19 June 2025
EMA/135976/2025
Committee for Medicinal Products for Human Use (CHMP)

Assessment report

Usymro

International non-proprietary name: ustekinumab

Procedure No. EMEA/H/C/006467/0000

Note

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

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List of abbreviations

$\%AUC_{ex}$	Percentage of extrapolated area in $AUC_{0\text{-}inf}$
ACN	Acetonitrile
ADA	Anti-Drug Antibody
ADCC	Antibody Dependent Cellular Cytotoxicity
ADCP	Antibody Dependent Cellular Phagocytosis
ADR	Adverse Drug Reaction
AE	Adverse Event
ALT	Alanine Aminotransferase
αMEM	Minimum Essential Medium α
ANCOVA	Analysis of covariance
ANOVA	Analysis of variation
ART	Ambient room temperature
AST	Aspartate Aminotransferase
ATC	Anatomical Therapeutic Chemical
AUC	Area Under Curve
$AUC_{0\text{-}672h}$	Area under the serum drug concentration-time curve from zero to 672h
$AUC_{0\text{-}inf}$	Area under the concentration-time curve from time 0 extrapolated to infinity
$AUC_{0\text{-}t}$	Area under the serum drug concentration-time curve from time 0 to the last quantifiable concentration
$AUC_{Tmax\text{-}inf}$	Area under the serum drug concentration-time curve from T_{max} to infinity
BMI	Body Mass Index
CD	Crohn's Disease
CDC	Complement Dependent Cytotoxicity
CE-SDS	Capillary electrophoresis sodium dodecyl sulfate
CfB	change from baseline
CHO	Chinese Hamster Ovary (cell line)
ChP	Chinese Pharmacopeia
CI	Confidence Interval
cIEF	Capillary isoelectric focusing
CL	Clearance
CL/F	Apparent clearance
C_{max}	Maximum Observed Serum Concentration (peak concentration)
CP	cut-point
CPP	Critical process parameters
CQA	Critical quality attributes
CSR	Clinical Study Report
CT	Computed Tomography
CTCAE	Common Terminology Criteria for Adverse Events
CV	coefficient of variation
D	Day (of study)
DES	Donor Equine Serum
DLQI	Dermatology Life Quality Index
DMF	Dimethylformamide
DTT	Dithiothreitol

EC	European Commission
ECG	Electrocardiogram
ECL	Electrochemiluminescence
ELISA	Enzyme-linked Immunosorbent Assay
EMA	European Medicines Agency
EOS	End-of-study
ERC	Extraction recovery control
EU	European Union
FAS	Full analysis set
FBS	Fetal bovine serum
Fc	fragment crystallizable (region of antibody)
FDA	Food and Drug Administration
GCP	Good Clinical Practice
GCV	Geometric Coefficient of Variation
GLP	Good Laboratory Practise
GMR	geometric mean ratio
HC	Heavy chain
HHL	Heavy-heavy-light
hIgG1	human immunoglobulin G1
HL	Heavy-light
HPC	high positive control
HPLC	High-performance liquid chromatography
HRP	Horseradish Peroxidase
IAM	Iodoacetamide
IC	Informed Consent
ICE	Intercurrent Event
ICF	Informed Consent Form
ICH	International Council for Harmonisation
IEC-HPLC	Ion exchange chromatography-HPLC
IgG	Immunoglobulin G
IgG1κ	Immunoglobulin isotype class G subclass 1 kappa
IL	Interleukin
IL-12	Interleukin 12
IL-12Rβ1	IL-12 receptor subunit beta 1
IL-23	Interleukin 23
INN	International Non-proprietary Name
IP	Investigational Product
IPC	In-process control
ITT	Intent-to-Treat
IV	Intravenous
JAK2	Janus Kinase 2
LC	Light chain
LOCF	Last Observation Carried Forward
LoE	Lack of Efficacy
LPC	low positive control
LS	Least Squares

MA	Marketing Authorisation
MAA	Marketing Authorisation Application
mAb	Monoclonal Antibody
MAD	Mutual Acceptance of Data
MAH	Marketing Authorisation Holder
Max	Maximum
MCF	Multiplicative Correction Factor
MedDRA	Medical Dictionary for Regulatory Activities
Min	Minimum
MMRM	Mixed-effects Model for Repeated Measures
MOA	Mechanism of Action
MRD	minimum required dilution
N	number of subjects with observation
NAb	Neutralizing Anti-drug Antibody
NADA	Neutralising Anti-Drug Antibody
NANA	N-acetylneuraminic acid
NC	Negative Control
NGHC	Non-glycosylated heavy chain
NGNA	N-glycolylneuraminic acid
NK	Natural Killer (cell)
NK92MI	A NK cell line derived from a male with malignant non-Hodgkin's lymphoma
NMPA	National Medical Products Administration
NOAEL	No-Observed Adverse Effect Level
Non-CCP	Non-critical process parameters
NOR	Normal operating ranges
NR	Non-reduced
OD	Optical Density
OECD	Organisation for Economic Co-operation and Development
PAR	Proven acceptable ranges
PASI	Psoriasis Area and Severity Index
PBS(T)	Phosphate buffered saline (with Tween 20)
PC	Positive control
PD	Pharmacodynamics
PFS	Prefilled Syringe
Ph. Eur.	European Pharmacopeia
PK	Pharmacokinetics
PKS	Pharmacokinetic Set
popPK	population pharmacokinetics
PPA	Process performance attributes
PPS	Per-Protocol Set
PsA	Psoriatic Arthritis
PsO	Plaque Psoriasis
PSTCP	plate-specific titer cut point
PT	Preferred Term
RBC	Red Blood Cell
RLU	relative light units

RMP	Reference Medicinal Product
RORγt	RAR-related orphan receptor gamma
RSD	Relative Standard Deviation
SAE	Serious Adverse Event
SAF	Safety Analysis Set
SAP	Statistical Analysis Plan
SAS	Safety Analysis Set
SC	Subcutaneous
SCPF	screen cut point factor
SD	Standard Deviation
SDS	Sodium dodecyl sulfate
SE	Standard Error
SEC-HPLC	Size exclusion HPLC
SIR	Signal Inhibition Ratio
SmPC	Summary of Product Characteristics
SOC	System Organ Class
Sp2/0	Murine Myeloma (cell line)
sPGA	static Physician's Global Assessment
STAT3	Signal transducer and Activator of Transcription protein 3
Stelara-BAT2206	The switch from Stelara to BAT2206 on TP2
Stelara-Stelara	The switch from Stelara to Stelara on TP2
$T_{1/2}$	Half-life
TAMC	Total aerobic microbial count
TB	Tuberculosis
TEAE	Treatment-Emergent Adverse Event
TK	Toxicokinetics
T_{max}	Time to maximum observed serum concentration
TMB	3,3',5,5'-Tetramethylbenzidine
TP	treatment period
TP1	treatment period 1
TP2	treatment period 2
TPC	titer cut point
TPCF	titer cut point factor
TRAE	Treatment-Related Adverse Event
Tyk2	Tyrosine Kinase 2
TYMC	Total yeasts and molds count
UC	Ulcerative Colitis
US	United States
USP	US Pharmacopeia
UV	Ultraviolet

1. Background information on the procedure

1.1. Submission of the dossier

The applicant Elc Group s.r.o. submitted on 28 June 2024 an application for marketing authorisation to the European Medicines Agency (EMA) for Usymro, 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

Usymro 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

Usymro 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)

Usymro, 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

Usymro 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.

Paediatric Crohn's disease

Usymro is indicated for the treatment of moderately to severely active Crohn's disease in paediatric patients weighting at least 40 kg, who have had an inadequate response to, or were intolerant to either conventional or biologic therapy.

1.2. Legal basis, dossier content

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.

The chosen reference 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 90 mg/mL (45 mg per vial) Solution for injection in vial, Stelara 90 mg/mL (45 mg per PFS) Solution for injection in pre-filled syringe, Stelara 90 mg/mL (90 mg per PFS) Solution for injection in pre-filled syringe, and Stelara 5 mg/mL (130 mg per vial) Concentrate for solution for infusion
- Marketing authorisation holder: Janssen-Cilag International NV
- Date of authorisation: 16 January 2009
- Marketing authorisation granted by:
  - Union
- Marketing autorisation numbers: EU/1/08/494/001, EU/1/08/494/003, EU/1/08/494/004, EU/1/08/494/005

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

- Product name, strength, pharmaceutical form: Stelara 90 mg/mL (45 mg per vial) Solution for injection in vial, Stelara 90 mg/mL (45 mg per PFS) Solution for injection in pre-filled syringe, Stelara 90 mg/mL (90 mg per PFS) Solution for injection in pre-filled syringe, and Stelara 5 mg/mL (130 mg per vial) Concentrate for solution for infusion
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Medicinal product which is or has been authorised in accordance with Union provisions in force and to which bioequivalence has been demonstrated by appropriate bioavailability studies:

- Product name, strength, pharmaceutical form: Stelara 90 mg/mL (45 mg per PFS) solution for injection in pre-filled syringe and Stelara 90 mg/mL (90 mg per PFS) solution for injection in pre-filled syringe
- Marketing authorisation holder: Janssen-Cilag International NV
- Date of authorisation: 16 January 2009
- Marketing authorisation granted by:
  - Union
  - Marketing authorisation numbers: EU/1/08/494/001, EU/1/08/494/003, EU/1/08/494/004, EU/1/08/494/005
- Bioavailability study number(s): BAT-2206-001-CR, BAT-2206-002-CR

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 (SA) on the development relevant for the indication subject to the present application:

Date	Reference	SAWP co-ordinators
29 January 2021	EMA/SA/0000047481	Andrea Laslop, Juha Kolehmainen
22 July 2021	EMA/SA/0000062023	Ferran Torres, Andrea Laslop

The applicant received SA on the development of ustekinumab biosimilar (BAT2206) for the treatment in the same indications as the reference product Stelara from the CHMP on 29 January 2021 (EMA/SA/0000047481). The SA pertained to the following quality, non-clinical, and clinical aspects:

- Design of the comparability studies to support manufacturing process changes from the pilot scale to the commercial scale; analytical biosimilarity assessment; stability studies; cell bank characterisation.
- Adequacy of non-clinical development programme.
- Design of the proposed pharmacokinetic study and clinical comparability study; demonstration of PK comparability via the subcutaneous route only; extrapolation of clinical study data to all authorised indications of the reference product.

The applicant received SA on the development of ustekinumab biosimilar (BAT2206) for the treatment in the same indications as the reference product Stelara from the CHMP on 22 July 2021 (EMA/SA/0000062023). The SA pertained to the following clinical aspects.

