28, 40, and 52
Database lock	Jan 23, 2023 (Final CSR)		

Results and Analysis			
Analysis description	**Primary Analysis**		
Analysis population and timepoint description	Per-protocol Set (PPS): PPS consisted of all patients in Full Analysis Set (FAS) who weighed ≤ 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 the primary efficacy assessment. Major PDs that led to exclusion from this set was pre-defined prior to unblinding the treatment group assignment for analyses.		
Primary efficacy results (for EMA)	Treatment group	SB17	Stelara
	Number of patients (n)	243	249
	LSMeans (Standard Error [SE]) of percent change from baseline in PASI at Week 12	85.7 (2.53)	86.3 (2.41)
	Adjusted difference [95% CI] (SB17 – Stelara)	–0.6 [–3.780, 2.579]	
Analysis description	**Sensitivity Analysis of Primary Efficacy Variable**		

Analysis population and timepoint description	Full Analysis Set (FAS): FAS consisted of all patients who were randomised. Following the intent-to-treat principle, patients were analysed according to the treatment group that they were assigned to at Randomisation. However, patients who did not have any efficacy assessment result after randomisation or did not receive IP during the study period were excluded from FAS.		
Sensitivity analysis of primary efficacy results (for FDA)	Treatment group	SB17	Stelara
	Number of patients (n)	246	252
	Method: based on available case LSMeans (SE) of percent change from baseline in PASI at Week 12	85.7 (2.42)	86.3 (2.31)
	Adjusted difference [90% CI] (SB17 – Stelara)	–0.7 [–3.329, 1.948]	
	Treatment group	SB17	Stelara
	Number of patients (n)	249	254
	Method: using multiple imputation LSMeans (SE) of percent change from baseline in PASI at Week 12	85.7 (2.43)	86.4 (2.32)
	Adjusted difference [90% CI] (SB17 – Stelara)	–0.7 [–3.343, 1.933]	
Analysis population and timepoint description	PPS consisted of all patients FAS who weighed ≤ 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 PDs that had impact on the primary efficacy assessment. Major PDs that led to exclusion from this set was pre-defined prior to unblinding the treatment group assignment for analyses.		
Sensitivity analysis of primary efficacy results (for EMA)	Treatment group	SB17	Stelara
	Number of patients (n)	243	249
	LSMeans (SE) of percent change from baseline in PASI at Week 12	85.7 (2.53)	86.3 (2.41)
	Adjusted difference [90% CI] (SB17 – Stelara)	–0.6 [–3.267, 2.066]	
Analysis description	**Supportive Analysis for Primary Efficacy Variable**		

Analysis population and timepoint description	FAS consisted of all patients who were randomised. Following the intent-to-treat principle, patients were analysed according to the treatment group that they were assigned to at Randomisation. However, patients who did not have any efficacy assessment result after randomisation or did not receive IP during the study period were excluded from FAS.				
Supportive analysis of primary efficacy results (for EMA)	Treatment group	SB17		Stelara	
	Number of patients (n)	246		252	
	Method: based on available case LSMeans (SE) of percent change from baseline in PASI at Week 12	85.7 (2.42)		86.3 (2.31)	
	Adjusted difference [95% CI] (SB17 – Stelara)	–0.7 [–3.836, 2.456]			
	Treatment group	SB17		Stelara	
	Number of patients (n)	249		254	
	Method: using multiple imputation LSMeans (SE) of percent change from baseline in PASI at Week 12	85.7 (2.43)		86.3 (2.32)	
	Adjusted difference [95% CI] (SB17 – Stelara)	–0.7 [–3.849, 2.439]			
Analysis description	**Secondary Efficacy Analysis**				
Analysis population and timepoint description	FAS consisted of all patients who were randomised. Following the intent-to-treat principle, patients were analysed according to the treatment group that they were assigned to at Randomisation. However, patients who did not have any efficacy assessment result after randomisation or did not receive IP during the study period were excluded from FAS.				
Secondary efficacy results	Treatment group	SB17	Stelara Overall	Stelara+ SB17	Stelara+ Stelara
	Number of patients (n)	249	254	122	122
	Percent Change from Baseline in PASI other than Week 12	Week 28: SB17: 95.59; Stelara Overall: 95.32; Stelara+SB17: 95.64; Stelara+Stelara: 94.99. Week 52: SB17: 95.82; Stelara Overall: 95.05; Stelara+SB17: 95.59; Stelara+Stelara: 94.52.			

	PASI Response Rate	Week 28: PASI50 – SB17: 237/238 (99.6%); Stelara Overall: 245/245 (100.0%); Stelara+SB17: 122/122 (100.0%); Stelara+Stelara: 122/122 (100.0%) patients; PASI75 – SB17: 234/238 (98.3%); Stelara Overall: 240/245 (98.0%); Stelara+SB17: 120/122 (98.4%); Stelara+Stelara: 119/122 (97.5%) patients; PASI90 – SB17: 202/238 (84.9%); Stelara Overall: 204/245 (83.3%); Stelara+SB17: 104/122 (85.2%); Stelara+Stelara: 99/122 (81.1%) patients; PASI100 – SB17: 109/238 (45.8%); Stelara Overall: 110/245 (44.9%); Stelara+SB17: 58/122 (47.5%); Stelara+Stelara: 52/122 (42.6%) patients. Week 52: PASI50 – SB17: 233/233 (100.0%); Stelara Overall: 234/235 (99.6%); Stelara+SB17: 117/117 (100.0%); Stelara+Stelara: 117/118 (99.2%) patients; PASI75 – SB17: 221/233 (94.8%); Stelara Overall: 223/235 (94.9%); Stelara+SB17: 111/117 (94.9%); Stelara+Stelara: 112/118 (94.9%) patients; PASI90 – SB17: 201/233 (86.3%); Stelara Overall: 198/235 (84.3%); Stelara+SB17: 101/117 (86.3%); Stelara+Stelara: 97/118 (82.2%) patients; PASI100 – SB17: 121/233 (51.9%); Stelara Overall: 120/235 (51.1%); Stelara+SB17: 67/117 (57.3%); Stelara+Stelara: 53/118 (44.9%) patients.
	Physician's Global Assessment (PGA)	Week 28: proportions of patients with PGA responses 'cleared' or 'minimal' (SB17: 223/238 [93.7%] patients; Stelara Overall: 226/245 [92.2%] patients; Stelara+SB17: 113/122 [92.6%] patients; Stelara+Stelara: 112/122 [91.8%] patients); Week 52: proportions of patients with PGA responses 'cleared' or 'minimal' (SB17: 210/233 [90.1%] patients; Stelara Overall: 205/235 [87.2%] patients; Stelara+SB17: 102/117 [87.2%] patients; Stelara+Stelara: 103/118 [87.3%] patients).
	Change from Baseline in Dermatology Life Quality Index (DLQI)	Week 28: SB17: 11.0; Stelara Overall: 10.7; Stelara+SB17: 10.5; Stelara+Stelara: 11.1. Week 52: SB17: 11.5; Stelara Overall: 11.2; Stelara+SB17: 10.9; Stelara+Stelara: 11.5.
Notes	Patients disposition (by treatment group) in the Enrolled Set is summarised in the original dossier	

2.6.5.3. Clinical studies in special populations

Not applicable for biosimilars.

2.6.5.4. In vitro biomarker test for patient selection for efficacy

Not applicable.

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

Not applicable.

2.6.5.6. Supportive study(ies)

Not applicable.

2.6.6. Discussion on clinical efficacy

Design and conduct of clinical studies

The clinical development programme to compare the clinical efficacy, safety and immunogenicity between the proposed biosimilar Eksunbi and the reference product, Stelara focused on a pivotal randomised, double-blind, active-controlled phase III study (SB17-3001).

The phase III clinical study was set out to establish clinical equivalence between Eksunbi to Stelara in adult patient with moderate to severe plaque-type psoriasis (PsO), which is considered a sensitive population (see also discussion below). The study (SB17-3001) was conducted in accordance with the EMA guidelines [EMEA/CHMP/BMWP/42832/2005 Rev. 1; EMA/CHMP/BMWP/403543/2010]. The study was not aimed at establishing efficacy per se since the efficacy of Stelara in the respective therapeutic indications has already been established in the pivotal clinical trials and published literature reports [Stelara SmPC; Stelara US PI; Stelara EMA Scientific Discussion].

Although the Phase III study is complete, the final clinical study report was not available at the time of submission of the initial application. Therefore, the applicant presented interim efficacy data to week 40 (with partial data to 52 weeks), along with the full study report which was submitted with the responses.

The overall study design is acceptable to the CHMP, although it is noted that the design did not allow for the generation of clinical data for the Eksunbi 130 mg concentrate for solution for infusion.

In relation to the efficacy data, the applicant presented demographic and baseline characteristics which are considered to be equally balanced between both the Eksunbi and Stelara treatment arms. There were no major differences between treatment arms.

Adult patients were included who were required to have had PsO for at least 6 months, involved total affected BSA ≥ 10%, PASI ≥12, and Physicians Global Assessments PGA ≥3 (moderate) at screening and at randomisation. Patients were considered to be a candidate for phototherapy or systemic therapy for psoriasis at Screening. Furthermore, patients with body weight >95 kg were not included, hence all patients received ustekinumab 45 mg to begin with, which is acceptable to the CHMP and in agreement with the SA recommendations. It was observed that the inclusion criteria did not demand former failed systemic therapies including ciclosporin, methotrexate (MTX) or PUVA (psoralen and ultraviolet A), which is part of the proposed PsO indication. This could influence the response rate as in general patients with former failures may be less likely to respond to other therapies as well, but it was noted that treatment arms should be comparable and the chosen population more sensitive, which is endorsed by the CHMP.

The most important exclusion criteria include that patients are naïve to ustekinumab and naïve to any other IL-12 or IL-23 inhibitor, IL-17 inhibitor, rituximab, or integrin inhibitor biologics. Furthermore, any therapeutic monoclonal antibody or fusion receptor protein was not allowed within the previous 6 months, other biologics within the longer of either 5 half-lives or 3 months. Patients must not have

received phototherapy or conventional systemic therapy for psoriasis within 4 weeks or topical therapy for psoriasis within 2 weeks. Hence patients were to be in ustekinumab monotherapy in the trial.

Overall, the eligibility criteria were considered acceptable.

The applicant chose to perform a clinical study in patients with PsO. This was rationalised by the larger treatment effect size between patients with Stelara and placebo (or control) in PsO patient population, compared to results for the other indications in the original studies, and therefore examination in PsO patients should be the most sensitive to observe differences in terms of efficacy between Eksunbi and Stelara. This argumentation was agreed by the CHMP and was supported in the SA meetings. Furthermore, the applicant provided a justification for extrapolation to the other indications. Inclusion of ustekinumab-naïve patients is in accordance with the EMA guideline [EMEA/CHMP/BMWP/42832/2005 Rev. 1] as treatment-naïve patients are seen as best to assess potential differences in the risk of immunogenicity. Previous treatments could have resulted in ADAs and may thereby hamper interpretation of the efficacy (and safety). Further, for psoriasis treatment, treatment is intended as monotherapy (without immunosuppressants etc.), which will also make the interpretation of the results clearer.

Patients, Investigators, and other study personnel were blinded in the study treatment period. The pre-filled syringes were identical in appearance. In cases of breaking the double-blind, the subject was permanently discontinued. The blinding procedures are endorsed by the CHMP.

The overall study population is considered representative of the target population in plaque-type psoriasis and is reflective of the intended indication.

In relation to the phase III study on clinical equivalence (SB17-3001), on Day 1, eligible patients were randomised in a 1:1 ratio to Eksunbi or Stelara treatment groups.

Only one dose, 45 mg was used in the study, which is an adequate dose for patients with body weight ≤100kg. This was also endorsed during a scientific advice procedure, since body weight is considered as a major intrinsic factor affecting ustekinumab exposure and response. However, as outlined, a dose of 90mg could be administered if patients gained weight >100kg over the course of the study. The Applicant’s approach to handling potential weight gain in patients is acceptable to the CHMP as the narrower BW range at inclusion should allow for a more homogenous study population as recommended during previous EMA SA discussions. Nevertheless, there was also the option of increasing the dose to 90mg ustekinumab in the event of the patient gaining weight and thus moving into the higher dosing band.

In this respect, only a relatively small number of patients ended up gaining weight during the study and were subsequently treated with 2 x 45mg doses (90mg) of either Eksunbi or Stelara. The number of patients requiring 90mg doses of ustekinumab was generally balanced as clarified by the applicant in the final CSR.

Initial loading doses of Eksunbi or Stelara were administered at Weeks 1 and 4, followed by 45mg dosing of ustekinumab once every 12 weeks (Weeks 16, 28 and 40). A final assessment was carried out at the end of the study at Week 52.

Furthermore, at Week 28, patients were re-evaluated and depending on their PASI response, those patients who had been initially randomised to Eksunbi group continued to receive Eksunbi. Patients initially randomised to receive Stelara were again re-randomised in a 1:1 ratio, to switch to either Eksunbi or to continue treatment with Stelara. In the context of this biosimilar application, the comparison between patients continuously treated with Eksunbi and patients who remained in Stelara group after evaluation at Week 28 (i.e. Eksunbi/Eksunbi vs Stelara/Stelara) is considered relevant and the process of re-randomisation after Week 28 increases the number of patients who remain on Stelara

for the comparison of secondary endpoints because week 28 provides an important period with patients on EU-Stelara for the comparison of secondary endpoints before re-randomisation, whilst the shorter transition period makes the week 52 assessment important for a meaningful length of the transition period. The CHMP noted that only responders continued in the transition period, and therefore efficacy endpoints hereafter should be interpreted with caution.

From Week 28, non-responders (PASI < 50) did no longer receive treatment, however it was not completely clear if any changes in dosing interval occurred in partial responders (PASI50-75). In the responses, the applicant clarified that there were no strategies for dose escalation. This is acceptable to the CHMP.

At Week 40, all patients still on treatment received the final study drug administration. At Week 52 all patients still on study underwent final efficacy and/or safety and immunogenicity assessments.

In general, the overall study design is acceptable to the CHMP. It is noted that recommendations from EMA SA procedures have been generally followed, by the Applicant.

Specifically, the applicant adapted the process of re-randomisation to ensure that this occurred at the later timepoint of week 28, even though week 16 had been originally proposed. This approach is acceptable to the CHMP.

In relation to the target population, the phase III study was conducted in patients with moderate-to-severe plaque psoriasis (PsO). Patients were required to have PsO for at least 6 months (with stable disease for at least 2 months), an involved BSA ≥10%, PASI ≥12, and Physicians Global Assessments PGA ≥3 (moderate) at screening and at baseline and be candidates for systemic therapy.

The baseline demographic characteristics and disease characteristics were mostly balanced at baseline. The duration of PsO was 15.03 years in the Eksunbi group and 16.13 years in the Stelara group. Mean PASI at baseline were 22.52 in the Eksunbi group and 22.07 in the Stelara group. At baseline most patients had a 'moderate' PGA score (n=157 (63.1%) patients and n=160 (63.0%) and an equal proportion had PGA score ≥4 (36.9% vs 37%)). It is noted that in the Stelara+Eksunbi and Stelara+Stelara disease characteristics were also overall symmetric at baseline (week 0). The total psoriasis body surface area (BSA) involvement at baseline was 27.31% in the Eksunbi and 26.66% in the Stelara group at baseline. In addition, DLQI score at baseline were also comparable across treatment groups.

A higher proportion of patients in the Eksunbi group had a history of psoriatic arthritis 25.7% vs 21.3% in the Stelara group. This is acceptable to the CHMP, even though psoriasis arthritis presence may be linked to a different response to therapy, as these patients are in general sicker. More patients were current smoker in the Stelara arm (29.1% vs 24.9% in the Eksunbi group).

Most patients had used topical treatment beforehand, whereas only around half of the patients had received prior conventional systemic treatment for psoriasis (47% in the Eksunbi group and 52% in the Stelara group). An almost equal proportion had received prior biologic therapy (6.8% in the Eksunbi group and 7.5% in the Stelara group). A similar proportion of subjects in the Eksunbi and Stelara groups received concomitant medication (118 (47.4%) and 117 (46.1%) respectively). COVID-19 vaccine was the most commonly reported, followed by paracetamol, ibuprofen and azithromycin. The exclusion criteria were very restrictive with regards to concomitant immunosuppressive therapy and the same drugs were prohibited throughout the study. The applicant provided a tabulated overview list of patients per treatment group receiving any of these prohibited concomitant medication at baseline or during the study including topical and systemic corticosteroids, glucocorticoids, antibiotics and immunosuppressants. No specific concerns arise from the data presented.

The CHMP considered that study objectives are appropriate to compare the clinical efficacy, safety and tolerability, PK and immunogenicity of the proposed biosimilar Eksunbi and Stelara.

In relation to the primary efficacy endpoint, this was the percentage improvement from baseline in Psoriasis Area and Severity Index (PASI) score (LS means) at week 12. Percent change from baseline is seen as an adequate strategy to express results and the continuous variable PASI score were recommended over the dichotomous endpoint PASI75. The primary endpoint was assessed at week 12, after two doses of ustekinumab.

As recommended to the applicant in previous scientific advice procedures, Week 12 was not considered the most sensitive time point to detect potential differences between treatments as the time/response curve already reaches the plateau by then, therefore the applicant was advised to provide data for an earlier time points from around Week 8 as secondary endpoints. The onset of efficacy of ustekinumab in PsO patients is often rapid (PHOENIX I and II), so while it is accepted that week 12 might not be the most sensitive time-point as the time/response curve have reached a plateau by then. It is however considered acceptable to the CHMP, as earlier time-points are addressed in the secondary endpoints. Of note in the PHOENIX I study the primary efficacy endpoint was also assessed at week 12. (PASI-75 at week 12).

In summary, the applicant ’s overall approach is agreed by the CHMP, as data on secondary efficacy endpoints has also been provided by the applicant which includes earlier timepoints, including week 8.

Secondary efficacy endpoints include percent change from baseline in PASI week 2, 4, 8, 16, 20, 24, 28, 40, and 52. Hereof the most relevant time-point is week 8 (see above). The dichotomous endpoint (PASI50, PASI75, PASI90, and PASI100 response rate) were assessed at Week 2, 4, 8, 12, 16, 20, 24, 28, 40, and 52. Hereof the most widely used is proportion of patients experiencing a 75% improvement from baseline PASI (PASI-75) score at week 8/12. Quality of life are assessed as change from baseline in DLQI at Week 4, 12, 16, 28, 40, and 52. Secondary endpoints were not ranked. Overall study endpoints are considered appropriate to the CHMP to compare the clinical efficacy of Eksunbi and EU-Stelara.

The equivalence margin of 15% was derived from the meta-analysis of the reference product pivotal studies (PHOENIX 1 and 2) in addition to publicly available bibliographic data. Based on this equivalence margin, a sample size of 192 patients per treatment group was calculated with the assumptions of common standard deviation (SD) of 31.33, 10% loss from the primary analysis and approximately 100 remainders per treatment group after transition at Week 28 at the overall 5% significance level, providing over 90% power. Overall, 464 patients (232 patients per treatment group) were randomised into the study to determine equivalence of percent change from baseline in PASI at Week 12.

As mentioned in the protocol of Study SB17-3001, the margin is not derived from statistical methods (e.g., 50% of the effect size). The margin is derived from the recommendations from regulatory agencies as well as the existing data of clinically meaningful margin for PASI evaluation and accounted from previous psoriasis biosimilar studies which employed similar efficacy endpoints.