- Handling of type I error control and dynamic randomisation in study BAT-2206-001-CR; revised design of a Phase 3 study (study BAT-2206-002-CR), including handling of patients with early termination, wash-out period in patients who have recently used any monoclonal antibodies, timing of assessing the primary endpoint, number of patients to observe long-term safety and immunogenicity, and change of the transition time point re-randomization of patients receiving EU-Stelara.

1.6. Steps taken for the assessment of the product

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

Rapporteur: Outi Mäki-Ikola Co-Rapporteur: Simona Badoi

The application was received by the EMA on	28 June 2024
The procedure started on	18 July 2024
The CHMP Rapporteur's first Assessment Report was circulated to all CHMP and PRAC members on	4 October 2024
The CHMP Co-Rapporteur's first Assessment Report was circulated to all CHMP and PRAC members on	21 October 2024
The PRAC Rapporteur's first Assessment Report was circulated to all PRAC and CHMP members on	21 October 2024
The CHMP agreed on the consolidated List of Questions to be sent to the applicant during the meeting on	14 November 2024
The applicant submitted the responses to the CHMP consolidated List of Questions on	21 February 2025
The CHMP Rapporteurs circulated the CHMP and PRAC Rapporteurs Joint Assessment Report on the responses to the List of Questions to all CHMP and PRAC members on	31 March 2025
The PRAC agreed on the PRAC Assessment Overview and Advice to CHMP during the meeting on	10 April 2025
The CHMP agreed on a list of outstanding issues in writing and to be sent to the applicant on	25 April 2025
The applicant submitted the responses to the CHMP List of Outstanding Issues on	16 May 2025
The CHMP Rapporteurs circulated the CHMP and PRAC Rapporteurs Joint Assessment Report on the responses to the List of Outstanding Issues to all CHMP and PRAC members on	4 June 2025
The CHMP, in the light of the overall data submitted and the scientific discussion within the Committee, issued a positive opinion for granting a marketing authorisation to Usymro on	19 June 2025

2. Scientific discussion

2.1. Problem statement

2.1.1. Disease or condition

Not applicable for biosimilars.

2.1.2. Epidemiology

Not applicable for biosimilars.

2.1.3. Clinical presentation, diagnosis

Not applicable for biosimilars.

2.1.4. Management

Not applicable for biosimilars.

2.2. About the product

Usymro (BAT2206) 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. It has been developed as a biosimilar to Stelara.

The therapeutic indications for BAT2206 proposed are

Adult patients with:

- moderate to severe plaque psoriasis who failed to respond to, or who have a contraindication to, or are intolerant to other systemic therapies including ciclosporin, methotrexate (MTX) or PUVA (psoralen and ultraviolet A).
- active psoriatic arthritis when the response to previous non-biological disease-modifying anti-rheumatic drug (DMARD) therapy has been inadequate.
- 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.

Paediatric patients with:

- 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.
- moderately to severely active Crohn's disease in paediatric patients weighing at least 40 kg, who have had an inadequate response to, or were intolerant to either conventional or biologic therapy.

Except for the treatment of ulcerative colitis, which is not sought for BAT2206, the proposed indications of BAT2206 are the same as those currently authorised for the reference product, Stelara in EU. The strengths of BAT2206 match those of Stelara.

The following presentations are applied for:

Route	Strengths	Presentation
Subcutaneous Injection	45 mg/0.5 mL	In a single-dose prefilled syringe (PFS) with needle safety device (NSD) consisting of a Type I glass syringe barrel with a brominated butyl rubber stoppered plunger rod, a stainless- steel needle, an elastomer + polypropylene rigid needle shield (needle cover), and an NSD.
	90 mg/1 mL	
	45 mg/0.5 mL	In a single-dose vial consisting of a 2 mL Type I glass vial closed by a chlorobutyl rubber stopper covered with a crimped-on aluminum ring and a plastic flip-off cap.
Intravenous Infusion	130 mg/26 mL (5 mg/mL)	In a single-dose vial consisting of a 30 mL Type I glass vial closed by a chlorobutyl rubber stopper covered with a crimped-on aluminum ring and a plastic flip-off cap.

The applied presentations match those of Stelara. Stelara is also available in a pre-filled pen autoinjector presentation. No such presentation has been developed for Usymro.

2.3. Type of application and aspects on development

The legal basis for this application refers to:

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

BAT2206 has been developed in accordance with the EMA's Guidelines on similar biological medicinal products (CHMP/437/04 Rev 1, October 2014) and on similar biological medicinal products containing biotechnology-derived proteins as active substance: non-clinical and clinical issues (EMEA/CHMP/BMWP/42832/2005 Rev1, December 2014).

2.4. Quality aspects

2.4.1. Introduction

The finished product is supplied in four presentations containing BAT2206 (ustekinumab) as active substance:

45 mg (0.5 mL) solution for injection in prefilled syringe (PFS)

90 mg (1.0 mL) solution for injection in PFS

45 mg (0.5 mL) solution for injection in vial

130 mg (26 mL) concentrate for solution for infusion in vial

Other ingredients are: EDTA disodium salt dihydrate (only 130 mg IV presentation), L-histidine, L-histidine monohydrochloride monohydrate, Methionine (only 130 mg IV presentation), Polysorbate 80, Sucrose and Water for injections.

Each PFS consists of a type I glass 1 mL syringe with a fixed stainless-steel needle and a needle cover containing dry natural rubber (a derivative of latex). The syringe is fitted with a passive safety guard.

Each vial presentation consists of a type I glass vial (2 mL for the 45 mg vial presentation and 30 mL for the 130 mg vial presentation) closed with a coated chlorobutyl rubber stopper.

USYMRO (BAT2206, ustekinumab) is available in a pack of 1 prefilled syringe or 1 vial.

BAT2206 was developed as a biosimilar for EU-Stelara (ustekinumab). BAT2206 has the same route of administration, dosage form, and product strength as Stelara. The reference biological medicinal product Stelara was originally approved in the EU in January 2009 (EMEA/H/C/000958).

2.4.2. Active substance

2.4.2.1. General information

BAT2206 (ustekinumab) is a human IgG1 monoclonal antibody composed of two heavy and two light chains. Each heavy chain contains 449 amino acids and each light chain 214 amino acids. BAT2206 contains a total of 16 disulphide bonds and the theoretical molecular weight is approximately 148 kDa without glycans. Each heavy chain contains an N-linked glycan at a consensus glycosylation site on asparagine 299, the predominant glycan moieties being G0F and G1F. The general information of BAT2206 has been appropriately provided.

Ustekinumab binds specifically to the shared p40 subunit of human IL-12 and IL-23, thereby preventing p40 binding to the IL-12Rβ1 cell surface receptors. Ustekinumab cannot bind to IL-12 or IL-23 already bound to IL-12Rβ1 receptors, therefore, ustekinumab is not likely to have Fc-mediated effector functions. The proposed mode of action for BAT2206 is inhibition of IL-12 and IL-23 -mediated signalling.

2.4.2.2. Manufacture, process controls and characterisation

BAT2206 active substance (AS) is manufactured and release tested at Bio-Thera Solutions, Ltd., 155 Yaotianhe Street, Huangpu District, Guangzhou, Guangdong, China, 511356 in accordance with GMP. All facilities involved in the manufacturing and testing of the AS comply with EU GMP.

Description of manufacturing process and process controls

The manufacturing process of BAT2206 is well-established for production and purification of monoclonal antibodies. In contrast to the reference medicinal product Stelara, which is produced in Sp2/0 murine cells, BAT2206 AS is expressed in Chinese hamster ovary (CHO) cells.

The batch numbering system is considered adequate to guarantee traceability of each unique batch.

Overall, the manufacturing process for BAT2206 has been adequately described. Critical process parameters and critical in-process controls have been clearly indicated. The handling of the final AS has been adequately described.

Control of materials

The history of the host cell line derived from CHO-K1 cell line was adequately described. The light and heavy chain sequences of ustekinumab were obtained from a patent and a Stelara review report and were confirmed by mass spectrometric analysis of the reference medicinal product. Construction of the expression plasmid has been described in sufficient detail.

A three-tiered cell bank system was established including the PCB, the master cell bank (MCB), and the working cell bank (WCB). Additionally, the limit of in vitro cell age (LIVCA) was established. No animal or human derived materials were used in the preparation of cell banks. Cell banks were adequately characterised for identity, consistent expression level and viability of the cells, correct sequence of ustekinumab, and consistent copy number of the heavy and light chains. Genetic stability, protein expression and product quality were appropriately demonstrated for the LIVCA. Storage stability of cell banks is adequately controlled, and it is confirmed that cell banks are stored in two different locations. Overall, the cell banks were described in sufficient detail and in accordance with current guidance of ICH Q5D and Q5A(R2). A protocol for the renewal of the WCB has been provided and is acceptable.

Raw materials used in the manufacturing process of BAT2206 are appropriately described. No materials of animal and/or human origin are used in the manufacture of BAT2206 DS. Materials originating from plant or from recombinant expression in are appropriately described. Non-compendial raw materials are tested against internal specifications. It has been confirmed that an agreement is in place with suppliers to notify the MAH in case of changes to the media.

Control of critical steps and intermediates

Process parameter impacting on critical quality attributes (CQAs) have been classified as critical process parameters (CPP), whereas other process parameters are controlled as non-CPP to ensure process consistency. Proven acceptable ranges (PARs) have been determined for each process parameter regardless of the criticality. Normal operating ranges (NORs) are within or equal to PARs, and an excursion outside NOR results a deviation and a subsequent investigation. Overall, process parameters, their criticality classification, and associated NORs and PARs are considered adequate and appropriately justified.

The manufacturing process is controlled by in-process controls (IPC) with associated acceptance criteria. All safety related IPCs, such as microbial and bacterial impurities, viral safety parameters, process-related impurities, and filter integrity tests are categorised as critical IPC. Overall, the IPC and associated acceptance criteria are considered adequate and sufficiently justified. A confirmation is given that deviation from acceptance criteria for safety related critical IPCs for unprocessed bulk leads to batch rejection.

CPPs and non-CPPs, as well as specification for IPCs are clearly described. IPC methods are appropriately qualified. In conclusion, the control strategy is considered adequate to ensure intended and consistent quality of the BAT2206 DS.

Process validation

BAT2206 AS manufacturing process has been validated by process performance qualification (PPQ) batches produced by commercial manufacturing process. Process parameters and IPCs met their pre-defined ranges for upstream and downstream manufacturing process steps. Deviations were appropriately investigated raising no concerns of the manufacturing process consistency. Impurity clearance data demonstrated that the purification process of BAT2206 is reproducibly capable to remove process-related impurities and elemental impurities to acceptable safety level.