For the clinical meaningfulness of the margin, it should first be noted that there is not an officially recognised equivalence margin for psoriasis studies [Wan et al., 2019]. Generally, however, the clinical margin size could be considered to be related to minimally clinically important difference (MCID) [Lin CJ and Saver JL, 2020]. There is no known MCID for the percent change of PASI, however PASI50 [Carlin et al., 2004] or PASI75 is a widely recognised threshold for clinical meaningfulness, and since PASI50 is smaller, a 50% change in PASI could be considered as a MCID. In terms of PASI percent change, this would mean an equivalence margin of [−50%, 50%]. Thus, using a narrower equivalence

margin of [−15%, 15%] than the [−50%, 50%] margin in Study SB17-3001 suggests that the set margin is clinically significant to assess equivalence in primary endpoint.

Moreover, as the effect size of Stelara in terms of percent change from baseline in PASI is approximately 70%, the equivalence margin of [−15%, 15%] used in Study SB17-3001 is stringent enough to preserve at least 80% of the effect size of Stelara, higher than other biosimilar studies discussed below (60% to 70%).

The equivalence margin of [−15%, 15%] is also consistent with the equivalence margins adopted in other psoriasis clinical studies for biosimilar products, which range from [−10%, 10%] to [−18%, 18%]. Therefore, the proposed equivalence margin of [−15%, 15%] in Study SB17-3001 is considered to be clinically meaningful to reflect equivalence in efficacy in terms of percent change from baseline in PASI at Week 12 between Eksunbi and Stelara.

The clinical justification of the 15% non-inferiority margin has been provided which had been previously considered during EMA SA. The clinical justification of the equivalence margin is acceptable to the CHMP

In this context, the sample size of 464 allowed enough power to detect the equivalence in the 95% CI or 90% CI of the difference in the percent change from baseline in PASI at Week 12.

The sample size is acceptable to the CHMP and considered reproduceable for the parameters provided. As stated, scientific advice for the equivalence margins was sought with +/-15% limits agreed based on clinical and statistical criteria. The general methods described in this submission are supported by the CHMP.

Overall, the approach to patient randomisation was endorsed by the CHMP. Patients were randomised in a 1:1 ratio to receive either Eksunbi or Stelara via subcutaneous injection.

Investigative products (IPs; Eksunbi or 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.

Specifically, the per-protocol analysis set was used for the analysis of the primary endpoint. This approach is agreed by the CHMP. It was highlighted that the overall number of Major protocol deviations indicates that 46.2% of patients in the Eksunbi treatment group had major protocol deviations, yet for the PP set, 97.8% were included in the analyses. The distribution of these PD’s appears similar between groups, but it was not entirely clear why so few were excluded for the PP analysis.

In total, numbers in the full analysis set (FAS) were comparable. There were n=249 patients in the Eksunbi treatment group FAS versus n=254 in the Stelara Overall group.

In the per-protocol set (PPS), there were n=243 in the Eksunbi treatment group compared to n=249 patients in the Stelara Overall group. The numbers across treatment arms for the PPS were generally balanced.

A summary including number and proportion of subjects with PDs and number of subjects for each PD by treatment group was presented.

PDs related to COVID-19 by treatment group and those related to war in Ukraine by treatment group are also presented separately by the applicant.

A total of 244 (48.5%) subjects had PDs and 235 (46.7%) subjects had at least one major PD; Eksunbi: 115 (46.2%) subjects vs Stelara Overall: 120 (47.2%) subjects.

The most common major PDs which led to exclusion from PPS were related to study procedures in 6 (1.2%) subjects, followed by exclusion criteria in 4 (0.8%) subjects. The frequency and pattern of PDs were comparable between the two treatment groups.

The primary endpoint was calculated in the Per-protocol set. Missing secondary efficacy endpoints, safety, and PK data were not imputed. For the supportive and sensitivity analysis of the primary endpoint (FAS population), missing data for PASI score was imputed. A MAR approach assumed that subjects who withdraw from a study or missed the assessment had missing values similar to subjects who completed the study in that treatment group. The missing value was imputed by multiple imputation method with the assumption of monotone missing pattern and regression method. Multiple imputation was conducted based on change from baseline values. This approach did not address the potential impact of other types of intercurrent events, and in order to clarify how the analyses conducted fits into the estimand frame, the applicant was requested to specify the already reported results in terms of the estimand frame, with particular focus on identification and handling of intercurrent events. In case that the conducted analyses do not include the treatment policy strategy and the hypothetical stratum strategy, results from these estimands were also requested. For any imputation of values excluded from analysis due to intercurrent events, the applicant provided results from different imputation models, and justifications on the assumptions related to the imputation (missing at random or missing not at random) and the choice of actual imputation (e.g. copy increment of treatment group or copy increment of reference group). The Applicant's response to this point was considered acceptable.

It is noted that few data are missing or the primary endpoint, but in general the applicant s reporting of intercurrent events, including those PD's that potentially can impact on the validity of the efficacy assessment, was not sufficient in the initial submission and the applicant was requested to discuss and provide an overview of frequency by treatment group and type, with possible need for narratives on selected PD's. The applicant's response to this point was considered acceptable.

Overall, it is noted that major protocol deviations occurred at a high rate overall in this study, although numbers of PDs reported were broadly comparable between the Eksunbi and Stelara treatment arms. An update and overview of data for patients with major PDs was provided as part of the discussion on the complete data set.

The per protocol dataset (primary analysis) consisted of 492 patients (out of 503 randomised).

During conduct of the study all most half of the patients experienced a major protocol deviation in both the Eksunbi group and the Stelara group. The high rate of major protocol deviations was found concerning given that almost ¼ had deviations related to IP. Therefore, the applicant was requested to list (in a short, tabulated overview) the IP compliance cases per treatment group with description of the IP compliance issue and discuss how these protocol deviations were handled and if they could have influenced results.

For five patients in each group the deviation caused exclusion from the per-protocol set (primary endpoint analysis set), the applicant was requested to provide complete list of reason in all of these 10 patients and clarify numbers (as 503 patients were randomised 492 patients were in the Per protocol set=11 patients). In total, 658 patients were screened and 503 patients were randomised, 249 patients to Eksunbi and 254 patients to Stelara. N=155 patients were screenings failures and main reason for failing screening was not fulfilling the eligible criteria. Of the 503 randomised patients, 481 (95.6%) patients completed 28 weeks of the study, whereas currently only 21.4% patients completed 52 weeks of the study (data will come in the Day 120 responses). The rate of completion at week 28 was comparable between the two treatment groups (237 [95.2%] patients in the Eksunbi and 244 [96.1%] patients in the Stelara groups. In total 237 patients in the Eksunbi group continued to receive

Eksunbi until Week 40. The Stelara treatment group were further randomised at week 28 into two treatment groups: Stelara+Stelara (n=122) and Stelara+Eksunbi (n=122) until Week 40.

Discontinuations before week 28 occurred in 12 (4.8%) patients from the Eksunbi treatment group and 10 (3.9%) patients from the Stelara treatment group. The most common reason for discontinuation was related to war in Ukraine. After week 28, 2 (0.8%) patients in the Eksunbi and 6 (2.5%) patients in the Stelara treatment groups discontinued. As the primary endpoint was assessed at week 12, the applicant provided a list of reasons and number of discontinuations up to week 12. The applicant's response to this point was considered acceptable.

In their responses the applicant presented the full data set and the outstanding issues relating to handling of missing data and protocol deviations related to investigated product have all been adequately addressed.

Efficacy data and additional analyses

The primary endpoint indicating clinical equivalence was met in this study: the adjusted LSMeans difference of the percent change from baseline in PASI at Week 12 for the PPS was −0.6 (SE: 1.62) and the 95% CI of the adjusted treatment difference was [−3.780, 2.579], all of these values were entirely contained within the pre-defined equivalence margin of [−15%, 15%].

The adjusted LSMeans difference of the percent change from baseline in PASI at Week 12 for the FAS available cases was −0.7 (SE: 1.60) and the 95% CI of the adjusted treatment difference was [−3.836, 2.456], and for FAS multiple imputation, −0.7 (SE: 1.60), 95% CI [−3.849, 2.439], all of these values were still well within the pre-specified margin of [−15%, 15%].

The applicant also provided an analysis using a 90% CI, which, although not relevant for this application still indicated that the LSMeans difference of the percent change from baseline in PASI at Week 12 for the PPS is −0.6 (SE: 1.62, 90% CI [−3.267, 2.066]), the FAS available cases is −0.7 (SE: 1.60, 90% CI [−3.329, 1.948]), and FAS multiple imputation is −0.7 (SE: 1.60, 90% CI [−3.343, 1.933]), all within the pre-specified margin of [−10%, 10%].

Therefore, the sensitivity analyses showed that results were consistent over the FAS analysis set with narrower pre-defined equivalence margin of [−10%, 10%] but with a 90% CI instead.

Within this submission, the pre-specified equivalence range [-15%, 15%] has been clinically justified by the applicant. Although it is large, the 95% CI for both the ITT and the PPS analysis clearly demonstrated equivalent clinical efficacy of Eksunbi and Stelara within a narrow range, therefore clinical comparability is concluded by the CHMP. The primary outcome was calculated in the per-protocol set. The per-protocol analysis set includes 97.8% of all treated subjects. Therefore, no important differences are expected between the different approaches in terms of outcome. The 95% CI of the mean difference between the treatment groups in PASI percent change from baseline to week 12 was within the prespecified equivalence margin of (-15, +15). The observed mean difference was -0.6 percentage points (95% CI 3.780, 2.579), i.e., neither clinically nor statistically significant.

In relation to the timing of the primary efficacy analysis, the applicant has chosen Week 12 as the cut off for this analysis. This approach is accepted by the CHMP. However, it is highlighted that by the Week 12 timepoint, the plateau is almost reached. In this context, and as discussed during previous CHMP Scientific Advice, the sensitivity to detect differences between both treatments, Eksunbi and Stelara, may possibly be higher during the steeper part of the time/response curve which would occur at any earlier timepoint, most probably around Week 8 instead of Week 12.

Despite this, it is acknowledged that the applicant provided additional data for timepoints earlier than Week 12 including Weeks 2, 4, 8, which allows for the opportunity to evaluate similarity at the earlier time points. This approach can be accepted and it aligns to the CHMP Scientific advice recommendations (EMA/CHMP/SAWP/493969/2019) whereby, it was recommended to add an additional measure of efficacy at week 8 (e.g. mean change from baseline) as a secondary endpoint, in order to fulfil the EMA guidelines to use also an earlier time point for the detection of potential product differences, which are potentially higher at the steeper part of the efficacy curve.

Further supportive efficacy data which was obtained at earlier timepoints is also supportive of clinical equivalence.

Based on the reported results, equivalence has been demonstrated for the primary efficacy endpoint. In addition, the results appear robust to several sensitivity analysis with different imputations and of other analysis set (FAS) and with different CI and margins. The uncertainty relating to the imputation of missing data and protocol deviations has been adequately justified by the applicant in their responses.

In general, secondary efficacy endpoints such as PASI75, PASI90, and PASI100 response rate, PGA, and DLQI were also broadly similar between the treatment groups at all timepoints.

At Week 12, PASI75 response rate was 81.7% for Eksunbi and 81.0% for Stelara; PASI90, 53.7% for Eksunbi and 57.5% for Stelara; PASI100: 19.9% for Eksunbi and 22.6% for Stelara, and PGA 0/1: 85.0% for Eksunbi and 87.3% for Stelara (all for the FAS).

The secondary endpoint Percent Change from Baseline in PASI were comparable between arms over time.

The PASI response rates (PASI50, PASI75, PASI90, and PASI100) were comparable between the Eksunbi and Stelara treatment groups over time.

PASI 75 response was similar between the 2 treatment groups through week 28 and across the treatment groups over the entire study period.

PASI75 were 81% in the Stelara group and 81.7% in the Eksunbi group at week 12.

The proportions of patients with Physician's Global Assessment (PGA) responses 'cleared' or 'minimal' were similar between the Eksunbi and Stelara treatment groups until Week 40. At week 52, higher proportion had cleared or minimal in the Eksunbi group, but number are small and influenced by missing data. The general DLQI response across time was similar between the two treatment groups. Overall, results from secondary outcomes are considered by the CHMP comparable between Eksunbi and Stelara.

In summary, the percentage change in PASI from baseline through Week 52 was comparable between Eksunbi and Stelara. Results for patients with body weight >100kg were provided but at the time of interim analysis, only a small number of patients had moved into this higher weight band and had therefore required treatment with the higher 90mg dose of ustekinumab. The number of patients in this subgroup was overall very low and similar across Eksunbi and Stelara.

Data presented up to Week 28 and into subsequent transition phase through to week 52 did not reveal any major differences between the treatment groups.

Subgroup analyses were limited by numbers (except sex). This is acceptable to the CHMP, as studies in vulnerable populations are in general not required in a biosimilar application, as for these patient specific efficacy data already exist, and a homogenic and sensitive population are aimed for. is the CHMP noted that most of the included patients were naïve to biologics, which is expected to add to the efficacy-sensitivity of the population.

In summary, the mean PASI score was similar at baseline with 22.52 and 22.07 in the Eksunbi and Stelara Overall treatment groups, respectively.

At Week 2, the mean PASI score was similar between the two treatment groups (Eksunbi: 17.84; Stelara Overall: 17.24).

By Week 4, the mean PASI score had dropped to approximately half the baseline mean values, indicating an improvement in the patients' condition.

At Week 52, all patients still in study underwent final efficacy assessments. The mean PASI score of the Eksunbi and Stelara Overall treatment groups fell to 0.92 and 1.06, respectively; at this timepoint, the percent change from baseline (%CFB) of two treatment groups was 95.82% and 95.05% in the Eksunbi and Stelara Overall treatment groups (95.59% for Stelara+Eksunbi and 94.52% for Stelara+Stelara treatment groups), respectively all for the FAS.

The time-response curve provided with the full CSR is similar between all treatment groups (Eksunbi, Stelara, Eksunbi+Eksunbi, Stelara+Eksunbi, Stelara+Stelara treatment groups), supporting the robustness of the primary efficacy analysis.

As outlined in the discussion on pharmacokinetics, numerically higher exposure values were observed with Eksunbi compared to Stelara, particularly at the Week 8 timepoint.

In the context of immunogenicity findings in Study SB17-3001, at baseline there was a higher incidence of ADA-positive subjects in the Eksunbi treatment group (3.2% (n=8)), compared to the other treatment groups where the incidences were all 0.8%. At week 28, however the Eksunbi treatment group had a lower incidence; 13.7% (n=32/234) compared to Stelara Overall: 26.4% (n=64/242). At week 52, overall, ADA-positivity was lowest in the Eksunbi treatment group: 14.9% (n=37/249) compared to; Stelara Overall: 40.6% (n=103/254), Stelara +Eksunbi: 38.5% (n=47/122), Stelara + Stelara: 42.6% (n=52/122).

To Week 52, a total of 140 (27.8%) patients (37 [14.9%] patients in the Eksunbi, 103 [40.6%] patients in the Stelara, 47 [38.5%] patients in the Stelara+Eksunbi, and 52 [42.6%] patients in the Stelara+Stelara treatment groups) had overall ADA positive results in the overall period. The incidence of ADA and NAbs were noted to be relatively lower in Eksunbi than Stelara by visit and overall status. The titre distribution for ADA tended to be more comparable between treatment groups.

On the basis of the data provided, Eksunbi appears to be less immunogenic than Stelara. In relation to the potential impact of immunogenicity on efficacy, the percent change from baseline in PASI at Week 12 was broadly similar per overall ADA status.

However, while clinical efficacy was considered to be broadly comparable between both treatment groups in the phase III study, it was highlighted that the potential clinical impact of the immunogenicity (i.e. modestly lower ADA formation) of Eksunbi compared with Stelara still required further consideration and should be further discussed by the Applicant.

In particular, the applicant was asked to further discuss the totality of the available efficacy results in patients ADA /nAB negative in the subgroup analyses. The applicant provided the requested analysis of the effect of ADA status on % change in PASI, given that Eksunbi appeared to be less immunogenic than Stelara and in light of the slightly higher exposure to Eksunbi in ADA negative patients (ref: Biosimilar guideline EMEA/CHMP/BMWP/42832/2005 Rev1). The percent change from baseline in PASI at Week 12 was equivalent between the Eksunbi and Stelara treatment groups without ADAs. LSMeans at Week 12 was −2.2 [−6.194, 1.805], which was within the pre-defined equivalence margin of [−15%, 15%]. In addition, the PASI score up to Week 52 are comparable between treatment groups in ADA negative subgroup.

Overall, NAb was defined as positive if there was at least one positive NAb measurement at any time during the period (including baseline). The incidence of overall NAb was lower in the Eksunbi compared to the Stelara treatment groups. The percent change from baseline in PASI at Week 12 was equivalent between the Eksunbi and Stelara treatment groups for the overall NAb negative subgroup in the Per-protocol Set. The adjusted difference in LSMeans at Week 12 was −2.3 and the 95% CI of the adjusted treatment difference was [−6.121, 1.424]. In addition, the PASI score up to Week 52 are comparable between treatment groups in NAb negative subgroup.

In conclusion, the efficacy analyses in patients who were not ADA or NAb positive support the primary efficacy outcome between the Eksunbi and EU Stelara.

Overall, the CHMP concluded that equivalence from the efficacy point of view demonstrated between Eksunbi and Stelara.

2.6.7. Conclusions on clinical efficacy

The study SB17-3001 was adequately powered, included a study population sensitive for detecting potential differences between the biosimilar and the reference product and had relevant endpoints.

Equivalence was demonstrated in both the FAS and PPS, when using different equivalence margins, and when analysing by 90% or 95% CIs.

The CHMP concluded that clinical comparability is demonstrated between Eksunbi and Stelara in the phase III clinical study based on the available data which is supportive of clinical efficacy equivalence across primary and secondary endpoints in psoriasis patients.

On the basis of the data provided, Eksunbi appears to be less immunogenic than Stelara. In relation to the potential impact of immunogenicity on efficacy, the percent change from baseline in PASI at Week 12 was broadly similar per overall ADA status.

In this application, no PK or clinical data was available for the IV administration. The submitted PK data for IV administration of ustekinumab within the submitted responses for Eksunbi was found acceptable. As the evaluation of SC administration covers both absorption and elimination of ustekinumab, it is possible to waive the evaluation of IV administration and allow extrapolation to all indications, as the applicant has satisfactorily demonstrated comparability in both absorption and elimination for the subcutaneous route. In line with requirements outlined in the Guideline on Similar Biological Medicinal Products Containing Monoclonal Antibodies – Non-clinical and Clinical Issues (EMA/CHMP/BMWP/403543/2010) to waive the evaluation of intravenous administration, the similarity to Stelara for the subcutaneous route has been demonstrated separately for both absorption and elimination.

In conclusion, the data provided in relation to the efficacy of Eksunbi compared to Stelara support equivalence between Eksunbi and Stelara and biosimilarity in terms of efficacy is concluded.

2.6.8. Clinical safety

The clinical safety of Eksunbi has been assessed in two clinical studies, a clinical Phase I pharmacokinetic (PK) study in healthy subjects (SB17-1001) and a clinical Phase III efficacy and safety study in patients with moderate to severe plaque PsO (SB17-3001).

Safety of Eksunbi in these studies was assessed as part of the secondary objectives and included adverse events (AEs), serious AEs (SAEs), adverse events special interest (AESI) (e.g., systemic

hypersensitivity, infections, pulmonary events, and injection site reactions), vital signs and laboratory evaluations, as well as immunogenicity.

In this MAA, the applicant initially submitted an interim clinical study report (CSR) for Study SB17-3001, collected up to data cut-off date of Sep 15, 2022, containing a full set of 40-week data and a subset of 52-week data of approximately 103 patients from the Phase III Study SB17-3001. The final CSR with full 52-week data of the Phase III study was submitted at Day 120 List of Questions during the MAA procedure. The study was completed on Dec 08, 2022, and the final CSR is dated 5 April 2023.

While the applicant intends to make Eksunbi available in the same dosage forms, strengths and presentations as approved for Stelara in the EU, in the present MAA, only the 45 mg/0.5 mL and 90 mg/1.0 mL prefilled syringe (PFS) presentations and IV 130mg are applied for.

2.6.8.1. Patient exposure

Study SB17-1001

The Safety Set (SAF) of Study SB17-1001 consisted of all subjects who received investigational product (IP). A total of 201 subjects were randomised to receive a single dose of ustekinumab with 67 subjects in each treatment group (Eksunbi, EU Stelara, or US Stelara).

Study SB17-3001

The recommended posology of ustekinumab in PSO is an initial dose of 45 mg administered subcutaneously, followed by a 45 mg dose, 4 weeks later and then every 12 weeks thereafter in patients < 100kg. In Study SB17-3001, the Main Period involved 3 dosing timepoints (Week 0, Week 4 and Week 16) and 2 dosing timepoints in the Transition Period (Week 28 and 40).

A total of 503 patients were randomised in 1:1 ratio to receive either Eksunbi or Stelara via subcutaneous (SC) injection at Week 0, Week 4 and Week 16, 481 (95.6%) patients completed 28 weeks of the study. (Eksunbi: 249; Stelara Overall: 254) and 466 (96.9%) patients completed 52 weeks of the study.

At Week 28, patients who achieved PASI50 response and were considered eligible, entered into the transition period. A total of 237 patients in the Eksunbi treatment group continued to receive Eksunbi until Week 40. A total of 244 patients in the Stelara treatment group were further randomised into two treatment groups: 122 patients continued Stelara treatment (hereafter referred to as 'Stelara+Stelara treatment group') and 122 patients transitioned to receive Eksunbi (hereafter referred to as 'Stelara+Eksunbi treatment group') until Week 40, the last assessment was done at Week 52.

The completion rate at Week 52 was comparable between the two treatment groups (233 [98.3%] patients in the Eksunbi and 233 [95.5%] patients in the Stelara Overall treatment groups, respectively). From the 244 patients in the Stelara Overall treatment group who entered the transition period, 117 (95.9%) patients from the Stelara+Eksunbi treatment group and 116 (95.1%) patients from the Stelara+Stelara treatment group completed the study.

Patients were analysed according to the IP received. As a result, of the 503 patients randomised, a total of 503 (100.0%) patients were included in the SAF1 and 481 (95.6%) patients were included in the SAF2.

Safety Set 1 (SAF1) consisted of all patients who received at least one IP during the study period. Safety Set 2 (SAF2) consisted of all patients in the SAF1 who received at least one IP after re randomisation at Week 28.

The mean duration of exposure to IP up to Week 28 to Week 52 are balanced between groups. The mean duration of exposure up to Week 52 was 271.8 days (271.7 days in the Eksunbi, 271.9 days in the Stelara Overall, 280.4 days in the Stelara+Eksunbi, and 279.1 days in the Stelara+Stelara treatment groups). The proportion of patients receiving 2 doses of IP (i.e., 90 mg with weight > 100 kg) was low and comparable between the treatment groups.

Demographic characteristics and baseline characteristics

Demographic characteristics and baseline characteristics for both studies are presented further below.

In Study SB17-1001, a slight lower mean value for weight and BMI in the EU Stelara treatment group. Body weight was identified as a statistically different variable between three treatment groups with p-value of 0.0199. In Study SB17-3001, demographic characteristics and baseline disease characteristics were comparable across the treatment groups in the Randomised Set (RAN) with no statistically significant differences.

In Study SB17-1001, the proportion of subjects who had taken prior medications in the Eksunbi were comparable, EU Stelara, and US Stelara treatment groups was 11 (16.4%) subjects, 14 (20.9%) subjects and 18 (26.9%) subjects, respectively.

The most commonly reported prior medication by Preferred Terms (PT) was 'COVID-19 vaccine' (11 [16.4%] subjects in the Eksunbi, 13 [19.4%] subjects in the EU Stelara, and 16 [23.9%] subjects in the US Stelara treatment groups), followed by 'paracetamol' (none in the Eksunbi, 1 [1.5%] subject in the EU Stelara, and 1 [1.5%] subject in the US Stelara treatment groups), and 'etonogestrel' (none in the Eksunbi and the EU Stelara treatment groups, and 1 [1.5%] subject in the US Stelara treatment group). Incidences across groups are comparable and have low numbers therefore no concern for a confounding effect.

Concomitant medications in Study SB17-3001 reported small imbalances in paracetamol, ibuprofen and 'other emollients and protectives' in the overall treatment period. Paracetamol and ibuprofen use was more balanced when reported by period- main and transition period and the difference in emollient use is considered to have minimal impact on safety analysis, 'other emollients and protectives' (Eksunbi:15 [6.0%] patients; Stelara Overall: 6 [2.4%] patients). Prior phototherapy was balanced between groups.

2.6.8.2. Adverse events

Study SB17-1001

A summary of the adverse events in the clinical Phase I study (SB17-1001) is presented in Table 41 below.

The proportion of subjects who experienced TEAEs was similar among the Eksunbi, EU Stelara, and US Stelara treatment groups. A total of 251 TEAEs were reported in 129 (64.2%) subjects.

There were no reported deaths, serious adverse events (SAE), or severe TEAEs during the study. A total of 14 TEAEs related to COVID-19 was reported in 14 (7.0%) subjects: 4 subjects in the Eksunbi, 3 subjects in the EU Stelara, and 7 subjects in the US Stelara treatment group. There were 13 discontinuations (4 [6.0%] subjects in the Eksunbi, 3 [4.5%] subjects in the EU Stelara, 6 [9.0%] subjects in the US Stelara treatment group) due to TEAEs during the study, which were all due to COVID-19 and assessed as not related to the IP by the investigator.

All of TEAEs were mild to moderate in severity and all recovered/resolved during the study, except one case of moderate 'epicondylitis' in the Eksunbi treatment group (not related to the IP) and one case of

mild ‘blood creatinine phosphokinase increased’ in the US Stelara treatment group (not related to the IP).

The Eksunbi group had modestly higher frequencies in overall TEAEs reported in moderate TEAEs compared with the EU and US Stelara treatment groups (31 [46.3%] subjects in the Eksunbi, 25 [37.3%] subjects in the EU Stelara, 15 [22.4%] subjects in the US Stelara treatment group).

Table 41. Summary of adverse events (Safety Set, Study SB17-1001)

Treatment	SB17 N = 67			EU Stelara N = 67			US Stelara N = 67			Total N = 201		
Category	**n**	**%**	**E**	**n**	**%**	**E**	**n**	**%**	**E**	**n**	**%**	**E**
Any AEs	46	68.7	109	39	58.2	80	45	67.2	71	130	64.7	260
Any TEAEs	46	68.7	105	39	58.2	79	44	65.7	67	129	64.2	251
TEAE severity												
Mild	15	22.4	53	14	20.9	39	29	43.3	42	58	28.9	134
Moderate	31	46.3	52	25	37.3	40	15	22.4	25	71	35.3	117
Severe	0	0.0	0	0	0.0	0	0	0.0	0	0	0.0	0
TEAE causality												
Not related	29	43.3	78	24	35.8	58	31	46.3	53	84	41.8	189
Related	17	25.4	27	15	22.4	21	13	19.4	14	45	22.4	62
Any SAEs	0	0.0	0	0	0.0	0	0	0.0	0	0	0.0	0
TEAE	0	0.0	0	0	0.0	0	0	0.0	0	0	0.0	0
Non-TEAE	0	0.0	0	0	0.0	0	0	0.0	0	0	0.0	0
Serious TEAE causality												
Not related	0	0.0	0	0	0.0	0	0	0.0	0	0	0.0	0
Related	0	0.0	0	0	0.0	0	0	0.0	0	0	0.0	0
TEAEs diagnosed/related with COVID-19	4	6.0	4	3	4.5	3	7	10.4	7	14	7.0	14
TEAEs leading to study discontinuation	4	6.0	4	3	4.5	3	6	9.0	6	13	6.5	13
Deaths	0	0.0	0	0	0.0	0	0	0.0	0	0	0.0	0

AE = adverse event; E = frequency of AEs; N = the total number of subjects in the Safety Set; n = number of subjects with event; SAE = serious AE; TEAE = treatment-emergent AE
Percentages were based on the number of subjects in the Safety Set.
If a subject had multiple events with different severity (or causality), then the subject was counted only once at the worst severity (or causality) for the number of subjects (n).
Source: Section 2.7.4, Table 9

TEAEs occurring in ≥ 5% of subjects in any treatment group reported during the study are provided in Table 42. The most frequently reported TEAEs in all treatment groups at PT level were 'headache' and 'nasopharyngitis'.

Table 42. Number (%) of Subjects with Treatment-emergent Adverse Events in >5.0% of Subjects in any Treatment and Number of Events by Preferred Term (Safety Set, Study SB17-1001)

Treatment	SB17 N = 67			EU Stelara N = 67			US Stelara N = 67			Total N = 201		
Preferred Term	**n**	**%**	**E**	**n**	**%**	**E**	**n**	**%**	**E**	**n**	**%**	**E**
Any TEAE	46	68.7	105	39	58.2	79	44	65.7	67	129	64.2	251
Any other TEAEs with incidence > 5% of subjects	35	52.2	53	30	44.8	45	31	46.3	40	96	47.8	138
Nasopharyngitis	8	11.9	9	10	14.9	11	7	10.4	7	25	12.4	27
Gastroenteritis	5	7.5	5	0	0.0	0	1	1.5	1	6	3.0	6
Rhinitis	5	7.5	5	2	3.0	3	3	4.5	3	10	5.0	11
COVID-19	4	6.0	4	3	4.5	3	7	10.4	7	14	7.0	14
Pharyngitis	4	6.0	4	1	1.5	1	1	1.5	1	6	3.0	6
Blood creatine phosphokinase increased	2	3.0	2	0	0.0	0	6	9.0	6	8	4.0	8
Back pain	4	6.0	4	6	9.0	6	3	4.5	3	13	6.5	13
Headache	13	19.4	16	15	22.4	19	8	11.9	11	36	17.9	46
Oropharyngeal pain	4	6.0	4	2	3.0	2	1	1.5	1	7	3.5	7

E = frequency of TEAEs; N = the total number of subjects in the Safety Set; n = number of subjects with event; TEAE = treatment-emergent adverse event
Percentages were based on the number of subjects in the Safety Set.
Source: Section 2.7.4, Table 10

The proportion of subjects who experienced TEAEs considered to be related to the IP were 17 (25.4%) subjects in the Eksunbi group, 15 (22.4%) subjects in the EU sourced Stelara group, and 13 (19.4%) subjects in the US sourced Stelara group.

The most frequently reported TEAEs suspected to be IP related were headache and pharyngitis: For headache, 5 (7.5%) subjects in the Eksunbi group, 4 (6.0%) subjects in the EU sourced Stelara group, and 3 (4.5%) subjects in the US sourced Stelara group. For pharyngitis, 3 (4.5%) subjects in the Eksunbi group, 1 (1.5%) subject in the EU sourced Stelara group, and 1 (1.5%) subject in the US sourced Stelara group. All other TEAEs suspected to be IP related were reported in 2 or less subjects per treatment group.

Three events of injection site reactions were reported in 3 subjects: 1 event of injection site erythema in 1 (1.5%) subject in the Eksunbi group, 1 event of injection site pain in 1 (1.5%) subject in the Eksunbi group, and 1 event of injection site reaction in 1 (1.5%) subject in the US sourced Stelara group. The severity of all injection site reactions was mild or moderate.

Gastrointestinal disorders are reported with a slightly higher incidence in the Eksunbi group 8 (11.9%), 6 (9.0%) subjects in the EU sourced Stelara group, and 3 (4.5%) subjects in the US sourced Stelara group. Related events also are reported as higher, 5 (7.5%) subjects in the Eksunbi group, 2 (3.0%) subjects in the EU sourced Stelara group, and 1 (1.5%) subject in the US sourced Stelara group. Abdominal pain, nausea and vomiting and diarrhoea are comparable between groups. Gastroenteritis is

reported as higher in the Eksunbi group and could attribute to the overall higher number of GI disorders in Eksunbi; all are assessed as not related.

Study SB17-3001

The safety results are presented in 3 separate time periods:

- Overall Period (SAF1)
- Main Period (SAF1), IP administration at Weeks 0, 4, 16
- Transition Period (SAF2), IP administration at Weeks 28, 40.

TEAEs summary

- *Overall Period (SAF1)*

A total of 274 (54.5%) patients (133 [53.4%] patients in the Eksunbi, 141 [55.5%] patients in the Stelara Overall, 64 [52.5%] patients in the Stelara+Eksunbi, and 70 [57.4%] patients in the Stelara+Stelara treatment groups) experienced at least one AE in the overall period, of which 269 (53.5%) patients had 590 TEAEs. The proportion of patients who reported at least one TEAE is comparable across the treatment groups. The majority of the TEAEs were mild or moderate in severity, and the incidences of mild, and severe TEAEs were comparable across the treatment groups. Moderate TEAEs were more frequently observed in the Eksunbi treatment group (94 [18.7%] patients in total: (52 [20.9%] patients in the Eksunbi, 42 [16.5%] patients in the Stelara Overall, 21 [17.2%] patients in the Stelara+Eksunbi, and 20 [16.4%] patients in the Stelara+Stelara treatment groups). Following further examination of the totality of the data, no additional safety concerns were raised by the observed modest increased trend in moderate TEAEs reported. The proportion of TEAEs related to IP and SAEs were similar across the treatment groups. There was no death reported in the study.

An overall summary of all AEs by treatment groups for the Safety Set 1 (SAF1) is provided in Table 43.

Two (0.8%) patients had 2 TEAEs that led to discontinuation of IP in the Stelara Overall treatment group (all from the Stelara+Stelara treatment group) and no TEAE that led to IP discontinuation was reported in the Eksunbi treatment group. At PT level, 1 patient had TEAE of 'hepatic steatosis' and 1 patient had TEAE of 'prostate cancer'.

A total of 13 (2.6%) patients reported 14 SAEs in the overall period: 7 (2.8%) patients in the Eksunbi, 6 (2.4%) patients in the Stelara Overall (2 [1.6%] patients in the Stelara+Eksunbi, and 3 [2.5%] patients in Stelara+Stelara treatment groups). All SAEs were not related to IP.

Table 43. Summary of all adverse events in the overall period (Safety Set 1, Study SB17-3001)

Number of Patients Experiencing	SB17 N = 249			Stelara Overall N = 254			Stelara+SB17[a] N = 122			Stelara+Stelara[a] N = 122			Total N = 503		
	n	%	E	n	%	E	n	%	E	n	%	E	n	%	E
No Adverse Event (AE)	116	46.6		113	44.5		58	47.5		52	42.6		229	45.5	
Any AE	133	53.4	310	141	55.5	305	64	52.5	149	70	57.4	140	274	54.5	615
Treatment Emergent Adverse Event (TEAE)	132	53.0	300	137	53.9	290	62	50.8	143	68	55.7	132	269	53.5	590
TEAE Severity															
Mild	77	30.9	205	93	36.6	222	40	32.8	110	47	38.5	98	170	33.8	427
Moderate	52	20.9	92	42	16.5	66	21	17.2	32	20	16.4	33	94	18.7	158
Severe	3	1.2	3	2	0.8	2	1	0.8	1	1	0.8	1	5	1.0	5
TEAE Causality															
Related	11	4.4	22	15	5.9	25	5	4.1	11	8	6.6	12	26	5.2	47
Not related	121	48.6	278	122	48.0	265	57	46.7	132	60	49.2	120	243	48.3	543
TEAE of special interest	79	31.7	110	83	32.7	131	39	32.0	65	40	32.8	58	162	32.2	241
Systemic hypersensitivity	0	0.0	0	2	0.8	3	1	0.8	2	1	0.8	1	2	0.4	3
Infection	79	31.7	110	82	32.3	126	39	32.0	62	39	32.0	56	161	32.0	236
Pulmonary event	0	0.0	0	0	0.0	0	0	0.0	0	0	0.0	0	0	0.0	0
Injection site reaction	0	0.0	0	2	0.8	2	1	0.8	1	1	0.8	1	2	0.4	2
TEAE leading to discontinuation of IP	0	0.0	0	2	0.8	2	0	0.0	0	2	1.6	2	2	0.4	2
Any serious AE (SAE)	7	2.8	7	6	2.4	7	2	1.6	2	3	2.5	4	13	2.6	14
Serious TEAE Causality	7	2.8	7	6	2.4	7	2	1.6	2	3	2.5	4	13	2.6	14
Related	0	0.0	0	0	0.0	0	0	0.0	0	0	0.0	0	0	0.0	0
Not related	7	2.8	7	6	2.4	7	2	1.6	2	3	2.5	4	13	2.6	14
Serious TEAE leading to IP discontinuation	0	0.0	0	1	0.4	1	0	0.0	0	1	0.8	1	1	0.2	1
TEAE leading to death	0	0.0		0	0.0		0	0.0		0	0.0		0	0.0	
COVID-19 related TEAEs	24	9.6	28	30	11.8	31	12	9.8	12	16	13.1	17	54	10.7	59
TEAE for COVID-19	24	9.6	25	30	11.8	30	12	9.8	12	16	13.1	16	54	10.7	55
TEAE related to COVID-19	2	0.8	3	1	0.4	1	0	0.0	0	1	0.8	1	3	0.6	4
Serious TEAE for COVID-19	0	0.0	0	0	0.0	0	0	0.0	0	0	0.0	0	0	0.0	0
Serious TEAEs related to COVID-19	1	0.4	1	0	0.0	0	0	0.0	0	0	0.0	0	1	0.2	1
TEAEs related to war in Ukraine	2	0.8	4	1	0.4	1	0	0.0	0	1	0.8	1	3	0.6	5

AE = adverse event; COVID-19 = Coronavirus Disease 2019; E = frequency of adverse events; IP = investigational product; MedDRA = Medical Dictionary for Regulatory Activities; n = number of patients with available data within each category; N = number of patients in the Safety Set 1 in each treatment group; SAE = serious adverse event; TEAE = treatment emergent adverse event

[a] Based on patients in the Safety Set 2, Stelara+SB17 and Stelara+Stelara may not add up to Stelara Overall.

Percentages were based on number of patients in the Safety Set 1.

AEs were coded to System Organ Class and Preferred Term using MedDRA coding dictionary version 23.1.

If a patient had multiple events with different severity (or causality), then the patients was counted only once at the worst severity (or causality) for the number of patients (n).

Overall Incidence of TEAEs

- *Overall Period (SAF1)*

The TEAEs with incidence > 5% of patients by SOC and PT in the overall period for the SAF1 are presented in Table 44 below.

At the SOC level, the most frequently occurring TEAEs during the overall period belonged to "gastrointestinal disorders", "infections and infestations", "injury, poisoning and procedural complications", "investigations", "musculoskeletal and connective tissue disorders", "nervous system

disorders", "skin and subcutaneous tissue disorders", and "vascular disorders". All TEAEs with incidence > 5% of patients reported across all groups were in the SOC "infections and infestations" only.

The most frequently occurring TEAEs at the PT level were all from SOC "infections and infestations", which are 'COVID-19' in 47 (9.3%) patients, 'nasopharyngitis' in 46 (9.1%) patients and 'upper respiratory tract infection' in 28 (5.6%) patients. Overall, the incidences and frequency of the majority of the TEAEs by SOC or PT were comparable across the treatment groups.