Intermediate hold times were appropriately validated with commercial scale batches. The target maximum lifetimes for chromatography resins were validated using scale down models, in which the column heights exceeded the PARs. However, based on the column performance and product quality data, the scale down models are deemed representative of the commercial scale. A protocol for commercial scale resin lifetime verification study is appropriately provided.

Reusable membranes are cleaned and monitored for each batch in real time during manufacturing. The monitoring protocol and tests included are considered appropriate.

In conclusion, the process validation data demonstrates that the manufacturing process of BAT2206 AS is consistent and capable to produce AS with desired quality.

Extractables and leachables from materials used in the AS manufacturing were evaluated using a risk assessment tool and extractables studies conducted by manufacturers. The remaining risk is generally considered low.

Manufacturing process development

A quality target product profile (QTPP) has been determined based on the reference medicinal product. Quality attributes (QA) crucial for product safety, immunogenicity and efficacy were categorised as critical QAs (CQA) without any risk ranking approach. A risk ranking and filtering tool (RRF) was used to assess criticality of other QAs. Altogether 26 QAs were categorised as CQAs such as protein content, bacterial endotoxins, bioburden, viruses, mycoplasma, host cell protein, host cell DNA, visible/sub-visible particles, bioactivity, high mannose glycans, aggregates, fragments, charge heterogeneity, binding to IL-12/IL-23, and FcRn binding. Classification of CQAs is considered relevant and acceptable.

Upstream process development studies were conducted obtain similar quality profile as the reference medicinal product. Downstream process development studies included several DoE experiments to optimise parameters. Data presented for process development studies supports selected ranges for process parameters.

Scale-down models were described for the upstream and downstream manufacturing process, and the main parameters were shown to be highly similar. Despite of minor differences observed in the upstream process, the scale-down models can be considered sufficiently representative of the commercial scale and suitable for the process characterization studies. Additionally, a scale-down model for UF/DF step was adequately demonstrated to be representative of the commercial UF/DF step. Depending on a process step, either one-factor-at-the-time, a partial factorial, or a full factorial design was used. Overall, the ranges defined for process parameters are considered appropriate to support manufacturing consistency and desired product quality.

Comparability has been sufficiently demonstrated between early-stage process and Process A. Batch release data was compared between Process A and B indicating mainly comparable quality. Minor differences were observed. However, all results were within acceptance criteria raising no concerns on comparability between Process A and Process B.

A comparability evaluation was performed for clinical Process B, developmental Process B-1, and commercial Process B-2 according to the principles described in ICH Q5E. Several minor changes in key equipment and adjustments in the process parameters were described between the processes. Based on the provided in-process control data, batch release data and stability data, these changes had no significant impact on AS quality and stability. In conclusion, the comparability between developmental, clinical and commercial processes has been appropriately demonstrated.

Characterisation

A variety of orthogonal methods were used to characterise the structure, physicochemical properties as well as biological functions and activities of BAT2206. The primary reference standard was included in the characterization studies.

The primary structure of BAT2206 including intact and subunit molecular weight, amino acid sequence, N- and C-terminal sequences, disulfide bonds, and glycosylation site were demonstrated consistent with theoretical expectations. The primary sequence was confirmed. The presence and levels of detected post-translational modifications are generally acceptable for a therapeutic mAb.

Molecular size variants were determined. SEC-MALS analysis indicated the molecular mass of approximately 145.5 kDa and SV-AUC the purity of monomer >95%. Charge variants were analysed with IEC-HPLC demonstrating consistent peak shape and level of acidic variants, main peak and basic variants.

Biological functions and activities: BAT2206 specifically binds to p40 subunit shared by IL-12 and IL-23. Consistent binding activity to p40, IL-12, and IL-23 was demonstrated using ELISA methods, and consistent binding kinetics to IL-12 and IL-23 by SPR. Lack of binding to receptor-bound IL-12/IL-23 was demonstrated by cell-based assay. Competitive inhibition assay of IL-12Rβ1 to p40 by BAT2206 (ELISA) and cell-based neutralising activity assay against IL-12 were used to confirm specific binding and biological activity of BAT2206.

Fc binding affinity was characterised using BLI and SPR methods. Binding affinity to FcRn was reported as relative affinity to the PRS (range 88-128%). The equilibrium binding constants were determined for FcγRIa, FcγRIIa (131H/R), FcγRIIb, FcγRIIIa (158F/V), FcγRIIIb, and C1q. The lack of Fc effector functions, ADCC, CDC and ADCP, were sufficiently demonstrated with the PRS, one BAT2206 FP batch, and bevacizumab as a positive control using cell-based assays. Overall, the Fab- and Fc-related biological activities of BAT2206 are studied in sufficient detail.

Process-related impurities: impurities were identified as process-related impurities, and it was adequately demonstrated that the manufacturing process of BAT2206 is capable of clearing these impurities to the acceptable safety level. Process-related impurities are appropriately controlled in the release specification and as an IPC during manufacturing. Nitrosamine risk assessment report was provided and the assessment can be found later in FP section.

The analytical methods used for characterisation of BAT2206 DS/DP and for detection of process-related impurities are considered appropriate. Overall, the characterisation of BAT2206 has been adequately performed. Further assessment of BAT2206 characteristics can be found under Biosimilarity section 2.4.3.5.

2.4.2.3. Specification

The specification of BAT2206 AS includes compendial tests for colour, clarity, pH, bacterial endotoxins, and bioburden; and non-compendial tests for purity, charge variants, identity, protein content, process-related impurities, and potency. The proposed specification is set according to ICH Q6B, and it covers all relevant characteristics of BAT2206 AS.

The acceptance criteria for BAT2206 AS are established based on release and stability data from up to clinical or commercial scale AS batches. The selection of the batches is considered acceptable. For quantitative parameters, the acceptance limits were generated using the mean±3SD. Additionally, Process performance index (Ppk) and Process capability index (Cpk) with value >1.33 were used as indicators for sufficient

capability of the process. Furthermore, analytical and manufacturing variability, regulatory guidelines, pharmacopeial limits and published literature have been taken into account. The same acceptance criteria are proposed for the AS stability and release specification.

The proposed acceptance limits for compendial m are acceptable.

The proposed purity acceptance criteria are considered adequately justified.

Identification acceptance criteria are acceptable.

For AS protein content, these limits are acceptable.

The acceptance criteria for protein A and host cell DNA are appropriately justified based on general safety limits and are acceptable. The specification and IPC limits were tightened upon request.

For potency by binding activity ELISA, the acceptance criteria is appropriately supported by AS batch release data and stability data being acceptable. The acceptance criteria for cell-based potency assay is considered appropriately justified for AS release and stability specification.

Analytical procedures

Compendial bioburden method has been appropriately verified. Bacterial endotoxin test is assessed in the FP section.

Non-compendial methods have been satisfactorily described including principle of the method, procedure, operating conditions, materials and solutions, equipment, system suitability acceptance criteria and reporting of results. Potency is determined by binding activity of BAT2206 to p40 which is a shared subunit of IL-12 and IL-23, as well as by cell-based inhibition assay in which BAT2206 inhibits IL-12 binding to the cell surface receptor and therefore secretion of IFN-γ. An additional assay control is included in potency assays to monitor stability of the potency reference standard and the method. In general, the analytical methods were adequately validated and demonstrated to be suitable for the intended use. Issues related to the HCP assay and change in the calculation method of cell-based potency assay were appropriately addressed in D181 response raising no further concerns.

The batch analysis data has been provided for BAT2206 AS batches including batches used for phase I and III clinical studies, batches used for quality and/or stability studies, and PPQ batches. All results comply with the proposed commercial specification.

Reference standards have been adequately described. During early development, an interim reference standard was used for pre-clinical and clinical batch release, stability studies, and quality comparability studies, whereas the primary reference standard was used for long-term stability studies of clinical and PPQ batches, batch release testing, and quality similarity studies. The working reference standard has been prepared, and it is intended for batch release and stability testing, and for other routine testing. The PRS is reserved for calibration and stability studies of WRS.

The IRS, PRS, and WRS have been appropriately characterised. The potency of the IRS was adequately verified against one batch of Stelara, and the potency of the PRS was calibrated against the IRS. A potency value of 100% was assigned to the reference standards after calibration. Appropriate stability protocols are provided, and available stability data indicates good stability of the reference standards. The periodic re-testing is performed annually for the PRS and WRS, or after five years every third year for the PRS. The re-testing protocols and associated acceptance criteria are acceptable.

Container closure system (CCS) used for BAT2206 AS is a sterile, single-use, compendial bag in contact with the DS. The CCS is appropriately described and demonstrated to be suitable for storage of BAT2206 DS.

2.4.2.4. Stability

A shelf-life of 24 months at -60±10°C is proposed for BAT2206 AS based on the long-term stability data.

AS batches manufactured at commercial scale were used in the stability studies including clinical batches (Process B), Process B-1, and PPQ batches and from Process B-2. Relevant physicochemical, purity and potency-related quality attributes are included in the stability protocols. Acceptance criteria of stability testing are aligned with release specification.

Analytical methods used for stability testing are the same validated methods as described in 3.2.S.4.2. The stability-indicating property of methods has been sufficiently demonstrated. The stability data tables include information about which data has been obtained with previous vs. current method.

Currently available long-term stability data indicate good stability of BAT2206 AS with no significant changes or trends. Supportive long-term stability data shows minor trend in charge variants, however, all results meet the acceptance criteria. All stability data provided are within the stability specification.

According to the photostability studies the BAT2206 AS is photolabile and should be protected from light.

The proposed shelf-life of 24 months at -60±10°C is acceptable with the currently available long-term stability data.

2.4.3. Finished medicinal product

2.4.3.1. Description of the product and pharmaceutical development

The finished product (FP) of BAT2206 is supplied in four presentations as a sterile, preservative-free solution in single-dose container as follows:

Solution for injection (90 mg/mL) intended for subcutaneous administration

- 45 mg/0.5 mL prefilled syringe (PFS)
- 90 mg/1.0 mL PFS
- 45 mg/0.5 mL vial

Concentrate for solution for infusion (5 mg/mL) intended for intravenous administration

- 130 mg/26 mL vial

The qualitative and quantitative composition of each BAT2206 FP presentation is provided. The chosen excipients comply with Ph. Eur. and their function has been appropriately described. The qualitative composition of the finished FP of BAT2206 is stated in Table 1. No formula overages are included and the overfill ensures the administration of nominal volume of BAT2206 DP.

Table 1. Composition of the Finished BAT2206 DP

Presentation	Excipients
PFS and 45 mg vial presentations	L-histidine L-histidine monohydrochloride monohydrate Polysorbate 80 (E433) Sucrose Water for injections
130 mg vial presentation	EDTA disodium salt dihydrate L-histidine L-histidine monohydrochloride monohydrate Methionine Polysorbate 80 (E433) Sucrose Water for injections

Pharmaceutical development

Comprehensive and systematic studies were performed in accordance with ICH Q8 guideline. BAT2206 FP was developed to have the same route of administration and product strength as the reference product, EU-Stelara. Overall, the extensive and systematic formulation development studies demonstrated the robustness of the formulation. No changes in the BAT2206 FP formulation were made during the manufacture of developmental clinical and commercial batches.

Manufacturing process development - The lot size, manufacture site, production equipment and production line are same between clinical and commercial manufacturing processes, only in-process and parameter controls are tightened for commercial manufacturing process which are adequately presented. It can be agreed with the applicant that none of the process changes increase the safety risks for subjects.

The provided characterization studies are considered appropriate and demonstrate the robustness of AS thawing and compounding steps in the manufacturing process of the finished FP of BAT2206. The justification and the provided risk assessment for the proposed change are considered appropriate.

Container closure system - The primary container closure systems (CCS) of both vials consist of type I glass vial closed by a chlorobutyl rubber stopper and the primary CCS of PFS with NSD is composed of a 1 mL Type I glass syringe barrel equipped with a stainless-steel injection needle and a stoppered plunger-stopper. Appropriate Notified Body opinion in accordance with Article 117 of the Regulation (EU) 2017/745 on medical devices (the Medical Device Regulation, MDR) has been provided for the PFS with NSD.

The choice of materials for primary CCS of all BAT2206 FP presentations were appropriately justified.

2.4.3.2. Manufacture of the product and process controls

The manufacturing, packaging, labelling, batch release and stability testing of the finished FP of BAT2206 are performed by Bio-Thera Solutions, Ltd., China. The applicant has provided EudraGMDP/DUNS references and/or EU-GMP certificate numbers for all manufacturing and testing sites, which is considered a valid proof of EU-GMP compliance.

The standard manufacturing processes comprise of AS thawing, compounding, sterile filtration, aseptic filling and stoppering, capping (vial presentations), visual inspection, labelling and packaging. A narrative description of the full manufacturing process was provided, accompanied by a flow chart describing each step of the process including process parameter with proposed operating range and in-process controls with

proposed acceptance criteria. Overall, the manufacturing process description was adequately justified by the manufacturing development and process validation data. The batch numbering system was explained.

Process controls - The manufacturing processes of the finished BAT2206 FP are controlled by multiple process parameters (PP) and in-process controls (IPC). For PPs proven acceptable ranges (PAR), criticality and impacted attribute are presented. The ranges and criticality are based on prior knowledge, historical data, process development and process validation data. Rationale and justification for the classification of PPs applied as non-key, key, critical and non-critical was provided. The measures taken in case of PP fall outside normal operating ranges has been sufficiently described. The acceptance criteria of IPCs are based on historical data or to allow compliance with final FP specifications. The criticality of the IPC has not been defined as clearly as for PP but is considered sufficient. The actions taken in case of out of specifications has been sufficiently explained. Overall, the presented process controls and proposed PARs are considered acceptable and the proposed control strategy for the FP manufacturing process can be agreed.

Manufacturing process validation - The FP manufacturing processes covering all manufacturing steps were validated by producing three consecutive commercial scale PPQ lots for each BAT2206 FP presentation at the proposed commercial manufacturing site. Overall, all PPQ batches were successfully validated and the presented data met the proposed commercial specification acceptance criteria, thus demonstrating the consistency and reliability of the FP manufacturing processes.

The proposed process and hold times for commercial manufacturing process are clearly presented and summarized. The proposed aseptic filling time is in line with the relevant guideline on sterilisation (EMA/CHMP/QWP/850374/2015). Overall, the proposed process and hold times are adequately justified and validated and thus considered acceptable.

The aseptic process validation (media fills) was carried out at Bio-Thera Solutions, Ltd under worst case conditions for three media fill batches representing the commercial configuration. Appropriate validation data for both sterilization cycles have been provided.

Overall, adequate data of filter validation was presented which is considered acceptable.

The compatibility and extractable studies of disposable materials in contact with FP during manufacturing process were performed. The performed studies demonstrated appropriate compatibility and the amount of detected extractables was much lower than PDE.

The shipping validation studies of BAT2206 FP were conducted.

2.4.3.3. Product specification

Specifications are set in accordance with ICH Q6B principles and cover all relevant characteristics of the finished FP of BAT2206. Comprehensive panel of specification are set for BAT2206 FP presentations including tests for appearance, identity, purity and impurities, adventitious agents, potency, quantity and general properties including pH, osmolality, visible and subvisible particles and extractable volume. In case of purity and polysorbate content, separate acceptance criteria for release and shelf-life specifications are proposed and considered acceptable.

Batch analytical data was provided for all lots of BAT2206 DP. All batches met the acceptance criteria of release specification in place at the time indicating adequate batch-to-batch consistency and controlled manufacturing process. The turbidimetric method was used in the endotoxin testing of all PPQ batches.

Risk assessments for elemental impurities and nitrosamines are provided. Overall, the identified risk of elemental nitrosamine impurities was low and no further risk control measures are required. This conclusion can be agreed.

Supplier and certificate of analysis were provided for each CCS component and are considered acceptable. Specifications for primary and secondary container closure systems are provided and the used methods of analysis are Ph. Eur. or ISO 9626 and ISO 7864 compliant.

2.4.3.4. Stability of the product

The applicant has performed stability at the long-term storage condition (5°C±3°C), at the accelerated storage conditions (25°C±2°C, 6 months) and at stressed storage conditions (photostability, mechanical stress, 200 rpm for 7 days and high temperature 40±2°C for 21 days). The studies at long-term storage conditions are still on-going whereas the studies at accelerated (for up to 6 months) and stressed conditions are completed. All stability studies have been conducted with PPQ batches for each presentation and supportive batches. Overall, the FP stability program designed by the applicant follows ICH Q1A and ICH Q5C guidelines and the stability study protocols have been provided for all presentations and conditions.

The proposed shelf-life for the finished BAT2206 FP at 2-8°C are 36 months for 45 mg PFS with NSD and 24 months for 90 mg PFS with NSD and 45 mg and 130 mg vial presentations. Appropriate long-term stability data supporting the proposed shelf-life for each FP presentation has been provided. All stability data met the acceptance criteria and are considered acceptable.

The results showed that strong light exposure has negative impact on FP quality and thus should be stored protected from light.

In-use stability studies - PFS presentations are intended for SC administration and do not require any dilution prior use. The in-use stability study was conducted at 30 ℃ for 40 days with both PFS strengths and the results met the acceptance criteria of specifications. Based on this data the applicant proposes in-use period of 40 days at room temperature, which can be agreed.

The 130 mg vial is diluted with 0.9% NaCl-solution prior IV infusion. For in-use stability study, BAT2206 in 130 mg vial presentation was diluted in either in PP or PVC infusion bags and placed at 2-8℃ protected from light for 48 hours followed by storage at controlled room temperature (25°C±2°C) under light exposure (200-500 lux) for up to 8 hours. The experiments demonstrated that BAT2206 is stable and compatible with representative materials and light stress had no impact on the physical and chemical stability of BAT2206 while held in IV bags. The applicant is proposing in-use stability of 8 hours at room temperature after dilution in SmPC.

2.4.3.5. Biosimilarity

A comprehensive similarity exercise following the general principles outlined in the guideline on similar biological medicinal products containing biotechnology-derived proteins as active substance; Quality issues (EMA/CHMP/BWP/247713/2012) has been performed between the proposed biosimilar BAT2206 and the reference product Stelara (ustekinumab). The analytical similarity of BAT2206 is assessed in comparison to EU-Stelara, although both EU- and US-Stelara are included in the biosimilarity exercise. BAT2206, US-Stelara, and EU-Stelara are available in four presentations: 45mg/0.5mL PFS (SC), 90mg/1mL PFS (SC),

45mg/0.5mL Vial (SC), and 130mg/26mL Vial (IV). The qualitative compositions of SC and IV presentations of BAT2206 are similar to the corresponding presentation of the reference medicinal product.

Comparability between all four FP presentations has been adequately demonstrated and thus it can be concluded that the material used in the analytical biosimilarity studies is considered representative of the material used in clinical trials. The biosimilarity approach is reasonable and appropriately performed.

The number of batches is considered justified and suitable for demonstration of biosimilarity.

The comparative testing included analysis of primary structure, higher order structure, particles and aggregates, purity and product-related substances, general properties, biological and functional activities and thermal stability and degradation studies. All methods used in the similarity assessment were appropriately qualified or validated to confirm suitability of use.