Table 44. TEAEs with incidence > 5% of patients by SOC or PT in the overall period for the SAF1

System Organ Class	SB17 N = 249			Stelara Overall N = 254			Stelara+SB17[a] N = 122			Stelara+Stelara[a] N = 122			Total N = 503		
Preferred Term	n	%	E	n	%	E	n	%	E	n	%	E	n	%	E
Gastrointestinal disorders	**14**	**5.6**	**20**	**7**	**2.8**	**9**	**5**	**4.1**	**7**	**2**	**1.6**	**2**	**21**	**4.2**	**29**
Infections and infestations	**80**	**32.1**	**111**	**84**	**33.1**	**129**	**40**	**32.8**	**64**	**40**	**32.8**	**58**	**164**	**32.6**	**240**
Nasopharyngitis	23	9.2	26	23	9.1	30	12	9.8	16	10	8.2	12	46	9.1	56
COVID-19	18	7.2	19	29	11.4	29	12	9.8	12	15	12.3	15	47	9.3	48
Upper respiratory tract infection	12	4.8	15	16	6.3	19	8	6.6	10	8	6.6	9	28	5.6	34
Injury, poisoning and procedural complications	**11**	**4.4**	**12**	**12**	**4.7**	**14**	**7**	**5.7**	**7**	**5**	**4.1**	**7**	**23**	**4.6**	**26**
Investigations	**25**	**10.0**	**39**	**25**	**9.8**	**29**	**11**	**9.0**	**14**	**10**	**8.2**	**11**	**50**	**9.9**	**68**
Musculoskeletal and connective tissue disorders	**15**	**6.0**	**20**	**11**	**4.3**	**11**	**7**	**5.7**	**7**	**4**	**3.3**	**4**	**2**	**5.2**	**31**
Nervous system disorders	**12**	**4.8**	**16**	**10**	**3.9**	**11**	**7**	**5.7**	**8**	**3**	**2.5**	**3**	**22**	**4.4**	**27**
Skin and subcutaneous tissue disorders	**13**	**5.2**	**18**	**14**	**5.5**	**16**	**5**	**4.1**	**7**	**9**	**7.4**	**9**	**27**	**5.4**	**34**
Vascular disorders	**13**	**5.2**	**15**	**9**	**3.5**	**9**	**4**	**3.3**	**4**	**5**	**4.1**	**5**	**22**	**4.4**	**24**

AE = adverse event; COVID-19 = Coronavirus Disease 2019; E = frequency of TEAEs; IP = investigational product; MedDRA = Medical Dictionary for Regulatory Activities; n = number of patients with available data within each category; N = total number of patients in Safety Set 1 for each treatment group; TEAE = treatment-emergent adverse event
Percentages were based on the number of patients in the Safety Set 1.
AEs were coded to System Organ Class and Preferred Term using MedDRA, Version 23.1 coding dictionary.
[a] Based on patients in the Safety Set 2 who were re-randomized at Week 28, Stelara+SB17 and Stelara+Stelara may not add up to Stelara Overall.
Source: Section 5.3.5.1 Final CSR, Study SB17-3001, Table 14.3.1-2.3

In the overall period Study SB17-3001, the SOC of "Musculoskeletal and connective tissue disorders" reported slightly greater incidence of moderate TEAEs in the Eksunbi group. The imbalance of TEAEs was driven by unrelated musculoskeletal conditions such as plantar fasciitis, rotator cuff syndrome and synovial cyst, etc and the more common TEAEs were consistent with the known safety profile and mild to moderate in severity.

In the overall period Study SB17-3001, headache was reported at a higher incidence in the Eksunbi group 7 (2.8%) subjects compared to the Stelara+Stelara group 0 (0%) subject. However, the incidence is similar when comparing results from the Main Period, the Eksunbi group 7 (2.8%) subjects compared to the Stelara+Stelara group 6 (2.4%) subjects.

In the overall period Study SB17-3001, the SOC of "Gastrointestinal disorders" reported slightly greater incidence of TEAEs in the Eksunbi group (14 [5.6%] patients in the Eksunbi, 7 [2.8%] patients in the Stelara Overall, 5 [4.1%] patients in the Stelara+Eksunbi, and 2 [1.6%] patients in the Stelara+Stelara treatment groups). The main PTs presented in the below Table 45.

Table 45. Treatment-Emergent Adverse Events by System Organ Class and Preferred Term in Overall Period Safety Set 1

System organ class Preferred term	SB17 N=249 n (%)	E	Stelara Overall N=254 n (%)	E	Stelara+SB17* N=122 n (%)	E	Stelara+Stelara * N=122 n (%)	E	Total N=503 n (%)	E
Gastrointestinal disorders	14 (5.6)	20	7 (2.8)	9	5 (4.1)	7	2 (1.6)	2	21 (4.2)	29
Abdominal pain upper	5 (2.0)	5	0 (0.0)	0	0 (0.0)	0	0 (0.0)	0	5 (1.0)	5
Toothache	2 (0.8)	2	2 (0.8)	2	0 (0.0)	0	2 (1.6)	2	4 (0.8)	4
Vomiting	2 (0.8)	2	0 (0.0)	0	0 (0.0)	0	0 (0.0)	0	2 (0.4)	2
Abdominal pain	1 (0.4)	1	1 (0.4)	2	1 (0.8)	2	0 (0.0)	0	2 (0.4)	3
Cheilitis	1 (0.4)	1	0 (0.0)	0	0 (0.0)	0	0 (0.0)	0	1 (0.2)	1

Overall, the incidences and frequency of the majority of the TEAEs by SOC and PT were comparable apart from SOC GI disturbances across the treatment groups. Following further investigation of the observed imbalances in the SOC GI disturbances across the treatment groups, no apparent trends were discernible, and no safety concerns were raised.

TEAEs summary

- *Main Period (SAF1)*

A total of 250 (49.7%) patients (122 [49.0%] patients in the Eksunbi, and 128 [50.4%] patients in the Stelara treatment groups) experienced at least one AE during the screening and main period, of which 244 (48.5%) patients experienced 463 TEAEs. Most of the AEs were mild to moderate, with very few severe AEs.

The proportion of patients with TEAEs by severity class was comparable for mild, and severe TEAEs. Moderate TEAEs were again more frequently observed in the Eksunbi cohort, the number of events (E) higher also. The proportion of TEAEs related to IP were comparable between the two treatment groups.

One (0.4%) patient in the Stelara treatment group had 1 TEAE that led to discontinuation of IP and no TEAE led to permanent discontinuation in the Eksunbi treatment group. A total of 9 (1.8%) patients reported 9 serious AE (SAEs) in the screening and main period: 6 (2.4%) patients in the Eksunbi, 3 (1.2%) patients in the Stelara treatment groups, and all SAEs were TEAEs. All SAEs were not related to IP.

Overall Incidence of TEAEs

- *Main Period (SAF1)*

The TEAEs with incidence > 5% of patients by SOC and PT in the main period for the SAF1 are presented in Table 46. The proportion of patients with TEAEs with incidence > 5% of patients were comparable between the two treatment groups.

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 are 'nasopharyngitis' in 43 (8.5%) patients (22 [8.8%] patients in the Eksunbi, and 21 [8.3%] patients in the Stelara treatment groups), 'COVID-19' in 39 (7.8%) patients (16 [6.4%] patients in the Eksunbi, and 23 [9.1%] patients in the Stelara treatment groups), and 'upper respiratory tract infection' in 23 (4.6%) patients (10 [4.0%] patients in the Eksunbi, and 13 [5.1%] patients in the Stelara treatment groups) (Table 47).

Overall, the incidences and frequency of the majority of the TEAEs by PT were comparable between two treatment groups.

Table 46. TEAEs with incidence > 5% of patients by SOC and PT in the main period for the SAF1

System Organ Class	SB17 N = 249			Stelara N = 254			Total N = 503		
Preferred Term	**n**	**%**	**E**	**n**	**%**	**E**	**n**	**%**	**E**
Infections and infestations	**71**	**28.5**	**91**	**76**	**29.9**	**104**	**147**	**29.2**	**195**
Nasopharyngitis	22	8.8	24	21	8.3	24	43	8.5	48
COVID-19	16	6.4	16	23	9.1	23	39	7.8	39
Upper respiratory tract infection	10	4.0	12	13	5.1	16	23	4.6	28
Investigations	**21**	**8.4**	**32**	**19**	**7.5**	**20**	**40**	**8.0**	**52**

AE = adverse event; COVID-19 = Coronavirus Disease 2019; E = frequency of TEAEs; IP = investigational product; MedDRA = Medical Dictionary for Regulatory Activities; n = number of patients with available data within each category; N = total number of patients in Safety Set 1 for each treatment group; TEAE = treatment-emergent adverse event
Percentages were based on N in each column.
AEs were coded to System Organ Class and Preferred Term using MedDRA, Version 23.1 coding dictionary.
Source: Section 5.3.5.1 Final CSR, Study SB17-3001, Table 14.3.1-2.1

TEAEs Summary

- *Transition Period (SAF2)*

A total of 85 (17.7%) patients (39 [16.5%] patients in the Eksunbi+Eksunbi, 46 [18.9%] patients in the Stelara Overall, 17 [13.9%] patients in the Stelara+Eksunbi, and 29 [23.8%] patients in the Stelara+Stelara treatment groups) experienced at least one AE in the transition period, and all AEs were TEAEs (85 [17.7%] patients reported 127 TEAEs). The majority of the TEAEs were mild or moderate in severity. The majority of the TEAEs were not IP related, and proportion of TEAEs related to IP were similar across the treatment groups. An overall summary of all AE by treatment groups for the Safety Set 2 (SAF2) is provided in .

One (0.8%) patient had a TEAE which led to discontinuation of IP in the Stelara+Stelara treatment group and no TEAE led to IP discontinuation was reported in the Eksunbi treatment group.

A total of 4 (0.8%) patients reported 5 SAEs in the transition period and all were reported in the Stelara Overall treatment group (1 [0.4%] patient in the Eksunbi+Eksunbi, 3 [1.2%] patients in the Stelara Overall, 1 [0.8%] patients in the Stelara+Eksunbi, 2 [1.6%] patients in Stelara+Stelara treatment groups). All SAEs were not related to IP. There was no death reported in the study.

Table 47. TEAEs Summary in the Transition Period

Number of Patients Experiencing	SB17+SB17 N = 237			Stelara Overall N = 244			Stelara+SB17 N = 122			Stelara+Stelara N = 122			Total N = 481		
	n	%	E	n	%	E	n	%	E	n	%	E	n	%	E
No Adverse Event	198	83.5		198	81.1		105	86.1		93	76.2		396	82.3	
Any Adverse Event (AE)	39	16.5	60	46	18.9	67	17	13.9	23	29	23.8	44	85	17.7	127
Treatment Emergent Adverse Event (TEAE)	39	16.5	60	46	18.9	67	17	13.9	23	29	23.8	44	85	17.7	127
TEAE Severity															
Mild	21	8.9	39	32	13.1	47	12	9.8	17	20	16.4	30	53	11.0	86
Moderate	17	7.2	20	13	5.3	19	5	4.1	6	8	6.6	13	30	6.2	39
Severe	1	0.4	1	1	0.4	1	0	0.0	0	1	0.8	1	2	0.4	2
TEAE Causality															
Related	2	0.8	4	4	1.6	7	0	0.0	0	4	3.3	7	6	1.2	11
Not related	37	15.6	56	42	17.2	60	17	13.9	23	25	20.5	37	79	16.4	116
TEAE of special interest	20	8.4	20	20	8.2	22	9	7.4	9	11	9.0	13	40	8.3	42
Systemic hypersensitivity	0	0.0	0	0	0.0	0	0	0.0	0	0	0.0	0	0	0.0	0
Infection	20	8.4	20	20	8.2	22	9	7.4	9	11	9.0	13	40	8.3	42
Pulmonary event	0	0.0	0	0	0.0	0	0	0.0	0	0	0.0	0	0	0.0	0
Injection site reaction	0	0.0	0	0	0.0	0	0	0.0	0	0	0.0	0	0	0.0	0
TEAE leading to discontinuation of IP	0	0.0	0	1	0.4	1	0	0.0	0	1	0.8	1	1	0.2	1
Any serious AE (SAE)	1	0.4	1	3	1.2	4	1	0.8	1	2	1.6	3	4	0.8	5
Serious TEAE Causality	1	0.4	1	3	1.2	4	1	0.8	1	2	1.6	3	4	0.8	5
Related	0	0.0	0	0	0.0	0	0	0.0	0	0	0.0	0	0	0.0	0
Not related	1	0.4	1	3	1.2	4	1	0.8	1	2	1.6	3	4	0.8	5
Serious TEAE leading to IP discontinuation	0	0.0	0	1	0.4	1	0	0.0	0	1	0.8	1	1	0.2	1
TEAE leading to death	0	0.0		0	0.0		0	0.0		0	0.0		0	0.0	
COVID-19 related TEAEs	4	1.7	4	6	2.5	6	3	2.5	3	3	2.5	3	10	2.1	10
TEAE for COVID-19	4	1.7	4	6	2.5	6	3	2.5	3	3	2.5	3	10	2.1	10
TEAE Related to COVID-19	0	0.0	0	0	0.0	0	0	0.0	0	0	0.0	0	0	0.0	0
Serious TEAE for COVID-19	0	0.0	0	0	0.0	0	0	0.0	0	0	0.0	0	0	0.0	0
Serious TEAEs related to COVID-19	0	0.0	0	0	0.0	0	0	0.0	0	0	0.0	0	0	0.0	0
TEAEs related to war in Ukraine	0	0.0	0	1	0.4	1	0	0.0	0	1	0.8	1	1	0.2	1

AE = adverse event; COVID-19 = Coronavirus Disease 2019; E = frequency of adverse events; IP = investigational product; MedDRA = Medical Dictionary for Regulatory Activities; n = number of subjects with available data within each category; N = number of subjects in the Safety Set 2 in each treatment group; SAE = serious adverse event; TEAE = treatment emergent adverse event
Percentages were based on number of patients in the Safety Set 2.
AEs were coded to System Organ Class and Preferred Term using MedDRA coding dictionary version 23.1.
If a patient had multiple events with different severity (or causality), then the patients was counted only once at the worst severity (or causality) for the number of patients (n).
Source: Section 5.3.5.1 Final CSR, Study SB17-3001, Table 14.3.1-1.2

Overall Incidence of TEAEs

- *Transition Period (SAF2)*

There is no reported TEAEs with incidence of > 5% of patients in transition period.

While not meeting the criteria of 'reported TEAEs with incidence of > 5% of patients', the highest incidence of TEAEs in the Transition Period was in the SOC 'Infections and infestations' with PTs consistent with the SAF1 results.

TEAE of the Patient with Inadvertent IP Switch to Eksunbi

At Week 40, one patient in the Stelara+Stelara treatment group accidentally received Eksunbi instead of Stelara. Approximately 2 weeks after IP administration of Eksunbi at Week 40, the patient reported

one TEAE with SOC of "eye disorders" and PT of 'inflammation of lacrimal passage' which was mild in severity. The TEAE was not related to the IP, did not lead to the discontinuation of IP, and was resolved approximately 2 weeks after the date of onset.

Severe TEAEs

Overall Period

In terms of severity, the majority of the TEAEs were mild or moderate in severity in the overall period.

Out of a total of 590 TEAEs, 427 events in 170 (33.8%) patients (77 [30.9%] patients in the Eksunbi, 93 [36.6%] patients in the Stelara Overall, 40 [32.8%] patients in the Stelara+Eksunbi, and 47 [38.5%] patients in the Stelara+Stelara treatment groups) were mild in severity and 158 events in 94 (18.7%) patients (52 [20.9%] patients in the Eksunbi, 42 [16.5%] patients in the Stelara Overall, 21 [17.2%] patients in the Stelara+Eksunbi, and 20 [16.4%] patients in the Stelara+Stelara treatment groups) were moderate in severity in the overall period.

A total of 5 severe TEAEs were reported in 5 (1.0%) patients (3 [1.2%] patients in the Eksunbi, and 2 [0.8%] in the Stelara Overall treatment groups) in the overall period: 'fibula fracture', 'prerenal failure', and 'ischaemic stroke' in each patient of the Eksunbi treatment group, and 'tibia fracture' and 'prostate cancer' in each patient of the Stelara Overall treatment group (each in the Stelara+Stelara and Stelara+Eksunbi treatment group, respectively). All of the severe adverse events were also SAEs.

No imbalances were observed when looking at the results from the Main and Transition Period separately.

Related TEAEs

Overall Period

In terms of causality, the majority of the TEAEs were not related to IP (543 events were not related out of a total of 590 TEAEs) in the overall period. The number of TEAEs related to the IP were 47 events in 26 (5.2%) patients (11 [4.4%] patients in the Eksunbi, 15 [5.9%] patients in the Stelara Overall, 5 [4.1%] patients in the Stelara+Eksunbi, and 8 [6.6%] patients in the Stelara+Stelara treatment groups). The number of patients with TEAEs not related to the IP was comparable across the treatment groups. At PT level, the most frequently reported IP-related TEAEs were 'alanine aminotransferase increased'; 4 TEAEs in 3 (1.2%) patients in the Eksunbi, 3 TEAEs in 3 (1.2%) patients in the Stelara Overall (none in the Stelara+Eksunbi, and 1 TEAE in 1 [0.8%] patients in the Stelara+Stelara treatment groups), 'leukopenia'; 5 TEAEs in 2 (0.8%) patients in the Eksunbi, 2 TEAEs in 2 (0.8%) patients in the Stelara Overall (1 TEAEs in 1 [0.8%] patients in the Stelara+Eksunbi, and 1 TEAE in 1 [0.8%] patient in the Stelara+Stelara treatment groups) and 'nasopharyngitis'; 1 TEAE in 1 (0.4%) patient in the Eksunbi, 3 TEAEs in 3 (1.2%) patients in the Stelara Overall (2 TEAEs in 2 [1.6%] patients in the Stelara+Eksunbi, and 1 TEAE in 1 [0.8%] patient in the Stelara+Stelara treatment groups)

In general, the safety profile reported in Study SB17-3001 for Eksunbi is comparable to the Stelara treatment groups. The Eksunbi group had modestly higher frequencies in moderate TEAEs compared with the Stelara treatment groups. SOC and PT were comparable apart from SOC GI disturbances, whereby TEAEs were more frequently observed in the Eksunbi cohort. This trend is also mirrored in the Phase 1 SB17-1001 study.

2.6.8.3. Serious adverse events, deaths, and other significant events

Study SB17-1001

Deaths

No deaths occurred during the clinical Phase I study period.

Serious adverse events

No SAE was reported during the clinical Phase I study period.

Adverse events of Special Interest

Data not collected in SB17-1001.

Study SB17-3001

Deaths

No death was reported during the clinical Phase III study period.

Serious adverse events

Serious TEAEs in the Overall Period

The incidence of serious TEAEs (SAEs) by SOC and PT in the overall period for the SAF1 are summarised in Table 48. The incidence of serious TEAEs was comparable across the treatment groups in the overall period. A total of 13 (2.6%) patients (7 [2.8%] patients in the Eksunbi, 6 [2.4%] patients in the Stelara Overall, 2 [1.6%] patients in the Stelara+Eksunbi, and 3 [2.5%] patients in the Stelara+Stelara treatment groups) had 14 SAEs in the overall period. All 14 SAEs reported from 13 patients were not related to IP and recovered/resolved. One patient in the Stelara+Stelara treatment group reported severe SAE of 'prostate cancer', which resulted in permanent discontinuation of IP during the transition period. Last administration of IP was on Mar 04, 2022 (Week 28, Study Day 197), and discontinued from the study on May 27, 2022 (Study Day 281) permanently.