Table 2. Summary of biosimilarity assessment

Molecular parameter	Attribute	Methods	Key findings, conclusions
Primary structure	Intact mass	LC-MS	similar.
	Reduced mass	LC-MS	Similar.
	Reduced Peptide Map Primary amino acid sequence coverage N/C terminal sequencing	Reduced Peptide mapping	similar. The identical amino acid sequences are adequately confirmed.
	Site-specific PTM: Oxidation Deamidation Glutamic acid cyclization N-TERM(%), Occupance of glycosylation (%)		Some minor differences were observed in oxidation and deamidation levels, that are not considered clinically significant due to low levels. Glutamic acid cyclization levels were similar. C-terminal lysine truncation was different but not considered clinically significant. Total glycosylation levels were similar.
	Disulfide bonds	Non-reduced Peptide Mapping	Similar disulfide bonds.
	Free thiol	Ellman's method	The free thiol content in both products is so low that the difference in free thiol content does not preclude similarity.
	Glycosylation	Glycosylation site: peptide mapping Glycan map: HILIC-HPLC	Glycosylation site: Asn299 residue of the heavy-chain EEQYNSTYR peptide Terminal galactosylation: in similarity criteria High mannose: similar Afucosylation: similar levels Sialylation: The lower sialylation level in BAT2206 did not show significant differences between BAT2206 and Stelara in multiple comparisons of the functional and

Molecular parameter	Attribute	Methods	Key findings, conclusions
			biological properties in a variety of binding and cell-based assays, toxicology experiments, or clinical study. α-Galactosylation: different from EU-Stelara . The glycan map profiles of BAT2206 and EU-Stelara were not visually similar, because of some new and missing species detected for BAT2206 and EU-Stelara.
	Glycation	LC-MS	The glycation content of BAT2206 is significantly different than in EU-Stelara. There are no glycation sites in the CDR region. No impact on activity is anticipated.
	Isoelectric point (pI)	cIEF	The pI values are based on the main peaks of the profiles and are similar. The cIEF profiles differ in basic and acidic peaks, but these differences are justified and do not preclude similarity.
Higher order structure	Secondary structure	FTIR	The secondary and tertiary structures were similar and similar thermal stability was demonstrated.
		Far UV CD	
	Tertiary structure	Near UV CD	
	Thermal stability	Nano Differential Scanning Fluorimetry (NanoDSF)	
Particles and Aggregates	Particle size	DLS	Similar main peaks. There is a difference between 130mg Vial and 45mg PFS submicron particle size. Both presentations are similar with the corresponding presentation of the reference product (EU-Stelara).
	Aggregates	SEC-MALS	The aggregate peak mass and main peak mass are similar to reference product. The amount of aggregates in BAT2206 and the reference product were both low, and are likely not to affect the safety and efficacy of the product.
		SV-AUC	The measured monomer peak percentages show similarity of the two products.
Purity and Product-related Substances	Size variants	SEC-HPLC/SEC-UPLC	The HMW level in BAT2206 90mg/ml is different than in EU-Stelara. Overall, the HMW level is considered low in both BAT2206 and EU-Stelara and not likely to affect safety or efficacy. A further SEC-UPLC study was conducted to improve the resolution of the SEC method for the aggregates. All the three HMW peaks (aggregates 1, 2 and 3) appear in both BAT2206 and the reference products. Slightly different level of aggregate 3 was observed in BAT2206 compared to the reference product, however, this difference is not considered to have impact of the efficacy and safety. Overall, the total LMW level is low and not likely to affect safety or efficacy.
		nrCE-SDS	Similar levels of pre-peaks and main peaks in BAT2206 and EU-Stelara.

Molecular parameter	Attribute	Methods	Key findings, conclusions
			No new or missing peaks observed for BAT2206 compared to EU-Stelara in the nrCE-SDS profiles.
		rCE-SDS	The rCE-SDS profiles are visually similar between BAT2206 and EU-Stelara with no new or missing peaks observed for BAT2206.
		The differences seen with the three orthogonal methods for size variants are all minor differences and are not likely to be clinically meaningful.	
	Charge variants	IEC-HPLC	BAT2206 has lower level of acidic peaks compared to EU-Stelara. BAT2206 also has lower level of basic peaks compared to EU-Stelara. The level of main peak was higher in BAT2206 than in EU-Stelara. After CpB treatment, the basic region of both BAT2206 and EU-Stelara decreased significantly. However, the IEC-HPLC basic region of BAT2206 (90 mg/ml) was now different from EU-Stelara (90 mg/ml). After removal of N-glycans or after removal of only sialic acids (both accompanied by CpB treatment), the acidic region of BAT2206 and the reference product were analytically similar. The differences between BAT2206 and EU-Stelara in the levels of acidic and basic peaks are not considered clinically meaningful, based on charge variant characterisation studies.
General properties	Protein concentration	Spectrophotometric (280 nm)	Similar protein concentrations.
Thermal Stability and Degradation	Accelerated stability	High temperature at 25±3°C	Testing was carried out with SEC-HPLC (HMW), IEC-HPLC CpB treatment (charge variants), non-reduced CE-SDS (fragments), LC-MS (deamidation and oxidation), neutralising activity against IL-12, potency. The observed differences in the degradation profiles are considered minor and not clinically meaningful. The presented degradation profiles support the claim for biosimilarity.
	Forced degradation	High temperature (40±2°C)	
		Photostability (4500±500 lux)	
		High pH (250nM NH4HCO3)	
		Oxidation (0.04% H2O2)	
Fab-mediated biological activities	Binding to p40 antigen	Indirect ELISA	Similar binding.
	Binding to IL-12 antigen	Indirect ELISA	Similar binding.
	Binding to IL-23 antigen	Indirect ELISA	Similar binding.
	Binding kinetics to IL-12	SPR	Similar binding kinetics.
	Binding kinetics to IL-23	SPR	Similar binding kinetics.
	Lack of binding to receptor bound IL-12 on the cell surface	Flow cytometry	Similar lack of binding.

Molecular parameter	Attribute	Methods	Key findings, conclusions
	Lack of binding to receptor bound IL-23 on the cell surface	Flow cytometry	Similar lack of binding.
	Competitive Inhibition Activity of IL-12Rβ1 Binding to p40	Competitive ELISA	Similar competitive inhibition activity.
	Neutralizing activity against IL-12	Cell-based ELISA	Similar neutralising activity.
Fc-mediated biological activities	FcRn binding	Biolayer Interferometry Technology (BLI)	Similar binding affinity.
	FcγRIa, FcγRIIa (131H/R), FcγRIIb, FcγRIIIa (158V/F) and FcγRIIIb Binding	FcγRIa: SPR Others: BLI	Although based on the K_D values, the level of binding for BAT2206 is lower, the binding levels of FcγRIa, FcγRIIa (131H/R), FcγRIIb, FcγRIIIa (158V/F) and FcγRIIIb are considered similar.
	Binding to C1q	BLI	Although based on the K_D values, the level of binding for BAT2206 is slightly lower, the binding levels are considered similar.
	Lack of ADCC /ADCP /CDC activity	ADCC: Effector cell assay CDC: cell-based bioassay ADCP: reporter gene assay	Similar lack of ADCC / ADCP / CDC activity.

Similarity between BAT2206 and EU-Stelara has been demonstrated for the following physicochemical and biological properties:

- Primary structure
- Higher order structure
- Thermal stability and degradation studies
- General properties including protein concentration
- Biological and functional activity including Fab- and Fc-mediated activities:
    - Binding to p40 antigen
    - Binding to IL-12 antigen
    - Binding to IL-23 antigen
    - Binding kinetics to IL-12
    - Binding kinetics to IL-23

- Lack of binding to receptor bound IL-12 on the cell surface
- Lack of binding to receptor bound IL-23 on the cell surface
- Competitive Inhibition Activity of IL-12Rβ1 Binding to p40
- Neutralizing activity against IL-12
- FcRn binding
- FcγRIa, FcγRIIa (131H/R), FcγRIIb, FcγRIIIa (158V/F) and FcγRIIIb Binding
- Binding to C1q
- Lack of ADCC /ADCP /CDC activity

The totality of the presented biological and physiochemical data support the claim of biosimilarity for BAT2206 and EU-Stelara. All biological activities relevant to the primary mechanism of action, including binding to p40, IL-12 and IL-23 antigens, binding kinetics to IL-12 and IL-23, lack of binding to receptor bound IL-12 or IL-23 on the cell surface, competitive inhibition activity of IL-12Rβ1 binding to p40, neutralizing activity against IL-12, and FcRn binding, are similar. A significantly lower sialylation level in BAT2206 compared to EU-Stelara did not result in differences in binding studies or PK-profiles. Differences were also observed in charge variant levels analysed with IEC-HPLC. The level of both acidic and basic peaks in BAT2206 was lower than in EU-Stelara. The differences between BAT2206 and EU-Stelara in the levels of acidic and basic peaks are not considered clinically meaningful, based on charge variant characterisation studies. Furthermore, minor differences were observed in aggregate profiles and size variant profiles. These differences are not likely to be clinically meaningful and are adequately discussed and justified. Overall, the presented quality data support the biosimilarity of BAT2206 and EU-Stelara.

2.4.3.6. Adventitious agents

No materials of animal or human origin were used in the generation of cell banks or during the production of BAT2206 AS/FP, therefore, the risk for TSE contamination is considered negligible.

Cell banks have been tested negative for bacterial, fungi, mycoplasma, and mycobacterium contaminants. Bacterial endotoxins and bioburden/sterility are adequately controlled for raw materials and throughout the manufacturing and release of BAT2206 DS/DP. In conclusion, the risk of non-viral adventitious agents is adequately addressed for BAT2206.

Viral testing of cell banks indicates that MCB, WCB and LIVCA are free from endogenous viruses and adventitious viral contaminants, except for A- and C-type retroviral particles expected for CHO cells. Generally, cell banks have been adequately tested for viruses.

The unprocessed bulk harvests originating from commercial scale batches were tested negative for mycoplasma and viruses. Bioburden levels met the acceptance criteria. Unprocessed bulk harvests are routinely tested for mycoplasma, bacterial endotoxins, bioburden, adventitious viruses, and MMV.

Viral clearance studies were conducted in accordance with ICH Q5A(R2). A scale-down model of the commercial purification process was used to evaluate the ability of following purification process steps to remove or inactivate potential viral contaminants: protein A affinity chromatography, low pH virus inactivation, anion exchange chromatography (AEX), cation exchange chromatography (CEX), and virus filtration. Summary of verification data is provided to confirm the validity of the scale-down model.

Four model viruses X-MulV, MVM, PRV, and Reo3 selected for viral clearance studies were appropriately justified. The viral clearance capacity of each process step was assessed independently using the scale-down model under worst-case conditions. Each step was evaluated in duplicate, and the lower reduction factor was selected as the worst case and reported. Results obtained with new and aged resins were demonstrated to have comparable capacity to reduce viruses. The overall combined Log10 Reduction Values indicate satisfactory overall virus reduction.

The calculation of safety margin is appropriately presented for a specific model virus X-MuLV with the maximum BAT2206 dose of 520 mg indicating that less than one particle per million doses would be expected, which is acceptable.

Overall, the viral safety of BAT2206 is adequately addressed.

2.4.4. Discussion on chemical, and pharmaceutical aspects

BAT2206 (Usymro) is developed as an ustekinumab biosimilar to the reference medicinal product EU-Stelara.

The manufacturing processes for the active substance and finished product reflect a standard manufacture of monoclonal antibody products. Overall, the manufacturing process controls, process development and process validations as well as raw and starting materials used for the manufacture of BAT2206 have been appropriately described. The data support the conclusion that the manufacturing process reliably generates active substance and finished product meeting their predetermined specifications.

Comprehensive panels of release specifications are set for BAT2206 AS and FP.

The interim, primary and working reference standards for BAT2206 have been appropriately described and characterised.

The proposed AS shelf life of 24 months at -60±10°C is acceptable. The proposed FP shelf-life of 24 months for vial presentations (45 mg and 130 mg) and for 90 mg PFS with NSD presentation, 36 months for 45 mg PFS with NSD presentations at 2-8°C are acceptable.

The notified body opinion for BAT2206 PFS with NSD has been provided.

A comprehensive assessment of biosimilarity between BAT2206 and EU-Stelara has been presented. The totality of the presented biological and physiochemical data supports the claim of biosimilarity for BAT2206 and EU-Stelara. All biological activities relevant to the primary mechanism of action are similar. A significantly lower sialylation level in BAT2206 compared to EU-Stelara did not result in differences in binding studies or PK-profiles. Differences were also observed in charge variant levels analysed, aggregate profiles and size variant profiles. These differences are not likely to be clinically meaningful and are adequately discussed and justified. Overall, the presented quality data support the biosimilarity of BAT2206 and EU-Stelara.

2.4.5. Conclusions on the chemical, pharmaceutical and biological aspects

The quality of Usymro 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 has been presented to give reassurance on viral/TSE safety.

2.5. Non-clinical aspects

2.5.1. Introduction

A battery of *in vitro* pharmacodynamic (PD) studies have been performed to demonstrate the similarity between BAT2206 and EU-Stelara, including binding specificity, binding kinetics, comparative binding to multiple Fc receptors and C1q, antibody dependent cellular cytotoxicity (ADCC), antibody-dependent cellular phagocytosis (ADCP) and complement dependent cytotoxicity (CDC) activity of BAT2206 and RMP.

The applicant had also performed a large package of *in vivo* studies (PD in mouse models, pharmacokinetics/toxicokinetics (PK/TK) and toxicology studies in Cynomolgus monkeys). Validated ELISA methods were used for detection of drug substance and anti-drug antibodies (ADA) in Cynomolgus monkey serum.

Relevant EMA guidelines were followed in the development of biosimilar medical product with exception that no *in vivo* data is required in the EMA/CHMP/BMWP/403543/2010 if the *in vitro* non-clinical studies confirm the biosimilarity. The *in vivo* data package was justified by global product development (regulatory requirements of non-EU authorities). This data is considered as supportive information in this EU application.

2.5.2. Pharmacology

2.5.2.1. Primary pharmacodynamic studies

A comprehensive set of *in vitro* studies were conducted for analytical and functional characterisation and comparison of BAT2206, EU-Stelara and US-Stelara to demonstrate the biosimilarity. The characterisation included the assessment of Fab-mediated activities, Fc binding affinity as well as Fab and Fc mediated characterisation (i.e., ADCC, CDC and ADCP activity). No significant differences between BAT2206 and EU/US-Stelara in the Fab and FcRn mediated functional activities (relevant to mode of action) were recorded in these studies. Binding to representative isoforms of the Fc gamma receptors (FcγRI and FcγRIII), FcRn and complement C1q has been investigated. 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. However, in support of a comprehensive non-clinical package, binding to the FcγRs (with the exception of FcγRIIa-H131, FcγRIIa-R131) was assayed.

BAT2206 and EU-approved Stelara had similar biological activities in terms of Fab function in IL-12/IL-23 p40 binding activity, cell-based IL-12 or IL-23 binding inhibition activity, signaling inhibition activity and IFN-γ secretion inhibition activity.

The analytical biosimilarity program showed overall good comparability between the proposed biosimilar and its reference medicinal product.

No *in vivo* PD studies are required for biosimilar medicinal products in the EU (EMA/CHMP/BMWP/403543/2010) due to the known limitations of *in vivo* studies. These models are not considered sensitive enough to detect the possible small differences in the concentration-activity relationship between the biosimilar and the reference medicinal product (RMP), and the variability usually observed in the in *vivo* studies makes the comparison of biosimilar and RMP challenging. According to the applicant, these *in*

vivo studies were performed to comply with requirements of non-EU (global) authorities and are therefore considered only as supportive information in this EU application.

Two different mouse models were utilised to compare the anti-inflammatory effects of BAT2206 and EU-Stelara. The models are evaluated to be suitable for evaluating the IL-12 and IL-23 induced anti-inflammatory effects but are in doubt sensitive enough to compare the biosimilar to the RMP. No PK data was collected in the performed *in vivo* PD studies. Therefore, studies are lacking a comparative concentration-response assessment for BAT2206 and EU-Stelara. Also, the results show variability between animals on their response that cannot be thoroughly evaluated without PK data, making the comparison of BAT2206 and EU-Stelara challenging. However, even if there are uncertainties, these issues are not pursued further as this data is considered only supportive.

2.5.2.2. Secondary pharmacodynamic studies

Secondary PD studies are not required for similar biological medicinal products.

2.5.2.3. Safety pharmacology programme

Safety pharmacology studies are not required for similar biological medicinal products. No differences were noted in regard to the safety pharmacology endpoints in the repeat-dose toxicity studies in Cynomolgus monkeys after SC or IV administration.

2.5.2.4. Pharmacodynamic drug interactions

Pharmacodynamic drug interaction studies are not required for similar biological medicinal products.

2.5.3. Pharmacokinetics

Validated UV spectrophotometer method was used to quantitate BAT2206-IV injection and ustekinumab (Stelara) concentrations; and validated ELISA methods were used to quantify the BAT2206 and EU-Stelara as well as associated ADA concentrations in Cynomolgus monkey serum/plasma.

Despite the applicant's claim, these studies are not GLP compliant as the study site is located in China, and China is not part of the OECD GLP and MAD program. As this data is considered only supportive for this application, this can be accepted.

The applicant has performed one individual PK study and two repeat-dose toxicity studies including TK analysis in Cynomolgus monkeys. This is not in accordance with the 3R principles, as no absorption studies are required for biosimilar medicinal product. The applicant states that these studies were performed as request of other health authority. This data is considered only as supportive for this application.

In the PK study, the PK parameters of BAT2206 and EU/US-Stelara were compared after SC administration. Two doses of BAT2206, EU-Stelara and US-Stelara were administered (1 or 10 mg/kg) in Cynomolgus monkeys. No major differences in C_{max} or $AUC_{0\text{-}336h}$ were observed. The analysis showed moderate/high standard deviations in analysed parameters, however, the data fulfilled the set acceptance criteria (80-125%) for bioequivalence.

The TK studies investigated the TK parameters in Cynomolgus monkey after SC and IV administration. BAT2206 was administered in tree doses (3, 15, 45 mg/kg/week) whereas EU-Stelara in one dose (SC: 15 kg/mg/week, IV: 45 kg/mg/week). The biosimilarity exercise was therefore performed with one dose and this assessment concerns only the biosimilarity evaluation. The TK analysis did not reveal any difference between males and females. The C_{max} and AUC values were comparable between BAT2206 and EU-Stelara after both routes of administration. Some variation between individuals was observed. As number of animals is low (n=5), the differences in the mean C_{max} and AUC values are mainly explained by intraindividual variation (SD). No markable differences in mean or individual accumulation ratios were recorded.

The applicant's conclusions regarding comparability of PK and TK data for BAT2206 and EU-Stelara are accepted as no differences were reported in *in vitro* functional parameters thus demonstrating biosimilarity.

No distribution, metabolism or excretion studies; comparative studies assessing drug interactions or other PK studies are required for biosimilars.

2.5.4. Toxicology

2.5.4.1. Single dose toxicity

No single-dose toxicity studies are required for similar biological medicinal products.

2.5.4.2. Repeat dose toxicity

No animal toxicity testing (*in vivo* comparison) is required for biosimilar medicinal products in the EU (Guideline on similar biological medicinal products containing biotechnology-derived proteins as active substance: non-clinical and clinical issues (EMEA/CHMP/BMWP/42832/05 Rev.1)).

The supportive 4-week SC and IV administration monkey studies were performed with three different doses of BAT2206 and one dose of EU-Stelara, and the comparative nature of these studies is low. The *in vivo* studies are not required in the biosimilarity assessment in accordance with EU guideline for biosimilar medicinal products, and unnecessary use of especially non-human primates is not in accordance with the 3R principles. However, it is understood that these monkey studies were performed for global development purposes.

The batch used in the 4-week SC monkey study was manufactured in 200L scale (i.e., a pilot scale process) whereas the batch used in the 4-week IV monkey study was manufactured in 500L scale. Of note, the batches produced at 500L scale were used in the *in vitro* PD studies demonstrating the biosimilarity of BAT2206 and EU-Stelara. Used batches and their representativeness with clinical batches are discussed under Quality aspects, see section 2.4.

The overall picture of the toxicity was demonstrated to be similar for the BAT2206 and EU-Stelara. The compared dosing was 15 mg/kg for the SC administration and 45 mg/kg for the IV administration. As the NOAEL was set for 45 mg/kg for both studies, the comparative dosing for SC administration was too low to compare toxicity profiles. Overall, the limitations of the animal models (e.g., sensitivity and variability) are well-known and it is accepted that the performed studies did not demonstrate any differences concerning the biosimilarity assessment of BAT2206 and EU-Stelara.

2.5.4.3. Genotoxicity

Genotoxicity studies are not required for similar biological medicinal products.

2.5.4.4. Carcinogenicity

Carcinogenicity studies are not required for similar biological medicinal products.

2.5.4.5. Reproductive and developmental toxicity

DART studies are not required for similar biological medicinal products.

2.5.4.6. Toxicokinetic data

The TK analysis did not reveal any difference between males and females. The C_{max} and AUC values were comparable between BAT2206 and EU-Stelara after both routes of administration. Some variation between individuals was observed. As number of animals is low (n=5), the differences in the mean C_{max} and AUC values are mainly explained by intraindividual variation (SD). The data is presented in the Table 3 No markable differences in mean or individual accumulation ratios were recorded. The applicant's conclusions regarding comparability of TK data for BAT2206 and EU-Stelara are accepted.

Table 3. Mean BAT2206 and EU-Stelara TK parameters in monkey serum

Study ID/ species	**Dose (mg/kg)**	**Study day**	**Animal AUC (µg·h/ml)**		**C_{max} (µg/ml)**	
P17-S115-RD / Cynomolgus monkey	BAT2206 15	D1	17.67 ± 1.76		134.90 ± 17.77	
	EU-Stelara 15		17.07 ± 2.13		128.01 ± 15.99	
	BAT2206 15	D4	34.41 ± 6.83		266.97 ± 41.32	
	EU-Stelara 15		35.66 ± 10.33		285.62 ± 61.84	
S21009RD1/ Cynomolgus monkey			**Female**	**Male**	**Female**	**Male**
	BAT2206 45	D1	95 700	83 200	1200	993
	EU-Stelara 45		92 500	89 100	1160	1080
	BAT2206 45	D4	165 000	145 000	1830	1480
	EU-Stelara 45		163 000	140 000	1700	1350

2.5.4.7. Local Tolerance

No differences were reported concerning the local tolerance in the site of SC or IV administration in monkeys treated with BAT2206 and EU-Stelara.