Table 48. TEAEs (SAEs) by SOC and PT in the overall period for the SAF1

System Organ Class	SB17 N = 249			Stelara Overall N = 254			Stelara+SB17[a] N = 122			Stelara+Stelara[a] N = 122			Total N = 503		
Preferred Term	n	%	E	n	%	E	n	%	E	n	%	E	n	%	E
Any Serious TEAE	**7**	**2.8**	**7**	**6**	**2.4**	**7**	**2**	**1.6**	**2**	**3**	**2.5**	**4**	**13**	**2.6**	**14**
Cardiac disorders	**1**	**0.4**	**1**	**1**	**0.4**	**1**	**0**	**0.0**	**0**	**1**	**0.8**	**1**	**2**	**0.4**	**2**
Acute myocardial infarction	1	0.4	1	0	0.0	0	0	0.0	0	0	0.0	0	1	0.2	1
Atrial fibrillation	0	0.0	0	1	0.4	1	0	0.0	0	1	0.8	1	1	0.2	1
Gastrointestinal disorders	**0**	**0.0**	**0**	**1**	**0.4**	**1**	**1**	**0.8**	**1**	**0**	**0.0**	**0**	**1**	**0.2**	**1**
Salivary gland calculus	0	0.0	0	1	0.4	1	1	0.8	1	0	0.0	0	1	0.2	1
Infections and infestations	**0**	**0.0**	**0**	**1**	**0.4**	**1**	**0**	**0.0**	**0**	**0**	**0.0**	**0**	**1**	**0.2**	**1**
Pneumonia	0	0.0	0	1	0.4	1	0	0.0	0	0	0.0	0	1	0.2	1
Injury, poisoning and procedural complications	**3**	**1.2**	**3**	**1**	**0.4**	**1**	**1**	**0.8**	**1**	**0**	**0.0**	**0**	**4**	**0.8**	**4**
Fibula fracture	1	0.4	1	0	0.0	0	0	0.0	0	0	0.0	0	1	0.2	1
Joint dislocation	1	0.4	1	0	0.0	0	0	0.0	0	0	0.0	0	1	0.2	1
Meniscus injury	1	0.4	1	0	0.0	0	0	0.0	0	0	0.0	0	1	0.2	1
Tibia fracture	0	0.0	0	1	0.4	1	1	0.8	1	0	0.0	0	1	0.2	1
Musculoskeletal and connective tissue disorders	**1**	**0.4**	**1**	**0**	**0.0**	**0**	**0**	**0.0**	**0**	**0**	**0.0**	**0**	**1**	**0.2**	**1**
Musculoskeletal chest pain	1	0.4	1	0	0.0	0	0	0.0	0	0	0.0	0	1	0.2	1
Neoplasms benign, malignant and unspecified (incl cysts and polyps)	**0**	**0.0**	**0**	**1**	**0.4**	**1**	**0**	**0.0**	**0**	**1**	**0.8**	**1**	**1**	**0.2**	**1**
Prostate cancer	0	0.0	0	1	0.4	1	0	0.0	0	1	0.8	1	1	0.2	1
Nervous system disorder	**1**	**0.4**	**1**	**0**	**0.0**	**0**	**0**	**0.0**	**0**	**0**	**0.0**	**0**	**1**	**0.2**	**1**
Ischaemic stroke	1	0.4	1	0	0.0	0	0	0.0	0	0	0.0	0	1	0.2	1
Renal and urinary disorders	**1**	**0.4**	**1**	**0**	**0.0**	**0**	**0**	**0.0**	**0**	**0**	**0.0**	**0**	**1**	**0.2**	**1**
Prerenal failure	1	0.4	1	0	0.0	0	0	0.0	0	0	0.0	0	1	0.2	1
Reproductive system and breast disorders	**0**	**0.0**	**0**	**1**	**0.4**	**2**	**0**	**0.0**	**0**	**1**	**0.8**	**2**	**1**	**0.2**	**2**
Ovarian cyst torsion	0	0.0	0	1	0.4	1	0	0.0	0	1	0.8	1	1	0.2	1
Pelvic adhesions	0	0.0	0	1	0.4	1	0	0.0	0	1	0.8	1	1	0.2	1

E = frequency of adverse events; MedDRA = Medical Dictionary for Regulatory Activities; n = number of patients with available data within each category; N = number of patients in the Safety Set 1 in each treatment group; TEAE = treatment emergent adverse event
[a] Based on patients in the Safety Set 2, Stelara+SB17 and Stelara+Stelara may not add up to Stelara Overall.
Percentages were based on number of patients in the Safety Set 1.
AEs were coded to System Organ Class and Preferred Term using MedDRA coding dictionary version 23.1.
Source: Section 5.3.5.1 Final CSR, Study SB17-3001, Table 12-7

No imbalances were observed when looking at the results from the Main and Transition Period separately.

Adverse events of Special Interest

Adverse events of special interest (AESI) were collected using 4 different categories ('hypersensitivity', 'infections', 'pulmonary events', 'injection site reaction') which were pre-defined in the study protocol.

The proportion of patients with any AESI were comparable across the treatment groups for the SAF1 in the overall period (Table 49).

A total of 162 (32.2%) patients experienced at least one AESI in the overall period, and the proportion of patients were comparable across the treatment groups: 79 (31.7%) patients in the Eksunbi, 83 (32.7%) patients in the Stelara, 39 (32.0%) patients in the Stelara+Eksunbi, and 40 (32.8%) patients in the Stelara+Stelara treatment groups.

- 'Systemic hypersensitivity': 2 (0.8%) patients reported 3 events (2 events of abdominal pain in 1 patient, and 1 event of dermatitis allergic in 1 patient) in the Stelara treatment group during the main period only. None was reported in the Eksunbi treatment group. The patient who reported 'abdominal pain' was ADA positive at Week 8 and 12. The patient with 'dermatitis allergic' was ADA negative up to Week 40. No serious hypersensitivity such as anaphylactic shock was reported up to date.
- 'Infections': 79 (31.7%) patients in the Eksunbi, 82 (32.3%) patients in the Stelara treatment group in the overall period (39 [32.0%] patients both in Stelara+Eksunbi and Stelara+Stelara treatment groups). In the main period, 70 (28.1%) patients in the Eksunbi, and 75 (29.5%) patients in the Stelara treatment groups had AESI of 'infections'. In the transition period, 20 (8.4%) patients in the Eksunbi+Eksunbi, 9 (7.4%) patents in the Stelara+Eksunbi, and 11 (9.0%) patients in the Stelara+Stelara treatment groups had AESI of 'infections'.
    - As AESIs were reported per the Investigator's judgment, TEAEs that belong to the SOC infections and infestations were 71 (28.5%) patients in the Eksunbi treatment group, and 76 (29.9%) patients in the Stelara treatment group in the main period, and 20 (8.4%) patients for in the Eksunbi+Eksunbi, 12 (9.8%) patients in the Stelara+Eksunbi, and 11 (9.0%) patients in the Stelara+Stelara treatment group in the transition period.
- 'Injection site reactions': A total of 2 (0.8%) patients in the Stelara treatment group had 2 events (1 event of injection site erythema and injection site pain each) and none was reported in the Eksunbi treatment group in the main period. There were no injection site reactions reported in the transition period.
- 'Pulmonary events': no event was reported during the study.

Table 49. TEAEs of Special Interest by SOC and PT in the overall period for the SAF1

	SB17 N = 249			Stelara Overall N = 254			Stelara+SB17[a] N = 122			Stelara+Stelara[a] N = 122			Total N = 503		
AESI Category	**n**	**%**	**E**	**n**	**%**	**E**	**n**	**%**	**E**	**n**	**%**	**E**	**n**	**%**	**E**
Any TEAE of special interest	**79**	**31.7**	**110**	**83**	**32.7**	**131**	**39**	**32.0**	**65**	**40**	**32.8**	**58**	**162**	**32.2**	**241**
Systemic hypersensitivity	**0**	**0.0**	**0**	**2**	**0.8**	**3**	**1**	**0.8**	**2**	**1**	**0.8**	**1**	**2**	**0.4**	**3**
Gastrointestinal disorders	0	0.0	0	1	0.4	2	1	0.8	2	0	0.0	0	1	0.2	2
Skin and subcutaneous tissue disorders	**0**	**0.0**	**0**	**1**	**0.4**	**1**	**0**	**0.0**	**0**	**1**	**0.8**	**1**	**1**	**0.2**	**1**
Infections	**79**	**31.7**	**110**	**82**	**32.3**	**126**	**39**	**32.0**	**62**	**39**	**32.0**	**56**	**161**	**32.0**	**236**
Infections and infestations	79	31.7	109	82	32.3	124	39	32.0	61	39	32.0	56	161	32.0	233
Injury, poisoning and procedural complications	0	0.0	0	1	0.4	1	1	0.8	1	0	0.0	0	1	0.2	1
Musculoskeletal and connective tissue disorders	1	0.4	1	0	0.0	0	0	0.0	0	0	0.0	0	1	0.2	1
Respiratory, thoracic and mediastinal disorders	0	0.0	0	1	0.4	1	0	0.0	0	0	0.0	0	1	0.2	1
Injection site reactions	**0**	**0.0**	**0**	**2**	**0.8**	**2**	**1**	**0.8**	**1**	**1**	**0.8**	**1**	**2**	**0.4**	**2**
General disorders and administration site conditions	0	0.0	0	2	0.8	2	1	0.8	1	1	0.8	1	2	0.4	2
Pulmonary events	**0**	**0.0**	**0**	**0**	**0.0**	**0**	**0**	**0.0**	**0**	**0**	**0.0**	**0**	**0**	**0.0**	**0**

AESI = adverse events of special interest; COVID-19 = Coronavirus Disease 2019; E = frequency of adverse events; MedDRA = Medical Dictionary for Regulatory Activities; n = number of patients with available data within each category; N = number of patients in the Safety Set 1 in each treatment group; TEAE = treatment emergent adverse event
[a] Based on patients in the Safety Set 2, Stelara+SB17 and Stelara+Stelara may not add up to Stelara Overall.
Percentages were based on number of patients in the Safety Set 1.
AEs were coded to System Organ Class and Preferred Term using MedDRA coding dictionary version 23.1.
Source: Section 5.3.5.1 Final CSR, Study SB17-3001, Table 14.3.1-8.3

2.6.8.4. Laboratory findings

In Study SB17-1001, apart from 10 cases of clinically significant abnormalities in chemistry parameters in 10 subjects, there were no out-of-range values identified by the Investigator as clinically significant in laboratory data, vital signs, and electrocardiogram (ECG) parameters.

Individual clinically significant abnormalities in relation to the chemistry parameters, reported 3 subjects from the Eksunbi cohort and the remainder (n=7) from the US Stelara cohort (all increased CPK values and one abnormal urinalysis). Of the TEAEs reported for the Eksunbi cohort, 2 were increases from baseline in CPK, assessed as unrelated; and 1 an increase from baseline in ALT, assessed as related to the study drug. All TEAEs in the Eksunbi cohort were reported as resolved with no study drug discontinuation.

In Study SB17-3001, there were no notable differences values of vital signs, ECG results or physical examination between the Eksunbi and Stelara treatment groups. There were no notable differences in haematology or chemistry parameters observed between the Eksunbi and Stelara treatment groups, in either the main or in the transition period.

In relation to haematology, only neutrophil abnormalities were reported, which were comparable between treatment groups. Up to Week 52, clinically significant low neutrophil counts were reported in 1 (0.4%) subject in the Eksunbi treatment group vs 2 (0.8%) subjects in the Stelara Overall treatment group. The haematology shift patterns were comparable between the treatment groups, up to Week 28 and Week 52.

In relation to biochemistry, the incidences of clinically significant abnormalities were low, ranging from 0% to 2.0%, and were comparable between treatment groups. Slight decreases from baseline in CRP were observed over time; however, there was no noticeable difference across treatment groups up to

Week 52. The chemistry shift patterns were comparable between the treatment groups, up to Week 52.

2.6.8.5. In vitro biomarker test for patient selection for safety

Not applicable

2.6.8.6. Safety in special populations

Not applicable

2.6.8.7. Immunological events

In Study SB17-1001, sampling schedules were designed for detection of an immune response considering ustekinumab's median half-life (approximately 3 weeks) and drug tolerance. Investigation of immunogenicity was integrated with PK and safety. Accordingly, blood samples were collected for determination of ADAs and NAbs to ustekinumab at Day 1 (pre-dose), Day 29, Day 71 and Day 99/End of Study (EOS). Thus, any differences in immunogenicity should be further investigated with its correlation with safety and PK.

In Study SB17-3001, sampling schedules were designed to distinguish patients being transiently positive from patients developing a persistent antibody response. Given the ADA development, drug tolerance and ustekinumab's median half-life (approximately 3 weeks) in patients with PsO, blood samples for immunogenicity assessment were collected prior to IP administration and at the day of IP administration (Week 0, 4, 16, 28, and 40). To assess the impact of immunogenicity on safety, PK, and efficacy, immunogenicity sampling was performed before administration of the drug during the treatment period and incorporated into the PK schedule concomitantly. In addition, blood samples for immunogenicity assessment at Week 8, 12, and 52/early termination (ET) visit was also collected at any time during the period when the patient was staying at investigational sites.

Study SB17-1001

Immunogenicity results

Subjects were classified as positive for ADA to ustekinumab through titration. The overall incidence of subjects with positive post-dose ADA to ustekinumab across timepoints was numerically lower in the Eksunbi treatment groups compared to that in the EU or US Stelara treatment group but were generally comparable, 18 (26.9%), 23 (34.3%), and 23 (34.3%) subjects in the Eksunbi, EU Stelara, and US Stelara treatment groups, respectively.

Table 50. Incidence of subjects with positive post-dose ADA to Ustekinumab and Neutralising Antibodies NAb by Visit and Treatment Group (Safety Set)

Parameter		SB17 N=67		EU Sourced Stelara N=67		US Sourced Stelara N=67		Total N=201	
Timepoint	**Assessment**	**n/n'**	**(%)**	**n/n'**	**(%)**	**n/n'**	**(%)**	**n/n'**	**(%)**
ADA									
Day 1 pre-dose (Baseline)	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	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									
Day 1 pre-dose (Baseline)	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)

- 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.
- NAb results were summarised only for subjects with ADA positive.
- Percentages were based on n'.

The incidence of subjects with ADA at each timepoint was lower in the Eksunbi treatment group compared to that in the EU or US Stelara treatment group, except at Day 29. Overall, there was no significant difference in the incidence of post-dose ADA between Eksunbi and EU Stelara (p-value = 0.4536), Eksunbi and US Stelara (p-value = 0.4536), and EU Stelara and US Stelara (p-value = 1.0000).

The incidence of subjects with NAb at each timepoint was lower in the Eksunbi treatment group compared to that in the EU or US Stelara treatment group, except at Day 29. The incidence of subject with NAb at Day 99 was 5/14 (35.7%), 12/19 (63.2%), and 11/19 (57.9%) in the Eksunbi, EU Stelara, and US Stelara treatment groups, respectively.

Safety

Post-dose ADA Results and Safety

Among subjects with positive post-dose ADA results (18, 23, and 23 subjects in the Eksunbi, EU Stelara, and US Stelara treatment groups, respectively), 10 (55.6%) subjects, 13 (56.5%) subjects and 13 (56.5%) subjects had at least one TEAE, respectively. Among subjects with negative post-dose ADA results (49, 44, and 44 subjects in the Eksunbi, EU Stelara, and US Stelara groups, respectively), 36 (73.5%) subjects, 26 (59.1%) subjects, and 31 (70.5%) subjects had at least one TEAE, respectively. Incidence of any TEAEs was comparable among three treatment groups by ADA positive subgroup and ADA negative subgroup, low subject numbers were taken into consideration during the interpretation of data.

Study SB17-3001

Immunogenicity results

The incidence of ADA and NAb tended to be lower in Eksunbi than Stelara by visit and overall status. Overall, positive ADA up to Week 28 was 13.3% for Eksunbi and 39.4% for Stelara Overall, and positive ADA up to Week 52 was 16.5% for Eksunbi and 41.3% for Stelara Overall (39.3% for Stelara+Eksunbi and 43.4% for Stelara+Stelara). The titre distribution for ADA tended to be more comparable between treatment groups.

The overall inconclusive ADA up to Week 28 was low, 2.4% for Eksunbi, 0.4% for Stelara Overall treatment group (0.8% for Stelara+Eksunbi and 0.0% for Stelara+Stelara); up to Week 52, 2.0% for Eksunbi, 0.4% for Stelara Overall treatment group (0.8% for Stelara+Eksunbi and 0.0% for Stelara+Stelara).

Table 51. Incidence of subjects with positive post-dose ADA to Ustekinumab and Neutralising Antibodies NAb by Visit and Treatment Group (Safety Set)

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)

ADA: Anti-drug antibody (positive); NAb: Neutralising antibody (positive); N: Total number of subjects in the Safety Set 1 in each treatment group; n: Number of subjects with available data within each category. n': Number of subjects with available assessment results at each visit

Percentages were based on n'.

[a] Based on subjects in the Safety Set 2, Stelara+SB17 and Stelara+Stelara may not add up to Stelara Overall.

Source: Table 14.3-4.1, Table 14.3-4.3, and Table 14.3-4.4.

In Study SB17-3001, difference was observed in the incidence of the overall ADA positive results up to Week 52 (16.5% vs 41.3%) and NAbs per visit between the Eksunbi and the Stelara treatment groups. The incidence of ADAs in ustekinumab pivotal studies (PHOENIX I and II) was relatively lower (5.1% and 5.4%, respectively) compared to that of the Stelara treatment group in Study SB17-3001. However, different assay method was applied in pivotal studies of ustekinumab (PHOENIX I and II; ELISA), while ECL was applied to detect anti-drug antibodies to ustekinumab in Study SB17-3001.

The incidence of NAb tended to be lower in the Eksunbi than Stelara Overall treatment group by visit. At Week 28, the incidence of NAb was 75.0% for the SAF1 in both treatment groups. At Week 52, the incidence of NAb was 50.0% in the Eksunbi treatment group and 70.5% in the Stelara Overall treatment group for the SAF1 (64.7% in the Stelara+Eksunbi and 74.1% in the Stelara+Stelara treatment groups for the SAF2).

The incidence of ADA occurring after transition was comparable between treatment groups (overall positive ADA from Week 28 to 52; 5.6% for Eksunbi+Eksunbi, 5.1% for Stelara+Eksunbi and 6.7% for Stelara+Stelara).

Table 52. Incidence of overall ADA to Ustekinumab for Transition Period by Treatment Group (Safety Set 2)

Timepoint	Assessment	SB17+SB17 N = 237 n/n' (%)	Stelara Overall N = 244 n/n' (%)	Stelara+SB17 N = 122 n/n' (%)	Stelara+Stelara N = 122 n/n' (%)	Total N = 481 n/n' (%)
After transition overall (Week 28 to Week 52)	Positive	13/234 (5.6)	14/237 (5.9)	6/118 (5.1)	8/119 (6.7)	27/471 (5.7)
	Negative	191/234 (81.6)	137/237 (57.8)	71/118 (60.2)	66/119 (55.5)	328/471 (69.6)
	Inconclusive	30/234 (12.8)	86/237 (36.3)	41/118 (34.7)	45/119 (37.8)	116/471 (24.6)

N = Total number of patients in the Safety Set 2 in each treatment group; n = Number of patients with available data within each category; n′ = number of patients with available assessment results at each visit
Percentages were based on n′.
Baseline is Overall ADA up to Week 28 and baseline ADA titer is maximum ADA titer up to Week 28.
Source: Section 5.3.5.1 Final CSR, Study SB17-3001, Table 14.3-4.4

The incidence of ADAs tended to be lower in the Eksunbi than the Stelara treatment group by visit and overall status.

Safety

TEAEs by Overall ADA Result Up to Week 52 in the Overall Period (SAF1)

A total of 76 (52.1%) patients with overall ADA positive status had any TEAE. The proportion of patients with any TEAE in the overall ADA positive subgroup were comparable across the treatment groups (23 [56.1%] patients in the Eksunbi, 53 [50.5%] patients in the Stelara Overall, 22 [45.8%] patients in the Stelara+Eksunbi, and 27 [50.9%] patients in the Stelara+Stelara treatment groups).

A total of 189 (53.8%) patients with overall ADA negative status had any TEAE. The proportion of patients with any TEAE in the overall ADA negative subgroup was comparable across the treatment groups (106 [52.2%] in the Eksunbi, 83 [56.1%] patients in the Stelara Overall, 39 [53.4%] patients in the Stelara+Eksunbi, and 41 [59.4%] patients in the Stelara+Stelara treatment groups). Overall, the frequency of TEAEs by SOC and PT were generally consistent between treatment groups within each ADA subgroup, interpreting the data based on the lower number in the Eksunbi group compared to the Stelara groups.

There was no clear association between ADA and systemic hypersensitivity or injection site reaction. For the AESI category of systemic hypersensitivity, there were 3 events from 2 (0.8%) subjects in the Stelara treatment group (2 events of abdominal pain in 1 subject and 1 event of dermatitis allergic in 1 subject) which all occurred in the main period, while there were no events from the Eksunbi treatment group. The abdominal pain subject was ADA positive at Week 8 and Week 12; the dermatitis allergic subject was ADA negative up to Week 40. No serious hypersensitivity such as anaphylactic shock was reported during the study.

For the AESI category of injection site reactions, there were 2 (0.8%) subjects in the Stelara treatment group (1 event of injection site erythema and injection site pain each) and none in the Eksunbi treatment group during the main period. All two subjects were ADA negative up to Week 40. There were no injection site reactions reported in the transition period.

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

Not applicable

2.6.8.9. Discontinuation due to adverse events

Study SB17-1001

A total of 13 (6.5%) subjects discontinued study due to TEAEs. The 13 significant AEs, all COVID-19 infections, were reported for 4 subjects in the Eksunbi treatment group (2 mild and 2 moderate, in severity), 3 subjects in the EU Stelara treatment group (1 mild and 2 moderate, in severity) and 6 subjects in the US Stelara treatment group (5 mild and 1 moderate in severity). None were reported to be related to the IP by the Investigator. The subjects were discontinued from the study in accordance with the protocol. In the US Stelara treatment group, one subject discontinued the study by consent withdrawal which was not related to COVID-19, and later reported COVID-19 (mild in severity); 69 days after withdrawal of consent.

Study SB17-3001

In the overall period, 2 (0.8%) patients in the Stelara Overall treatment group (all in the Stelara+Stelara treatment group) had TEAEs that led to discontinuation of IP. At PT level, 1 patient had TEAE of 'hepatic steatosis' and 1 patient had TEAE of 'prostate cancer' that led to discontinuation of IP in the overall period.

All of the events were judged as not treatment-related.

2.6.8.10. Post marketing experience

Not applicable since the product not yet been approved for marketing in any country.

2.6.9. Discussion on clinical safety

Eksunbi is a proposed biosimilar to Stelara, which has a well-characterised safety profile, based on a decade of clinical use. The clinical safety of Eksunbi has been assessed in two clinical studies, a clinical Phase I pharmacokinetic (PK) study in healthy subjects (SB17-1001) and a clinical Phase III efficacy and safety study in patients with moderate to severe plaque PsO (SB17-3001). A pooled safety analysis of two studies has not been provided due to heterogeneity of the studies, which is acceptable to the CHMP.

For the pivotal Phase III study, the applicant initially submitted an interim clinical study report (CSR) for Study SB17-3001, collected up to data cut-off date of September 15th, 2022, containing a full set of 40-week data and a subset of 52-week data of approximately 103 patients.

The final CSR with full 52-week data of the Phase III study was subsequently submitted during the procedure. The study was completed on Dec 08, 2022, and the final CSR is dated April 5th, 2023. In general, the final CSR data is consistent with that already presented in the interim report. Overall, the safety profile remains unchanged and is comparable to the reference Stelara.

Patient Exposure

The Safety Set (SAF) of Study SB17-1001 consisted of all subjects who received investigational product (IP). A total of 201 subjects were randomised to receive a single dose of ustekinumab with 67 subjects in each treatment group (Eksunbi, EU Stelara, or US Stelara).

In Study SB17-3001, a total of 503 patients were randomised in 1:1 ratio to receive either Eksunbi or Stelara via subcutaneous (SC) injection at Week 0, Week 4 and Week 16, 481 (95.6%) patients completed 28 weeks of the study. (Eksunbi: 249; Stelara Overall: 254) and 466 (96.9%) patients completed 52 weeks of the study.

Patients were analysed according to the IP received. As a result, of the 503 patients randomised, a total of 503 (100.0%) patients were included in the SAF1 and 481 (95.6%) patients were included in the SAF2. The number of IP doses administered and the duration of exposure to the IP, including the mean duration of exposure up to Week 28 (193.5 days) and to Week 52 (271.8 days) were comparable across the treatment groups.

Safety Set 1 (SAF1) consisted of all patients who received at least one IP during the study period. Safety Set 2 (SAF2) consisted of all patients in the SAF1 who received at least one IP after re randomisation at Week 28.

Demographic and baseline characteristics

In Study SB17-1001, the demographic and baseline characteristics were generally balanced. A slight lower mean value for weight and BMI in the EU Stelara treatment group. Body weight was identified as a statistically different variable between three treatment groups with p-value of 0.0199. In Study SB17-3001, demographic characteristics and baseline disease characteristics were comparable across the treatment groups in the Randomised Set (RAN) with no statistically significant differences.

The mean duration of exposure in Study SB17-3001, to IP up to Week 28 and to Week 52 are balanced between groups. The proportion of patients receiving 2 doses of IP (i.e., 90 mg with weight > 100 kg) was low and comparable between the treatment groups.

A total of 12 subjects (8 [3.2%] from Eksunbi and 4 [1.6%] from Stelara Overall treatment group, 3 subjects from Stelara+Eksunbi and 1 subject from Stelara+Stelara) that gained weight over 100 kg at least 1 time up to Week 52, comparable between the treatment groups and 2.4% of the study population.

Adverse events SB17-1001

In Study SB17-1001 healthy volunteers, after single dose, overall, the percentage of subjects that experienced TEAEs was slightly higher in the Eksunbi group (68,7%, n=46) compared to the EU Stelara (58,2%, n=39) and US Stelara (64.2%, n=44) treatment groups. A total of 251 TEAEs were reported in 129 (64.2%) subjects.

All TEAEs were mild to moderate in severity and all recovered/resolved during the study, except one case of moderate ‘epicondylitis’ in the Eksunbi treatment group (not related to the IP) and one case of mild ‘blood creatinine phosphokinase increased’ in the US Stelara treatment group (not related to the IP). There was a higher frequency of moderate TEAEs reported in the Eksunbi cohort compared to both Stelara cohorts (% mild/moderate TEAEs respectively 22.4/46.3% in the Eksunbi, 20.9/37.3% EU-Stelara, and 43.3/22.4% US-Stelara cohort,).

The Eksunbi group had modestly higher frequencies in overall TEAEs reported in moderate TEAEs compared with the EU and US Stelara treatment groups (31 [46.3%] subjects in the Eksunbi, 25 [37.3%] subjects in the EU Stelara, 15 [22.4%] subjects in the US Stelara treatment group), including slightly more TEAEs subsequently considered related to IP by the investigator: Eksunbi; 25.4% (n=17), EU Stelara; 22.4% (n=15) and US Stelara: 19.4% (n=13). Low sample size does not allow for further interpretation of the trend.

The most frequently reported TEAEs in all treatment groups at PT level were ‘headache’ and ‘nasopharyngitis’, with comparable incidence across cohorts; Eksunbi: nasopharyngitis 11.9%, (n=8), headache 19.4% (n=13), EU Stelara: nasopharyngitis 14.9% (n=10)/ headache 22.4% (n=15) and US Stelara: nasopharyngitis 10.4% (n=7)/ headache 11.9% (n=8). This is consistent with the known safety profile of Stelara.

The proportion of subjects who experienced TEAEs considered to be related to the IP by the Investigator were comparable across the three treatment groups. The most frequently reported TEAEs suspected to be IP-related were 'headache' and 'pharyngitis'; both are known ADRs.

Gastrointestinal disorders are reported with a slightly higher incidence in the Eksunbi group 8 (11.9%), 6 (9.0%) subjects in the EU sourced Stelara group, and 3 (4.5%) subjects in the US sourced Stelara group. No conclusions can be drawn due to the low numbers in each cohort. A summary table of the SOC GI disorders, PTs and causality, for Study SB17-1001 was requested and together with data reported from Study SB17-3001, no specific trend or pattern of clinical relevance can be identified from the observed imbalances in the SOC GI disturbances across the treatment groups, and no safety concerns were raised.

There were 13 discontinuations due to TEAEs during the study, which were all due to COVID-19 and assessed as not related to the IP by the investigator.

In general, the safety profile reported in Study SB17-1001 for Eksunbi is comparable to the EU and US Stelara treatment groups. The Eksunbi group had modestly higher frequencies in overall TEAEs reported and moderate TEAEs compared with the EU and US Stelara treatment groups. SOC and PT were comparable apart from SOC GI disturbances, which were more frequently observed in the Eksunbi cohort, small sample size makes it difficult to interpret this data. The applicant discussed the imbalances observed in the Eksunbi cohort in frequency of moderate TEAEs and the PTs relating to SOC GI disturbances, inclusive of the final CSR data. No specific trend or pattern of clinical relevance can be identified from the observed imbalances, and no safety concerns are raised on review of the complete data set.

All cohorts had comparable frequencies in terms of related TEAEs, severe and serious TEAEs. There were no reported deaths, serious adverse event (SAE), or severe TEAE during the study. Overall, the comparative trends presented in Study SB17-1001 require further exploration in a Phase III study and the safety profile is consistent with the known safety profile of Stelara.

Modest differences in frequency of moderate TEAEs and SOC GI disturbances across groups in Study SB17-1001 are discussed further below, together with final results from Study SB17-3001.

Adverse events Study – SB17-3001

In Study SB17-3001, the safety results are presented in 3 separate time periods for SB17-3001, the Overall Period (SAF1 n=503), the Main Period (SAF1 n=503), IP administration at Weeks 0, 4, 16 and the Transition Period (SAF2 n=481), IP administration at Weeks 28, 40 with follow-up until Week 52.

In the Overall Period (SAF1), a total of 274 (54.5%) patients (133 [53.4%] patients in the Eksunbi, 141 [55.5%] patients in the Stelara Overall, 64 [52.5%] patients in the Stelara+Eksunbi, and 70 [57.4%] patients in the Stelara+Stelara treatment groups) experienced at least one AE. The proportion of patients who reported at least one TEAE is comparable across the treatment groups.

The majority of the TEAEs were mild or moderate in severity, and the incidences of mild, and severe TEAEs were comparable across the treatment groups. Moderate TEAEs were more frequently observed in the Eksunbi cohort 94 (18.7%) patients total (52 [20.9%] patients in the Eksunbi, 42 [16.5%] patients in the Stelara Overall, 21 [17.2%] patients in the Stelara+Eksunbi, and 20 [16.4%] patients in the Stelara+Stelara treatment groups). The proportion of TEAEs related to IP and SAEs, were similar across the treatment groups. There was no death reported in the study.

In general, the incidences and frequency of the majority of the TEAEs by SOC and PT were comparable across the treatment groups in the Overall period.

At the SOC level, the most frequently occurring TEAEs during the overall period belonged to "gastrointestinal disorders", "infections and infestations", "injury, poisoning and procedural complications", "investigations", "musculoskeletal and connective tissue disorders", "nervous system disorders", "skin and subcutaneous tissue disorders", and "vascular disorders". All TEAEs with incidence > 5% of patients reported across all groups were in the SOC "infections and infestations" only.

The most frequently occurring TEAEs at the PT level were all from SOC "infections and infestations", which are 'COVID-19' in 47 (9.3%) patients, 'nasopharyngitis' in 46 (9.1%) patients and 'upper respiratory tract infection' in 28 (5.6%) patients. This is consistent with the known safety profile of Stelara. Overall, the incidences and frequency of the majority of the TEAEs by SOC or PT were comparable across the treatment groups.

During the Main period, a total of 250 (49.7%) patients (122 [49.0%] patients in the Eksunbi, and 128 [50.4%] patients in the Stelara treatment groups) experienced at least one AE, of which 244 (48.5%) patients experienced 463 TEAEs. Most of the AEs were mild to moderate, with very few severe AEs.

In the transition period, a total of 85 (17.7%) patients (39 [16.5%] patients in the Eksunbi+Eksunbi, 46 [18.9%] patients in the Stelara Overall, 17 [13.9%] patients in the Stelara+Eksunbi, and 29 [23.8%] patients in the Stelara+Stelara treatment groups) experienced at least one AE in the transition period, and all AEs were TEAEs (85 [17.7%] patients reported 127 TEAEs).

In the overall period, a total of 5 severe TEAEs were reported in 5 (1.0%) patients (3 [1.2%] patients in the Eksunbi, and 2 [0.8%] in the Stelara Overall treatment groups) in the overall period: 'fibula fracture', 'prerenal failure', and 'ischaemic stroke' in each patient of the Eksunbi treatment group, and 'tibia fracture' and 'prostate cancer' in each patient of the Stelara Overall treatment group (each in the Stelara+Stelara and Stelara+Eksunbi treatment group, respectively).

In the overall period, the number of patients with TEAEs related to the IP was comparable between the treatment groups. At PT level, the most frequently reported IP-related TEAEs were 'alanine aminotransferase increased'; 'leukopenia'; and 'nasopharyngitis'; with frequency balanced across treatment groups.

The incidence of serious TEAEs was comparable across the treatment groups in the overall period. All 14 SAEs reported from 13 patients were not related to IP and recovering/resolving or recovered/resolved.

The safety trends reported in the overall period were consistent with those seen in the main period and transition periods.

In general, the safety profile reported in Study SB17-3001 for Eksunbi is comparable to the Stelara treatment groups. Further discussion and presentation of the final data from Study SB17-3001 has supported any imbalances noted, see below.

Modestly higher frequencies in moderate TEAEs were noted in the Eksunbi group, compared with the Stelara treatment groups. In addition, SOC and PT were comparable apart from SOC GI disturbances, whereby TEAEs were more frequently observed in the Eksunbi cohort. The higher trends are modest and small sample size in the subgroups may contribute to the observed imbalance, however given that the trend was also mirrored in the Phase 1 SB17-1001 study, the applicant was requested to further discuss, inclusive of up-to-date data from the SB17-3001 final report.

The applicant provided further discussion regarding the modest higher trend of moderate TEAEs observed in the Eksunbi cohort compared to the Stelara cohorts in both Phase 1 and 3 studies, including contextualisation to final data submitted. No differences in baseline characteristics or medical history provided a plausible explanation. The applicant provided a thorough discussion of the SOC's

where the percentages were higher in Eksunbi for the main and transition period, including case evaluations. When evaluated by PT, numbers were small, and no trend could be discerned in terms of relatedness. Overall, no clinically meaningful explanation can be deducted, and the issue was not further pursued by the CHMP.

The applicant also provided further discussion, inclusive of final data from SB17-3001, in relation to the observed slight imbalance in SOC "GI disorders" between Eksunbi and Stelara observed in both Study SB17-1001 and Study SB17-3001.

In Study SB17-1001, all events were mild to moderate in severity, recovered/resolved and the majority of events were short in duration. All the differences in each PT between the Eksunbi and EU/US treatment groups did not exceed 2:0. No trend noted of predisposing medical histories in the SOC "GI disorders" which could result in future gastrointestinal events.

In Study SB17-3001, SOC "GI disorders" was assessed by individual PT in the main and transition period. No severe cases of TEAEs were observed in any treatment group. Most of the TEAEs were mild in severity and considered not related to the investigational product (IP). There were 3 events from 2 patients that were reported to be related to the IP which are all mild in severity: 1 event of 'paraesthesia oral' in the Eksunbi treatment group and 2 events of 'abdominal pain' in 1 patient in the Stelara treatment group. All 3 events occurred on the day of IP injection.

The medical history for SOC "GI disorders" (that could possibly influence future GI events) was comparable between the Eksunbi (16 [6.4%] patients) and the Stelara Overall (18 [7.1%] patients) treatment groups.

The observed difference of TEAEs in SOC "GI disorder" was mainly driven by the imbalance in PT 'abdominal pain upper'. Further investigation into this PT revealed no specific trend or pattern of clinical relevance. Overall, no safety concerns are raised on review of the complete data set and the issue is not further pursued.

Adverse events of special interest (AESI)

AESIs were collected using 4 different categories ('hypersensitivity', 'infections', 'pulmonary events', 'injection site reaction') which were pre-defined in the study protocol. The proportion of patients with any AESI were comparable across the treatment groups for the SAF1 in the overall period. The distribution was comparable across treatment groups; 79 (31.7%) patients in the Eksunbi, 83 (32.7%) patients in the Stelara, 39 (32.0%) patients in the Stelara+Eksunbi, and 40 (32.8%) patients in the Stelara+Stelara treatment groups. In the Eksunbi treatment group, all AESI's reported were by the SOC Infections, and 109 out of 110 events were by the PT infections and infestations. No systemic hypersensitivity or injection site reactions were reported in the Eksunbi group and 2 subjects each in total experienced hypersensitivity and injection site reactions respectively in the Stelara treatment group. In the main period (up to week 28) and transition period (Stelara+Eksunbi switch group); incidences were likewise comparable between treatment groups, with a favourable safety profile in the Eksunbi treatment group. No safety concerns with regards to AESI's are raised.

Laboratory findings and vital parameters

Vital signs, and electrocardiogram (ECG) parameters were comparable across cohorts in both studies.

In Study SB17-1001, there were no clinically significant abnormalities with regards to haematology parameters. For chemistry parameters, clinically significant abnormalities were recorded in 10 subjects (alanine transaminase (ALT), n=1 and creatine phosphokinase (CPK), n=8 (2 Eksunbi, 6 Stelara)), WBC elevated in urinalysis, n=1). The three abnormal CPK values were reported as not clinically significant in each subject's eCRF by site mistake (even though assessed as clinically significant by the Investigator). An impact assessment was carried out, and the database was decided not to be unlocked. The applicant was invited to discuss the elevated CPK values, all occurring in young subjects and its impact on the safety profile**.**

The applicant provided further discussion of the 8 events of creatine phosphokinase (CPK) increase that were reported in 8 subjects in Study SB17-1001 (2 subjects in the Eksunbi and 6 subjects in the US Stelara treatment group). All 8 events of CPK elevation were by the principal investigator (PI) considered related to exercise/physical activities up 48 hours before the study visit. It is acknowledged that the mild elevations of CPK could indeed be causal to exercise/physical activities, and the CHMP agreed that no safety concerns are raised following review.

In Study SB17-3001, with regards to haematology parameters and chemistry parameters, shift patterns were generally comparable between treatment groups. In total 3 clinically significant low neutrophil abnormalities were observed during the 52-week period, one subject in the Eksunbi treatment group (0.4%) and two subjects in the Stelara overall group (0.8%) in the main period. The incidences of abnormal chemistry parameters were low, ranging from 0% to 2.0% and were comparable between treatment groups. There were no clinically meaningful trends impacting the known safety profile.

A total of 12 subjects (8 [3.2%] from Eksunbi and 4 [1.6%] from Stelara Overall treatment group, 3 subjects from Stelara+Eksunbi and 1 subject from Stelara+Stelara) that gained weight over 100 kg at least 1 time up to Week 52, comparable between the treatment groups and 2.4% of the study population.

Safety in special populations

In study SB17-1001 and SB17-3001, paediatric subjects below the age of 18 years were excluded and subjects with renal and/or hepatic impairment were also excluded. Regarding use in elderly, in study (SB17-3001), patients with age of ≥ 65 years, n=15 for Eksunbi and n=19 for Stelara Overall were enrolled. No safety patterns of clinical significance could be concluded from the sparse data. The proportions of subjects with any TEAE by age group (< 65 years) were comparable between the Eksunbi (53.4%) and Stelara Overall (52.8%) treatment group (50.0% for Stelara+Eksunbi and 53.8% for Stelara+Stelara).