2.5.4.8. Other toxicity studies

Antigenicity

The presence of anti-BAT2206 or anti-EU-Stelara antibodies were analysed in the single-dose SC PK study and repeat-dose SC and IV toxicity studies. No differences in the comparison of BAT2206 and EU-Stelara were identified in their ADA response. It should be noted that these data have only low predictivity for the immunogenicity potential in humans, and the relevance of the ADA formation for the clinical safety is discussed more in-depth under Clinical aspects, see section 2.6.

Haemolysis or haemagglutination potential

No differences in haemolysis or haemagglutination potential was observed in human or rabbit RBCs with SC or IV formulation of BAT2206 or EU-Stelara. It should be noted that this type of study is requested only in non-EU countries.

2.5.5. Ecotoxicity/environmental risk assessment

The use of Usymro is not expected to pose a risk to the environment as the active substance ustekinumab is a natural product (protein). In addition, ERA studies are not required for similar biological medicinal product.

2.5.6. Discussion on non-clinical aspects

The comparability assessment strategy for the BAT2206 and EU-Stelara focused on the battery of *in vitro* biological activity studies. In addition, several *in vivo* studies were performed. As no *in vivo* pharmacology or toxicology data are required for the comparability assessment of biosimilars in the EU, this data is considered to be only supportive. In addition, the *in vivo* data is produced in a country that is not part of the OECD MAD program and therefore is not considered to be GLP-compliant. As this data is considered only supportive for this application, this can be accepted.

Pharmacodynamics

The demonstration of biosimilarity of BAT2206 and EU-Stelara was focusing on the battery of receptor-binding studies or cell-based *in vitro* assays relevant for mode of action of ustekinumab, and similar Fab and FcRn mediated functional activities for BAT2206 and EU-Stelara have been demonstrated. These studies are also discussed in the Quality/biosimilarity sections of this report.

The *in vivo* PD studies in mouse models compared anti-inflammatory effects of BAT2206 and EU-Stelara. The sensitivity of these animal models is not adequate to compare the biosimilar to the RMP and thus do not significantly contribute to the biosimilarity assessment based on the *in vitro* biological activity studies.

BAT2206 is manufactured in a glyco-engineered Chinese hamster ovary (CHO) cell line whereas EU/US-Stelara is manufactured in a murine myeloma (Sp2/0) cell line. The impact on different manufacturing environment on the biological activities are evaluated in the Quality/biosimilarity sections of this report.

No secondary pharmacology or pharmacodynamic interactions studies were conducted with BAT2206 and EU-Stelara. These studies are not required for a biosimilar. No differences in the safety pharmacology endpoints were reported in the BAT2206 and EU-Stelara treated monkeys in the supportive 4-week repeat-dose toxicity studies.

Pharmacokinetics

A stand-alone PK study and two repeat-dose toxicity studies including TK analysis were performed in Cynomolgus monkeys. The data showed comparable C_{max} and AUC values between BAT2206 and EU-Stelara.

Toxicology

Two supportive repeat-dose toxicity studies in Cynomolgus monkeys showed no differences in the toxicity between the animals treated with the medicinal products BAT2206 or EU-Stelara.

ERA

The active substance is a natural substance, the use of which will not alter the concentration or distribution of the substance in the environment. Therefore, BAT2206 is not expected to pose a risk to the environment.

2.5.7. Conclusion on the non-clinical aspects

Overall, the available non-clinical data support the biosimilarity of Usymro versus the EU reference product 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.

- **Tabular overview of clinical studies**

Study reference	Population/ Sites/Location/ Study Start/ End Dates	Study design	Dose schedule and duration	Route of administration	N
BAT-2206-001-CR	Healthy Chinese male subjects 1 site in China 3 August 2020/19 April 2021	Randomised, double-blind, single-dose, parallel three-arm study to compare the PK, safety and immunogenicity of BAT2206 injection with Stelara (Ustekinumab, EU and US-sourced)	Single dose of 45 mg BAT2206 injection or 45 mg Stelara (EU) or 45 mg Stelara US)	SC injection	269 subjects (90, 89 and 90 subjects in the BAT2206, EU-Stelara and US-Stelara groups, respectively) treated. 90 subjects in each group enrolled.

BAT-2206-002-CR	Patients with moderate to severe plaque psoriasis 41 sites in 5 countries 06 July 2021/ 07 July 2023	Multicenter, randomised, double-blind, parallel-arm Phase III study to compare the efficacy, safety, immunogenicity, and PK of BAT2206 with Stelara (EU) in patients with moderate to severe plaque psoriasis	A SC dose of 45 or 90 mg BAT2206 or 45 or 90 mg EU-Stelara. Treatment was on Weeks 0, 4, and 16 during TP1 and on Weeks 28 and 40 during TP2.	SC injection	556 patients (278 patients in the BAT2206 group and 278 patients in the EU- Stelara group) in TP1.

2.6.2. Clinical pharmacology

2.6.2.1. Pharmacokinetics

Comparative PK data of BAT2206 has been generated in one PK similarity single-dose study in Chinese healthy male subjects (study BAT-2206-001-CR) following a single subcutaneous (SC) injection. Additionally, steady-state PK characteristics after repeat SC administration has been evaluated in a phase 3 confirmatory study in adult patients with moderate to severe plaque psoriasis (study BAT-2206-002-CR). Furthermore, a population PK study was conducted to analyse data from both studies.

Analytical methods

The bioanalytical method used for determining serum drug concentrations of BAT2206 and Stelara was a validated indirect enzyme-linked immunosorbent assay (ELISA). The validation followed ICH M10 guidance.

Two ECL based assays were used for the detection of ADAs, one for the phase 1 study and one for the phase 3 study. The analytical procedure ICSH 20-029 was used to analyse samples in the phase 1 study. During the sample analysis it was observed that the signal was not completely inhibited with the drug at the confirmatory stage. The root cause was determined to be the low target tolerance of the assay and therefore, a new assay, ICSH 23-034, was developed for the phase 3 study samples. The interference level of the new method was improved, and the target tolerance level was significantly improved. The C_{trough} concentrations were well below the drug tolerance level and 12.5-200 ng/ml of positive control could be detected. The assay was validated with normal human serum and the cut point was reassessed with patient serum in the clinical study. The poor performance of the original ADA assay may have resulted in false negative results, but this issue is not pursued further since the method was modified for the phase 3 clinical study which is considered more meaningful for the immunogenicity assessment.

The presence of neutralising antibodies (NAb) against BAT2206, ustekinumab (US), and ustekinumab (EU) was detected using an ECL based assay. The intensity of the luminescent signal exhibited an inverse correlation with the NAb content in the sample. Drug tolerance at 100 ng/mL PC (positive control) could not be accurately assessed since the method sensitivity was 93.1 ng/mL. Therefore, the drug tolerance of PC at 250 ng/mL with up to 100 µg/mL BAT2206 was reported. The validation followed current guidance except selectivity was only assessed in healthy human serum. The longest possible storage duration of the study samples in the clinical study BAT-2206-002-CR was 715 days. However, long-term stability was demonstrated only over 34 days. The applicant justifies the absence of long-term stability data with the fact that EMEA/CHMP/BMWP/14327/2006 Rev 1 Guideline on Immunogenicity assessment of therapeutic proteins does not request such data and literature demonstrates ADA/Nab stability over years when frozen. This is endorsed.

The validation reports and bioanalytical reports including ISR, when appropriate, were provided.

PK similarity study in healthy adult subjects (BAT-2206-001-CR)

The study design was acceptable. The amendments made to the study protocol after the start of the study have been relevant in relation to the clinical PK.

The eligibility criteria were acceptable and demographic baseline characteristics were well-balanced between the 3 treatment groups.

The primary objective was to compare PK similarity between BAT2206 45 mg SC injection and Stelara (EU-sourced), Stelara (US-sourced). Secondary objectives were to evaluate the safety, tolerability, and immunogenicity of BAT2206 injection and Stelara (EU-sourced), Stelara (US-sourced).

Each subject received either a single 45 mg SC injection of BAT2206, Stelara (EU-sourced), or Stelara (US-sourced).

PK blood samples were collected at pre-dose, and at 4 h, 12 h, 24 h (day 2), 3, 4, 5, 6, 7, 8, 9, 10, 11, 13, 15, 22, 29, 43, 57, 71, 85, 99, and 113 days after drug administration. The ADA samples were collected at pre-dose, and at 10, 15, 29, 57, 85, and 113 days after drug administration.

The primary PK parameters were: AUC_{inf} and C_{max}

The secondary PK parameters were: AUC_{0-t}, AUC_{0-672h}, $AUC_{Tmax-inf}$, $\%AUC_{ex}$, T_{max}, $t_{l/2}$, λz, CL/F and Vz/F.