Regarding use in pregnancy, in Study SB17-1001 and SB17-3001, non-childbearing potential female or childbearing potential female subjects or male subjects who consented to contraception per protocol from screening until 15 weeks after the IP administration were included, excluding pregnant and lactating women. In study SB17-1001 one subject in the Eksunbi treatment group reported pregnancy and was subsequently withdrawn from the study. In study SB17-3001, one subject in the Eksunbi treatment group, had a partner who reported pregnancy during the study, but denied consent for further information about the pregnancy. Conclusively, data on use of Eksunbi in special populations are not applicable which is acceptable to the CHMP.

Discontinuations

In Study SB17-1001, there were a total of 13 discontinuations due to COVID19, and of which none were considered related to IP (Eksunbi: 6.0%, EU Stelara: 4.5%, US Stelara:9.0%). In Study SB17-3001, there were no discontinuations in the Eksunbi treatment group, but 2 subjects in the Stelara+ Stelara treatment group discontinued due to hepatis steatosis and prostate cancer, respectively. Overall, the number of discontinuations is considered acceptable to the CHMP.

Immunogenicity

In Study SB17-1001, the overall incidence of subjects with positive post-dose ADA to ustekinumab across timepoints was numerically lower in the Eksunbi treatment groups compared to that in the EU or US Stelara treatment group.

Among subjects with positive post-dose ADA results (18, 23, and 23 subjects in the Eksunbi, EU Stelara, and US Stelara treatment groups, respectively), 10 (55.6%) subjects, 13 (56.5%) subjects, and 13 (56.5%) subjects had at least one TEAE, respectively. Incidence of any TEAEs was comparable among three treatment groups by ADA positive subgroup and ADA negative subgroup.

In Study SB17-3001, overall, ADA positive result up to Week 28 was 13.3% for the Eksunbi and 39.4% for the Stelara Overall treatment groups. Overall, ADA positive result up to Week 52 in the SAF1 was 16.5% for the Eksunbi and 41.3% in the Stelara Overall treatment groups (39.3% in the Stelara+Eksunbi and 43.4% in the Stelara+Stelara treatment groups for the SAF2). The titre distribution for ADA was comparable between the treatment groups and the majority of ADAs were low-titre as described in Stelara PI.

The incidence of ADA occurring after transition was comparable across the treatment groups (ADA from Week 28 to 52;13 [5.6%] patients in the Eksunbi+Eksunbi, 14 [5.9%] patients in the Stelara Overall, 6 [5.1%] patients in the Stelara+Eksunbi, and 8 [6.7%] patients in the Stelara+Stelara treatment groups).

The incidence of NAb tended to be lower in the Eksunbi than Stelara Overall treatment group by visit. At Week 28, the incidence of NAb was 75.0% for the SAF1 in both treatment groups. At Week 52, the incidence of NAb was 50.0% in the Eksunbi treatment group and 70.5% in the Stelara Overall treatment group for the SAF1 (64.7% in the Stelara+Eksunbi and 74.1% in the Stelara+Stelara treatment groups for the SAF2).

Overall, the frequency of TEAEs by SOC and PT were generally consistent between treatment groups within each ADA subgroup. There was no clear association between ADA and systemic hypersensitivity or injection site reaction. In the Stelara treatment group, 2 subjects in total experienced 3 events of hypersensitivity (1 subject with 2 events of abdominal pain (ADA-positive at week 8 and 12) and 1 subject with 1 event of dermatitis allergy (ADA-negative). Also, in the Stelara treatment group, 2 subjects experienced injection site reactions (0.8%), 1 event of injection site pain (ADA-negative up to week 40) and one event of injection site erythema. (ADA-negative up to week 40). All 5 events occurred within the first 28 weeks.

In both studies, the incidences of NAbs per visit are relatively lower in the Eksunbi than the Stelara treatment groups.

The clinical safety impact of the immunogenicity (i.e., modestly lower ADA formation) of Eksunbi compared to Stelara was not considered significant, based on comparable safety results.

In the absence of an available Eksunbi formulation of 45 mg solution for injection in vials offering weight-based dosing, the applicant was requested to discuss the potential for medication errors and consequent clinical harms arising as a result of the differing presentations available for the different

Ustekinumab products and based on these considerations discuss the need for strengthening of the proposed risk minimisation measures.

The concern about the potential medication error relates to the fact that it is not possible to administer to paediatric patients (weight < 60 kg) that require less than a full 45 mg dose, with the proposed Eksunbi formulations. An alternative ustekinumab product of 45 mg solution for injection in vials offering weight-based dosing is to be recommended instead.

To address this concern, the Applicant, has proposed to update the Section 4.2 Posology and method of administration of Eksunbi Summary of Product Characteristics (SmPC). The addition of the sentence is accepted by the CHMP.

2.6.10. Conclusions on clinical safety

Overall, the CHMP concluded that the Eksunbi clinical development programme and design of the studies is considered adequate to evaluate the comparability of Eksunbi and its reference product EU-Stelara in terms of safety and immunogenicity. To date, no relevant differences in safety have been detected. No specific trend or pattern of clinical relevance can be identified from the observed modest imbalances in either the moderate TEAEs or the SOC GI disturbances across the treatment groups, and no safety concerns were raised following a review of the complete data set.

In terms of immunogenicity, subjects (both healthy volunteers and patients) treated with Eksunbi had lower ADA and nAb frequencies than subjects treated with Stelara. No immunogenicity related difference was observed in the safety profile of the two products.

The safety profile of Eksunbi is considered similar to Stelara.

2.7. Risk management plan

2.7.1. Safety Concerns

Table 53. Summary of safety concerns

Summary of safety concerns	
Important identified risks	Serious systemic hypersensitivity reactions
Important potential risks	Serious infections (including mycobacterial and *Salmonella* infections) Malignancy Cardiovascular events Serious depression including suicidality Venous thromboembolism Exposure during pregnancy
Missing information	Long-term safety in paediatric psoriasis patients 6 years and older Long-term impact on growth and development in paediatric psoriasis patients 6 years and older Long-term safety in adult patients with moderately to severely active Crohn’s disease Long-term safety in adult patients with moderately to severely active ulcerative colitis

2.7.2. Pharmacovigilance plan

Not applicable.

2.7.3. Risk minimisation measures

Table 54. Summary table of pharmacovigilance activities and risk minimisation activities by safety concern

Safety concern	Risk minimisation measures	Pharmacovigilance activities
Serious systemic hypersensitivity reactions	Routine risk minimisation SmPC sections 4.3, 4.4, and 4.8 PL sections 2 and 4 Subject to restricted medical prescription Additional risk minimisation None	Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection Targeted Follow-up Questionnaire (TFUQ) Additional pharmacovigilance activities None
Serious infections (including mycobacterial and *Salmonella* infections)	Routine risk minimisation SmPC sections 4.3, 4.4, 4.5, 4.6 and 4.8 PL sections 2 and 4 Subject to restricted medical prescription Additional risk minimisation None	Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection TFUQs for serious infections and TB Additional pharmacovigilance activities **None**
Malignancy	Routine risk minimisation SmPC sections 4.4 and 4.8 PL section 2 Subject to restricted medical prescription Additional risk minimisation None	Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection TFUQ Additional pharmacovigilance activities None
Cardiovascular events	Routine risk minimisation Subject to restricted medical prescription Additional risk minimisation None	Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection TFUQ

Table 54. Summary table of pharmacovigilance activities and risk minimisation activities by safety concern

Safety concern	Risk minimisation measures	Pharmacovigilance activities
		Additional pharmacovigilance activities None
Serious depression including suicidality	Routine risk minimisation SmPC section 4.8 PL section 4 Subject to restricted medical prescription Additional risk minimisation None	Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection None Additional pharmacovigilance activities None
Venous thromboembolism	Routine risk minimisation Subject to restricted medical prescription Additional risk minimisation None	Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection TFUQ Additional pharmacovigilance activities None
Exposure during pregnancy	Routine risk minimisation SmPC section 4.6 PL section 2 Subject to restricted medical prescription Additional risk minimisation None	Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection None Additional pharmacovigilance activities None
Long-term safety in paediatric psoriasis patients 6 years and older	Routine risk minimisation Subject to restricted medical prescription Additional risk minimisation None	Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection None Additional pharmacovigilance activities None

Table 54. Summary table of pharmacovigilance activities and risk minimisation activities by safety concern

Safety concern	Risk minimisation measures	Pharmacovigilance activities
Long-term impact on growth and development in paediatric psoriasis patients 6 years and older	Routine risk minimisation Subject to restricted medical prescription Additional risk minimisation None	Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection None Additional pharmacovigilance activities None
Long-term safety in adult patients with moderately to severely active Crohn's disease	Routine risk minimisation Subject to restricted medical prescription Additional risk minimisation None	Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection None Additional pharmacovigilance activities None
Long-term safety in adult patients with moderately to severely active ulcerative colitis	Routine risk minimisation Subject to restricted medical prescription Additional risk minimisation None	Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection None Additional pharmacovigilance activities None

PL = package leaflet; PUVA = psoralen and ultraviolet A; SmPC = summary of product characteristics.

2.7.4. Conclusion

The CHMP considers that the risk management plan version 1.0 is acceptable.

2.8. Pharmacovigilance

2.8.1. Pharmacovigilance system

It is considered that the pharmacovigilance system summary submitted by the applicant fulfils the requirements of Article 8(3) of Directive 2001/83/EC.

2.8.2. Periodic Safety Update Reports submission requirements

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

2.9. Product information

2.9.1. User consultation

No full user consultation with target patient groups on the package leaflet has been performed on the basis of a bridging report making reference to Stelara 130 mg concentrate for solution for infusion for content and key safety messages, and Flixabi 100 mg powder for concentrate for solution for infusion for design. The bridging report submitted by the applicant has been found acceptable.

2.9.2. Additional monitoring

Pursuant to Article 23(1) of Regulation No (EU) 726/2004, Eksunbi (Ustekinumab) is included in the additional monitoring list as

- It contains a new active substance which, on 1 January 2011, was not contained in any medicinal product authorised in the EU;
- It is a biological product that is not covered by the previous category and authorised after 1 January 2011.

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

3. Biosimilarity assessment

3.1. Comparability exercise and indications claimed

Introduction

In this biosimilar application, the applicant is proposing a new biosimilar of ustekinumab, Eksunbi. The chosen reference product is the EU approved product Stelara (ustekinumab), which was authorised via the Centralised Procedure in the European Union on 15.01.2009 (marketing authorisation holder Janssen-Cilag).

Ustekinumab is a recombinant, fully human immunoglobulin G, subclass 1, κ light chain (IgG1κ) monoclonal antibody (mAb) that binds to the p40 subunit of interleukin (IL)-12 and IL-23, thereby preventing initiation of immune-response signalling pathways.

The reference product Stelara has a number of presentations and strengths approved (45 mg/0.5 mL in vial for SC use; 45 mg/0.5 mL in PFS for SC use; 90 mg/1.0 mL in PFS for SC use; 130 mg/26 mL in vial for IV use).

The applicant is proposing a number of presentations of the biosimilar Eksunbi, but all the presentations of the reference product Stelara are not applied for in this application. Of note, the 45 mg/0.5 mL vial presentation has not been proposed as part of this application.

In relation to the indications sought, the applicant is proposing the same indications for Eksunbi which are approved for the reference product Stelara.

The proposed indications include treatment of adult and paediatric patients, as follows:

- Plaque psoriasis (PsO)
- Paediatric plaque psoriasis (pPsO) in children and adolescents ≥ 6 to < 17 years of age
- Psoriatic arthritis (PsA)
- Crohn's disease (CD)
- Ulcerative colitis (UC)

Of note, the 45 mg/0.5 mL vial presentation of Stelara is indicated for patients in whom weight-based dosing is required body weight (e.g., b.w. <60 kg)

The currently applied for PFS presentations are suitable for the maintenance therapy of PsO, UC and CD as well as treatment of paediatric PsO in subjects with BW >60kg. In order to reflect the absence of the 45mg vial presentation, the applicant has proposed to include specific wording in the product information to highlight that the specific weight-based dosing presentation is not currently available for Eksunbi, but that other ustekinumab products are available for use in relevant populations. This proposal is acceptable to the CHMP.

The quality and in vitro non-clinical similarity between Eksunbi IV vial and Stelara IV vial is demonstrated using physiochemical assays and in vitro biological assays (Bridge 1).

In addition to this direct comparison, comparability between the Eksunbi IV vial and Stelara IV vial is indirectly made based on the extensive similarity comparison of SC PFS (Bridge 2), comparability between Eksunbi SC PFS and IV vial (Bridge 3) and the established PK comparability between Stelara SC PFS and IV vial.

In addition, clinical similarity between the two PFS presentations is demonstrated in PK from the Phase I study and in efficacy from the Phase III study and similarity in safety, tolerability and immunogenicity will be demonstrated from both studies.

Quality aspects

The biosimilarity of Eksunbi to the EU Stelara reference medicinal product (RMP) was assessed using a range of state-of-the-art analytical tests in line with the EMA *Guideline on Similar Biological Medicinal Products containing Biotechnology-derived proteins as active substance* (EMA/CHMP/BWP/247713/2012). Two separate biosimilarity exercises were presented for the PFS (45 mg subcutaneous) and vial (130 mg IV) presentations. The results are discussed below.

Clinical aspects

The clinical development programme comprises two comparative studies which aimed to establish equivalence to the reference product Stelara: one comparative PK study evaluating Eksunbi versus EU/US Stelara (Study SB17-1001) in healthy subjects and one comparative efficacy, safety, immunogenicity, and PK study (Study SB17-3001) (Eksunbi versus EU Stelara) in adult patients with moderate to severe PsO.

Study SB17-1001 is a phase 1 randomised, double-blind, single-dose, parallel group, 3-arm study comparing the pharmacokinetic, safety, tolerability and immunogenicity profiles of Eksunbi, EU-Stelara and US-Stelara in healthy adult subjects. Subjects received a single dose of 45 mg/0.5 mL of either Eksunbi, EU-approved Stelara, or US-licensed Stelara on Day 1 as an SC injection. According to the EMA guidelines, a single-dose study with the lowest therapeutic dose used for patients is considered the most adequate design to investigate the differences in target-mediated clearance.

The primary objective of the study was to demonstrate PK similarity of Eksunbi to both EU-Stelara and US-Stelara; as well as to demonstrate similarity between EU-Stelara and US-Stelara, in terms of C_{max} and $AUC_{0\text{-}inf}$. For an EU MA, the comparison between Eksunbi and EU-Stelara is of primary importance, while other comparisons are considered supportive.

Secondary objectives comprised additional PK parameters to support similarity, comparison of safety, tolerability and immunogenicity between Eksunbi and reference products.

The assessment of biosimilarity in terms of PK was based on 90% confidence intervals (CIs) for the ratio of the geometric means (Eksunbi/EU-Stelara) for C_{max} and $AUC_{0\text{-}inf}$ of the ustekinumab concentrations which had to be contained within the bioequivalence limits of 80-125%. The equivalence margins used in the study are in line with conventionally used margins for biosimilar products. Study objectives are overall adequate for the purpose of PK biosimilarity exercise.

Study SB17-3001 is a randomised, double-blind, multicentre, active control clinical study to compare the efficacy, safety, and immunogenicity of Eksunbi compared to Stelara in adult patients with moderate to severe chronic plaque-type psoriasis (PsO).

Of note, the data lock point of study SB17-3001 was Sep 15, 2022 (when all possible subjects completed the Week-28 visit and 103 subjects completed the Week-52 visit). The full data set was subsequently submitted by the applicant with the responses, allowing a final conclusion on efficacy.

Study SB17-3001 had the primary objective of evaluating therapeutic equivalence of Eksunbi compared to Stelara in the treatment of moderate to severe chronic PsO in adult patients.

The primary efficacy endpoint was percent improvement in Psoriasis Area and Severity Index (PASI) from Baseline to Week 12 in adult subjects with moderate to severe plaque psoriasis.

Clinical equivalence was demonstrated if the 95% CI for the adjusted mean difference in percentage PASI improvement between test and reference groups is contained within the equivalence margin range of [-15%, 15%]. A number of secondary endpoints were also evaluated in SB17-3001, these included the measurement of additional efficacy endpoints commonly used in patients with PsO (PASI50, PASI75, PASI90, and PASI100) Response rates were evaluated at a number of timepoints through to Week 52 (Week 2, 4, 8, 12, 16, 20, 24, 28, 40, and 52), percent change from baseline in PASI at Week 2, 4, 8, 16, 20, 24, 28, 40, and 52. Achievement of Physician's Global Assessment (PGA) response was also assessed at Week 2, 4, 8, 12, 16, 20, 24, 28, 40, and 52. A further secondary endpoint was the change from baseline in Dermatology Life Quality Index (DLQI) scores at Week 4, 12, 16, 28, 40, and 52.

It has been demonstrated that clinical efficacy is comparable between both treatment groups in the phase III study based on the complete 52-week data set.

In addition, it was highlighted during the procedure that the analysis of the impact of ADA positivity over 52 weeks on % change in PASI, by treatment group was not as informative for the overall biosimilarity conclusion regarding efficacy aspects of Eksunbi. In this context, in order to support biosimilarity in presence of lower immunogenicity of Eksunbi, the applicant provided an updated analysis of the effect of Eksunbi versus Stelara on % change in PASI, with specific focus on the ADA negative and nAB negative patient group. The applicant has outlined in their response that the percent

change from baseline in PASI at Week 12 was equivalent between the Eksunbi and Stelara treatment groups without ADAs. LSMeans at Week 12 was −2.2 [−6.194, 1.805], which was within the pre-defined equivalence margin of [−15%, 15%]. In addition, the PASI score up to Week 52 are comparable between treatment groups in ADA negative subgroup. The incidence of overall NAb was lower in the Eksunbi compared to the Stelara treatment groups. The percent change from baseline in PASI at Week 12 was equivalent between the Eksunbi and Stelara treatment groups for the overall NAb negative subgroup in the Per-protocol Set. The adjusted difference in LSMeans at Week 12 was −2.3 and the 95% CI of the adjusted treatment difference was [−6.121, 1.424]. In addition, the PASI score up to Week 52 are comparable between treatment groups in NAb negative subgroup. In conclusion, the efficacy analyses in patients who were not ADA or NAb positive support the primary efficacy outcome between the Eksunbi and EU Stelara.

3.2. Results supporting biosimilarity

Quality aspects

Two separate biosimilarity exercises were presented for the PFS (45 mg subcutaneous) and vial (130 mg IV) presentations. The testing panel includes primary and higher order structure, post-translational modifications, size and charge variants, protein concentration, as well as Fab and Fc-mediated biological functions.

Eksunbi and EU Stelara are similar with respect to primary and higher order structure. The C-terminal ends of Eksunbi and EU Stelara differ in that Eksunbi has a higher content of the Lys- removed form and low levels of an α-amidated proline variant. However, these minor differences in C-terminal variants do not impact on the conclusion of analytical similarity. Oxidation levels of Met_{51} and Met_{254} were similar but not fully aligned; as levels of oxidated variants are quite low, these minor differences are unlikely to be relevant.

The N-linked glycosylation profile of Eksunbi and Stelara is similar but, some differences were noted. N-acetylneuraminic acid (NANA) was detected only in Eksunbi while α-galactosylated or N-glycoylneuraminic acid (NGNA) were detected only in Stelara. These differences are expected due to the difference in host cell expression system but are not expected to have an adverse impact on immunogenicity as the species present in Stelara are known to be more immunogenic. The relative contents of G0F trended higher for Eksunbi than Stelara while levels of G1F and G2F were inside the defined similarity range (or slightly below it for the vial presentation). These differences are attributed to the difference in galactosylation between Eksunbi and the reference product and are not considered clinically meaningful given that neither molecule has CDC activity. There is a minor difference in afucosylation levels which is not considered significant as both molecules exhibit similar FcγRIIIa binding activities and ustekinumab is not associated with ADCC or CDC. For the relative contents of charged glycans, there is a significant difference between Eksunbi and Stelara. This difference is attributed to the different sialic acid forms present, as discussed above.

There are significant differences in terms of %acidic peaks, %main peak and %basic peaks between Eksunbi and Stelara evaluated by CEX-HPLC (without enzyme pretreatment). Eksunbi contains lower levels of acidic variants, lower levels of basic variants and higher levels of main peak vs Stelara. As such, a structure activity relationship study was performed to analyse the different charge variant fractions present in the biosimilar and reference product. Peptide mapping was performed along with SE-HPLC and biological characterisation (IL-23 neutralisation, IL-23 binding activity and FcRn binding activity). Overall, the difference in acidic variants between Eksunbi and Stelara is attributed to the difference in sialic acid content and the results of biological characterisation were comparable between acidic and load fractions for both Eksunbi and Stelara. The differences in basic variants between the

Eksunbi and Stelara products is attributed to C-terminal lysine differences. As C-terminal lysines are removed *in vivo* shortly after administration, there is no expected clinical impact. The biological characterisation of the basic fractions indicate that basic peaks were comparable to load sample with respect to IL-23 neutralisation and binding properties for both Stelara and Eksunbi. For FcRn binding, the basic fractions showed higher activity but, the difference was minor and not considered significant. The conclusion that the observed difference in charge variant profile does not have a clinically meaningful impact is agreed.

While minor differences are noted with respect to the results of SE-HPLC, CE-SDS non-reduced and CE-SDS reduced the results of %HMW, %LMW, %2H1L and %NGHC are consistent with a conclusion of biosimilarity. In terms of biological characterisation, the relative IL-23 neutralisation potency, IL-23 binding activity, IL-12 neutralisation potency and IL-12 binding activity of Eksunbi fell within the similarity range as defined for the EU RMP. In the case of FcRn binding, the results from Eksunbi PFS lots trend lower than those of the EU Stelara lots but fall within the similarity range. In the case of the Eksunbi vial lots, the results of FcRn binding fall slightly below the similarity range as defined by the reference product. Data has been provided to support that this apparent difference between Eksunbi and Stelara is due to the C-terminal lysine variants which will be removed rapidly in-vivo and the difference is, thus, not clinically relevant. The results of the additional biological activity characterisation support the biosimilarity of the Eksunbi and Stelara products (FcγR binding, C1q binding, ADCC and CDC). There was no ADCC or CDC activity observed for either Eksunbi or Stelara.

Clinical aspects

PK: Following a single SC dose of 45 mg/0.5 mL in the Phase 1 study, the mean serum ustekinumab concentration-time profiles for Eksunbi, EU-Stelara and US-Stelara were overall similar.

The geometric LSMean ratio (90% CI) of Eksunbi and EU sourced Stelara for AUC_{inf} and C_{max} were 0.99 (0.90 to 1.08) and 0.90 (0.82 to 0.98), respectively. These values for the 90% CIs were within the predefined equivalence margin of 0.8 to 1.25 however the geometric LSMean ratio (90% CI) of Eksunbi and EU Stelara for C_{max} was 0.90 (0.82 to 0.98), which is within the pre-defined equivalence margin, but does not include 1.

Based on the baseline comparability of demographics and baseline characteristics between the three treatment groups in Study SB17-1001 body weight was identified as a statistically different variable between the treatment groups (p-value = 0.0199). Accordingly, an ad-hoc analysis of covariance (ANCOVA) for the primary PK parameters with body weight as a covariate was performed, showing the geometric LSMean ratios (90% CI) between Eksunbi and EU Stelara for AUC_{inf} and C_{max} were 1.01 (0.92 to 1.11) and 0.93 (0.85 to 1.02), respectively, which were within the pre-defined equivalence margin of 0.8 to 1.25 and contains 1.

In relation to the Phase III Clinical study in patients with moderate to severe plaque PsO, it is considered that the mean serum concentrations of ustekinumab were generally comparable between the Eksunbi and Stelara treatment groups up to Week 28, however it was highlighted during the procedure that exposure to Eksunbi was marginally higher at several timepoints, notably higher at the week 8 timepoint when compared to Stelara. The applicant provided a further satisfactory discussion in relation to these apparent differences in systemic exposure in the target population and their possible clinical relevance (for more detail please see discussion on Clinical Pharmacology). The justification was accepted by the CHMP.

Efficacy

The primary endpoint indicating clinical equivalence was met in the phase III clinical study: the adjusted LSMeans difference of the percent change from baseline in PASI at Week 12 for the PPS was

−0.6 (SE: 1.62) and the 95% CI of the adjusted treatment difference was [−3.780 to 2.579], which was entirely contained within the pre-defined equivalence margin of [−15%, 15%].

The adjusted LSMeans difference of the percent change from baseline in PASI at Week 12 for the FAS available cases was −0.7 (SE: 1.60) and the 95% CI of the adjusted treatment difference was [−3.836 to 2.456], and for FAS multiple imputation, −0.7 (SE: 1.60), 95% CI [−3.849, 2.439], all of these values were still well within the pre-specified margin of [−15%, 15%].

The applicant also provided an analysis using a 90% CI, which, although not relevant for this application still indicated that the LSMeans difference of the percent change from baseline in PASI at Week 12 for the PPS is −0.6 (SE: 1.62, 90% CI [−3.267, 2.066]), the FAS available cases is −0.7 (SE: 1.60, 90% CI [−3.329, 1.948]), and FAS multiple imputation is −0.7 (SE: 1.60, 90% CI [−3.343, 1.933]), all within the pre-specified margin of [−10%, 10%].

Within this submission, the pre-specified equivalence range [-15%, 15%] has been clinically justified by the applicant and although it is somewhat large, the 95% CI for both the ITT and the PPS analysis clearly demonstrated equivalent clinical efficacy of Eksunbi and Stelara within a narrow range, therefore clinical comparability can be generally concluded.

In relation to the timing of the primary efficacy analysis, the applicant has chosen Week 12 as the cut off for this analysis. This approach is accepted. However, it is highlighted that the by the Week 12 timepoint, the plateau is almost reached. In this context, and as discussed during previous CHMP SA, the sensitivity to detect differences between both treatments, Eksunbi and Stelara, may possibly be higher during the steeper part of the time/response curve which would occur at any earlier timepoint, most probably around Week 8 instead of Week 12.

Despite this, it is acknowledged that the applicant provided additional data for timepoints earlier than Week 12 including Weeks 2, 4, 8, which allows for the opportunity to evaluate similarity at the earlier time points. This approach can be accepted and it aligns to the CHMP SA recommendations (EMA/CHMP/SAWP/493969/2019) whereby, it was recommended to add an additional measure of efficacy at week 8 (e.g. mean change from baseline) as a secondary endpoint, in order to fulfil the EMA guidelines to use also an earlier time point for the detection of potential product differences, which are potentially higher at the steeper part of the efficacy curve.

It is therefore relevant to consider that further supportive efficacy data which was obtained at earlier timepoints is also broadly supportive of clinical equivalence.

In general, secondary efficacy endpoints such as PASI75, PASI90, and PASI100 response rate, PGA, and DLQI were also broadly similar between the treatment groups at all timepoints. At Week 12, PASI75 response rate was 81.7% for Eksunbi and 81.0% for Stelara; PASI90, 53.7% for Eksunbi and 57.5% for Stelara; PASI100: 19.9% for Eksunbi and 22.6% for Stelara, and PGA 0/1: 85.0% for Eksunbi and 87.3% for Stelara (all for the FAS).

In summary, the percentage change in PASI from baseline through Week 40 was comparable between Eksunbi and Stelara. Results for patients with body weight >100kg were provided but at the time of interim analysis, only a small number of patients had moved into this higher weight band and had therefore required treatment with the higher 90mg dose of ustekinumab. In the final CSR, it was clarified that the number of patients in this subgroup was overall very low and similar across Eksunbi and Stelara.

Data presented up to Week 28 and into subsequent transition phase through to week 52 did not reveal any major differences between the treatment groups.

As outlined in the discussion on pharmacokinetics, numerically higher exposure values were observed with Eksunbi compared to Stelara, particularly at the Week 8 timepoint. The applicant was asked to

provide further discussion and clarification in relation to the possible reasons for this observed difference in systemic exposure in the target population. The possible clinical implications and impact of immunogenicity was discussed as part of the response. This finding did not appear to result in greater efficacy. The applicant has further clarified in the responses that the efficacy analyses in patients who were not ADA or NAb positive support the primary efficacy outcome between the Eksunbi and EU Stelara.

Safety

In the Phase 1 PK study in healthy volunteers, the proportion of subjects with TEAEs, as well as the proportion of subjects with treatment-related TEAEs, were comparable between groups. There were no deaths, SAEs, severe TEAEs, or discontinuation due to TEAEs related to the IP during the study. The most frequently reported TEAEs in both groups were headache. All TEAEs were mild to moderate in severity. Laboratory data, vital signs, and 12-lead ECG parameters were comparable between the two groups.

In the pivotal Phase III study in patients with moderate to severe plaque PsO, the incidences of TEAEs, SAEs, IP discontinuation due to AEs, and AESIs were comparable between the Eksunbi and Stelara treatment groups, as well as transition groups. There were no deaths reported during the study. The majority of TEAEs reported were mild to moderate in severity in the Eksunbi and Stelara treatment groups and were within the expected safety profile of ustekinumab. There were no particular safety signals after switching from Stelara to Eksunbi. Clinical laboratory evaluation, vital signs and physical examination findings were comparable between the Eksunbi and Stelara treatment groups.

Both studies supported a consistent immunogenicity profile of Stelara and Eksunbi in healthy subjects following single administration and in patients with PsO following repeat administration up to Week 40. The incidence of ADAs directed against Stelara was found to be higher than for Eksunbi in both settings. No immunogenicity related difference was observed in the safety profile of the two products.

3.3. Uncertainties and limitations about biosimilarity

There are no remaining uncertainties and limitations that have an impact on the conclusion of biosimilarity.

3.4. Discussion on biosimilarity

Quality

The analytical similarity exercise is comprehensive and supports the conclusion of biosimilarity.

PK aspects

It was advised during the EMA SA that additional PK parameters, such as partial AUCs, should be incorporated into the study protocols of the proposed clinical phase I and III studies and that especially the late partial AUCs should be comparable to support similar elimination between the proposed biosimilar and the originator product. This is considered important to support extrapolation of the SC data to the IV administration route, and consequently, to waive a clinical study using the IV presentation. No data on partial AUCs had been provided and this was considered an MO. As requested, the applicant made a statistical comparison of various partial AUCs of Eksunbi and EU Stelara in Study 1001. The analysis of variance (ANOVA) of partial AUC for Eksunbi and EU Stelara for the similarity assessment with various timepoints in elimination phase was assessed. The 90% confidence intervals (CIs) of the geometric least squares mean (LSMean) ratios of partial AUC for the comparison of Eksunbi and EU Stelara were all within the pre-defined equivalence margin of 0.8 to 1.25 and contained unity regardless of any given timepoints between 504 h to 2352 h. It is agreed the partial AUCs support the similarity in subcutaneous (SC) route of administration between Eksunbi and EU Stelara as well as the extrapolation of the SC data to the intravenous (IV) administration route of Eksunbi, the MO was satisfactorily resolved.

The PK bioequivalence has been demonstrated between Eksunbi and EU Stelara in Study SB17-1001, which was performed in the most sensitive and homogeneous population of healthy subjects. PK data assessed in psoriasis patients from Study SB17-3001 were provided as supportive data only. Taken together, the similarity in partial AUCs between Eksunbi and EU Stelara specifically in the elimination phase in Study SB17-1001 along with the results from Study SB17-3001 provides the evidence for extrapolation of the SC data to the IV administration route.

Efficacy

In this MAA, the applicant submitted the clinical study report (CSR) from the pivotal phase III clinical study which contained interim efficacy data collected up to data cut-off date of September 15, 2022. The final CSR provided contains a full set of 52-week data from the Phase III Study SB17-3001. The applicant provided the final CSR with the complete 52-week data set from the Phase III study at Day 120 List of Questions during the MAA procedure.

The primary endpoint, percent change from baseline in PASI at Week 12, was equivalent between the Eksunbi and Stelara treatment groups. The adjusted difference in LSMeans of the percent change from baseline in PASI at Week 12 for the PPS was −0.6 (SE: 1.62) and the 95% CI of the adjusted treatment difference was [−3.780 to 2.579], which was entirely contained within the pre-defined equivalence margin of [−15%, 15%].

When analysed using a 90% CI, the LSMeans difference for the PPS is −0.6 (SE: 1.62, 90% CI [−3.267, 2.066]), which was entirely contained within the pre-defined equivalence margin of [−10%, 10%].

Equivalence was demonstrated in both the FAS and PPS, when using different equivalence margins, and when analysing by 90% or 95% CIs.

The time-response curves of Eksunbi and Stelara treatment groups showing the percent change from baseline in PASI demonstrated almost overlapping response curves across time and supported the robustness of the primary efficacy analysis.

The percent change from baseline in PASI was also similar for age, gender, ADA status, prior biologic use, and prior history of psoriatic arthritis subgroups.

PASI50, PASI75, PASI90, and PASI100 response rates were also similar between Eksunbi and Stelara treatment group by visit.

The proportion of subjects achieving a PGA response 'cleared' or 'minimal' were similar between Eksunbi and Stelara treatment group by visit.

The degree of DLQI improvement was similar between Eksunbi and Stelara treatment group by visit.

In conclusion, it can be considered that clinical comparability has been demonstrated between Eksunbi and Stelara in the phase III clinical study based on the data presented which is considered supportive of clinical efficacy equivalence across primary and secondary endpoints in psoriasis patients.

Regarding immunogenicity and efficacy, on the basis of the data provided, Eksunbi appears to be less immunogenic than Stelara. In relation to the potential impact of immunogenicity on efficacy, the percent change from baseline in PASI at Week 12 was broadly similar per overall ADA status.

However, whilst clinical efficacy is broadly comparable between both treatment groups in the phase III study, it was highlighted that the potential clinical impact of the immunogenicity (i.e., modestly lower ADA formation) of Eksunbi compared to Stelara required some further consideration and this point was therefore specifically discussed further by the applicant in their responses.

In this context, the applicant provided an analysis of the effect of ADA status on % change in PASI, given that Eksunbi appears to be less immunogenic than Stelara and in light of the slightly higher exposure to Eksunbi in ADA negative patients (ref: Biosimilar guideline EMEA/CHMP/BMWP/42832/2005 Rev1).

As noted above, the efficacy analyses in patients who were not ADA or NAb positive support the primary efficacy outcome between the Eksunbi and EU Stelara.

Safety

As regards the safety profile of Eksunbi, no relevant differences in safety have been detected based on a review of the final data. The majority of TEAEs reported were mild to moderate in severity in the Eksunbi and Stelara treatment groups and were within the expected safety profile of ustekinumab.

In terms of immunogenicity, subjects (both healthy volunteers and patients) treated with Eksunbi had lower ADA and NAb frequencies than subjects treated with Stelara. No immunogenicity related difference was observed in the safety profile of the two products.

3.5. Extrapolation of safety and efficacy

The applicant is seeking approval for Eksunbi for the same indications approved for the reference medicinal product EU Stelara. Stelara is approved for the treatment of PsO, paediatric PsO, PsA, CD and UC in the EU.

However, at present, only prefilled syringe (PFS) presentations intended for subcutaneous use and one vial presentation for IV administration are applied for. The applicant has outlined that approval for a vial presentation for SC administration will be sought post-marketing by way of a line extension. The vial presentation currently omitted from the application is required for (1) body weight-based dosing of patients with paediatric PsO with body weight < 60 kg (vial for SC use). The applicant proposes to include amendments to the SmPC, to reflect on the unavailability of this vial presentation and refer to other products available on the market that should be used for treatment of paediatric PsO in patients

with BW<60kg. The extrapolation to the full range of indications to align with the Stelara indications, without this SC vial presentation is in acceptable to the CHMP and divergences from the reference product's SmPC in the section 4.2 to inform about the availability of other Ustekinumab products for administration of doses lower than 45 mg are accepted.

However, the extrapolation to full indications also implies extrapolation of data generated with subcutaneous administration to intravenous administration. In this context, the submitted PK data for IV administration of ustekinumab within the submitted responses for Eksunbi is acceptable. As the evaluation of SC administration covers both absorption and elimination of ustekinumab, it may be possible to waive the evaluation of IV administration and allow extrapolation to all indications, the applicant has satisfactorily demonstrated comparability in both absorption and elimination for the subcutaneous route. In line with requirements outlined in the Guideline on Similar Biological Medicinal Products Containing Monoclonal Antibodies – Non-clinical and Clinical Issues (EMA/CHMP/BMWP/403543/2010), in order to waive the evaluation of intravenous administration, similarity to Stelara for the subcutaneous route has to first be demonstrated separately for both absorption and elimination, which has now been done.

The efficacy and safety study was conducted in patients with moderate, to severe plaque psoriasis patients (PsO). This selected study population represents the most sensitive population to demonstrate biosimilarity and is considered acceptable.

Additionally, ustekinumab's MoA is similar in each of the reference medicinal product's indications (PsO, paediatric PsO, PsA, CD, UC), as the Th1 and Th17 cytokine pathways play a central role in their pathogenesis and are mediated by the ustekinumab targeted and inhibited IL-12 and IL-23.

Furthermore, the safety profile for ustekinumab is similar between these indications. Therefore, from the clinical point of view, extrapolation of the efficacy and safety data generated in PsO indication to all indications approved for the reference product is acceptable to the CHMP.

3.6. Conclusions on biosimilarity and benefit risk balance

From a quality perspective, the analytical similarity exercise is comprehensive and supports a conclusion of biosimilarity.

The PK bioequivalence has been demonstrated between Eksunbi and EU Stelara in Study SB17-1001, which was performed in the most sensitive and homogeneous population of healthy subjects. PK data assessed in psoriasis patients from Study SB17-3001 were provided as supportive data only. Taken together, the similarity in partial AUCs between Eksunbi and EU Stelara specifically in the elimination phase in Study SB17-1001 along with the results from Study SB17-3001 provides the evidence for extrapolation of the SC data to the IV administration route.

Efficacy data provided are supportive of comparability between Eksunbi and Stelara from a clinical efficacy point of view.

From a safety perspective, the safety profile is overall in accordance with the originator Stelara.

In conclusion, based on the review of the submitted data, Eksunbi is considered biosimilar to Stelara.

The overall benefit/risk balance of Eksunbi is positive.

4. Recommendations

Outcome

Based on the CHMP review of data on quality, safety and efficacy, the CHMP considers by consensus that the benefit-risk balance of Eksunbi is favourable in the following indication(s):

Plaque psoriasis

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

Paediatric plaque psoriasis

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

Psoriatic arthritis (PsA)

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

Crohn's Disease

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

Ulcerative colitis

Eksunbi is indicated for the treatment of adult patients with moderately to severely active ulcerative colitis who have had an inadequate response with, lost response to, or were intolerant to either conventional therapy or a biologic or have medical contraindications to such therapies (see section 5.1).

The CHMP therefore recommends the granting of the marketing authorisation subject to the following conditions:

Conditions or restrictions regarding supply and use

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

Other conditions and requirements of the marketing authorisation

- **Periodic Safety Update Reports**

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

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

- **Risk Management Plan (RMP)**

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

any agreed subsequent updates of the RMP.

An updated RMP should be submitted:

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

Not applicable.

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

Not applicable.