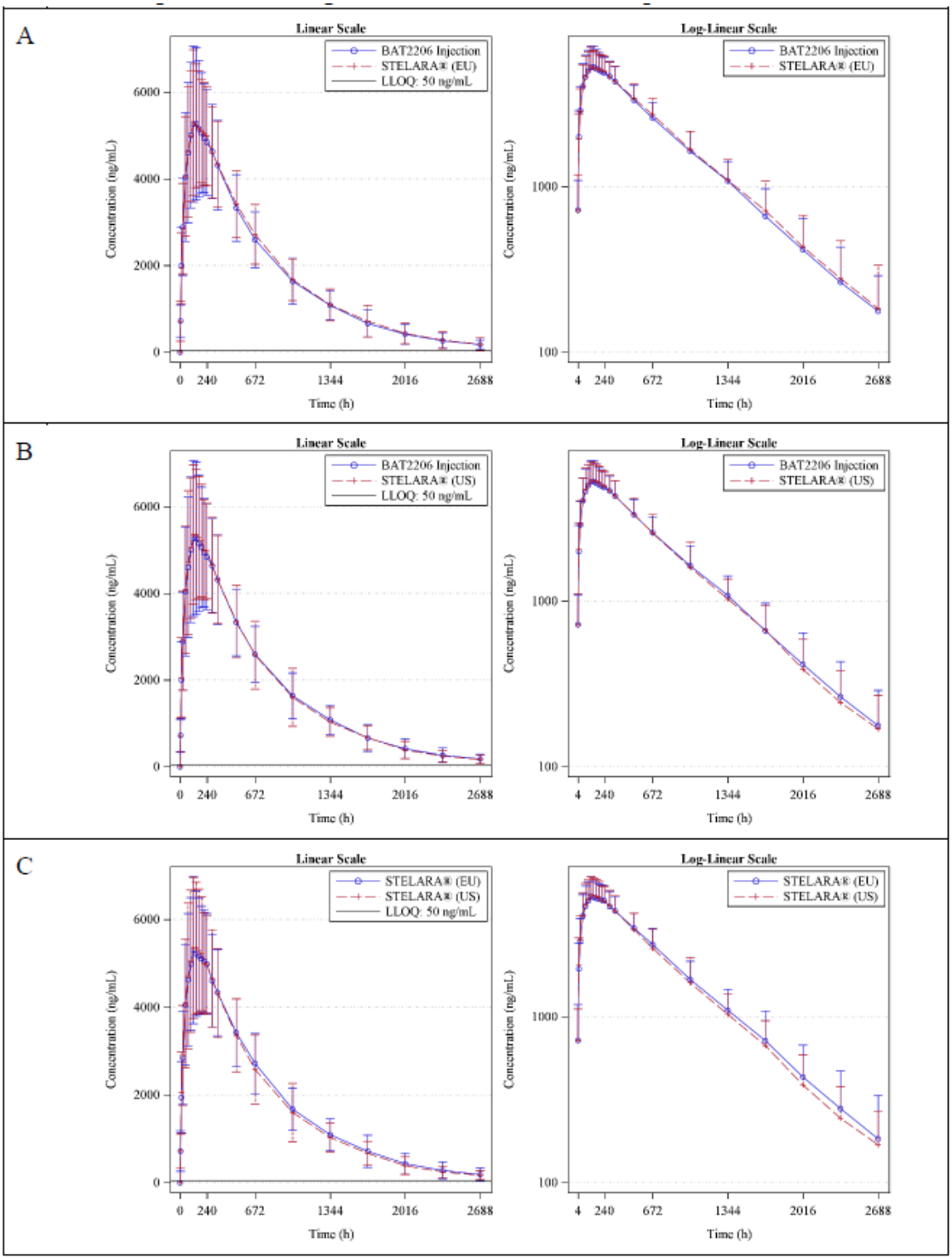
Major protocol deviations occurred in 4 subjects, including 2 subjects in the BAT2206 treatment group, 1 subject in the Stelara (EU-sourced) group and 1 subject in the Stelara (US-sourced) group. The major protocol deviations related to the time of PK/immunogenic blood sample collection and to the time of safety examination. Relevant to PK analysis, for 1 subject in the BAT2206 group, the 336h PK blood sample time deviated by +2 days and 20 minutes (allowable deviation was ± 2h). Other PK sample time deviations were not relevant, because they were from subjects who prematurely withdrew from the study and whose PK data were not included in the primary PK analysis.

PK results

There were three analysis sets related to the PK: PK concentration analysis set (PKCS), PK parameter analysis set (PKPS) and Bioequivalence Set (BES). The PKCS analysis set included n = 90 in the BAT2206 group, n = 89 in the Stelara (EU-sourced) group and n = 90 in the Stelara (US-sourced) group. One subject in the Stelara (EU-sourced) group withdrew voluntarily after randomisation and did not use study drug, so the subject was not included in PKCS, PKPS, and BES. Another subject in the Stelara (EU-sourced) group was excluded from the PKPS and BES because of missing PK blood sampling points. Two subjects in the Stelara (US-sourced) group were excluded from the AUC_{0-inf} subset of BES because of $\%AUC_{ex}$ >20% resulted by missing PK blood sampling points.

Pairwise comparisons showed that mean plasma concentration-time curves were similar among the three treatment groups in Figure 1.

Figure 1. Arithmetic mean ± SD plasma concentrations-time curves for pairwise comparisons among the three treatment groups



A: BAT2206 injection vs Stelara® (EU-sourced), B: BAT2206 injection vs Stelara® (US-sourced), C: Stelara® (EU-sourced) vs Stelara® (US-sourced), linear scale on the left, semi-logarithmic scale on the right.

PK parameters of the three treatment groups were comparable (see Table 4).

Table 4. Comparison of PK parameters between BAT2206 and two reference products (PKPS analysis set)

PK Parameters (Unit)	BAT2206 Injection	Stelara® (EU-sourced)	Stelara® (US-sourced)
C_{max} (μg/mL)	5.604 ± 1.710 (30.51) 5.354 (31.66)	5.701 ± 1.574 (27.61) 5.496 (27.89)	5.786 ± 1.522 (26.30) 5.581 (28.17)
AUC_{0-inf} (h*μg/mL)	4627 ± 1257 (27.16) 4460 (28.17)	4714 ± 1346 (28.55) 4556 (26.24)	4570 ± 1157 (25.31) 4427 (26.05)
AUC_{0-t} (h*μg/mL)	4499 ± 1197 (26.60) 4340 (27.93)	4576 ± 1209 (26.42) 4438 (25.05)	4402 ± 1168 (26.54) 4238 (29.47)
AUC_{0-672h} (h*μg/mL)	2656 ± 664.5 (25.02) 2571 (26.73)	2692 ± 617.6 (22.94) 2624 (23.33)	2684 ± 617.1 (22.99) 2613 (23.92)
$AUC_{Tmax-inf}$ (h*μg/mL)	3949 ± 1210 (30.63) 3765 (32.39)	4028 ± 1273 (31.59) 3869 (28.51)	3891 ± 1078 (27.70) 3746 (28.52)
$\%AUC_{ex}$ (%)	2.68 ± 1.86 (69.44) 2.18 (70.71)	2.58 ± 1.79 (69.35) 2.10 (71.24)	2.26 ± 1.53 (67.56) 1.88 (67.87)
T_{max} (h)	159 (48.0, 337) —	144 (96.0, 337) —	168 (12.0, 336) —
$t_{1/2}$ (h)	459 ± 94.6 (20.63) 450 (20.37)	470 ± 104 (22.17) 458 (22.80)	445 ± 99.1 (22.28) 433 (25.21)
λ_z (1/h)	0.0016 ± 0.0003 (20.56) 0.0015 (20.48)	0.0016 ± 0.0004 (23.55) 0.0015 (22.77)	0.0017 ± 0.0005 (30.66) 0.0016 (25.34)
CL/F (mL/h)	10.49 ± 3.096 (29.52) 10.09 (28.17)	10.20 ± 2.640 (25.87) 9.877 (26.24)	10.51 ± 2.816 (26.80) 10.16 (26.05)
V_z/F (mL)	6761 ± 1786 (26.42) 6544 (25.95)	6676 ± 1410 (21.12) 6531 (21.53)	6575 ± 1667 (25.35) 6344 (28.96)

Note: PK parameters are shown as Mean ± SD (%CV) and Geomean (%CV_b) and T_{max} is shown as Median (Min, Max). In PK parameter calculation, BQLs before T_{max} were set to 0; BQLs after T_{max} were set to "Missing". For subjects with $\%AUC_{ex}$ >20%, PK parameters AUC_{0-inf}, $AUC_{Tmax-inf}$, $t_{1/2}$, λ_z, CL/F, V_z/F and $\%AUC_{ex}$ were excluded in the descriptive analysis.

Abbreviations: C_{max} = maximum plasma concentrations; AUC_{0-inf} = area under the plasma drug concentration-time curve from time 0 to infinity; AUC_{0-t} = area under the plasma drug concentration-time

curve from time 0 to the last quantifiable concentration; $AUC_{0\text{-}672h}$ = area under the plasma drug concentration-time curve from zero to 672h; $AUC_{Tmax\text{-}inf}$ = area under the plasma drug concentration-time curve from T_{max} to infinity; $\%AUC_{ex}$ = percentage of extrapolated area in $AUC_{0\text{-}inf}$; T_{max} = time to maximum observed plasma concentration; $t_{1/2}$ = elimination half-life; λ_z = plasma drug concentration elimination rate constant in terminal phase; CL/F = apparent clearance; V_z/F = apparent volume of distribution; Mean = arithmetic mean; SD = standard deviation; %CV = coefficient of variation; Geomean= geometric mean; $\%CV_b$ = geometric coefficient of variation.

The 90% CIs for GMR of C_{max} and $AUC_{0\text{-}inf}$ were within the predefined equivalent interval (80.00-125.00%), which demonstrated that the three study drugs were pairwise PK equivalent (see Table 5).

Table 5. Statistical comparison of primary PK parameters (BES, 90% CI)

PK Parameters (Unit)	Group 1 Group 2	N Group 1 Group 2	Geomean Group 1 Group 2	GMR[1] (Group 1 Group 2)	90% CI[2]	Power (%)
C_{max} (μg/mL)	BAT2206 injection	90	5.354	97.41	(90.60,	99.75
	Stelara® (EU-sourced)	88	5.496		104.72)	
$AUC_{0\text{-}inf}$ (h*μg/mL)	BAT2206 injection	90	4460	97.89	(91.61,	99.96
	Stelara® (EU-sourced)	88	4556		104.60)	
C_{max} (μg/mL)	BAT2206 injection	90	5.354	95.94	(89.25,	99.37
	Stelara® (US-sourced)	90	5.581		103.13)	
$AUC_{0\text{-}inf}$ (h*μg/mL)	BAT2206 injection	90	4460	100.74	(94.30,	99.99
	Stelara® (US-sourced)	88	4427		107.62)	
C_{max} (μg/mL)	Stelara® (EU-sourced)	88	5.496	98.49	(92.00,	99.96
	Stelara® (US-sourced)	90	5.581		105.44)	
$AUC_{0\text{-}inf}$ (h*μg/mL)	Stelara® (EU-sourced)	88	4556	102.91	(96.52,	99.96
	Stelara® (US-sourced)	88	4427		109.72)	

[1] ANOVA was applied for primary PK parameters C_{max} and $AUC_{0\text{-}inf}$ after logarithmic transformation. Treatment group was chosen as the factor in the analysis. GMR and its 90% CI of PK parameters of group 1 and group 2 were computed.

[2] If the GMR's 90% CI of primary PK parameters of group 1 and group 2 was within the range of

(80.00-125.0%), then drugs of group 1 and group 2 showed PK similarity.

Note: In PK parameter calculation, BQLs before T_{max} were set to 0; BQLs after T_{max} were set to "Missing". For subjects with $\%AUC_{ex}$ >20%, PK parameters $AUC_{0\text{-}inf}$, $AUC_{Tmax\text{-}inf}$, $t_{1/2}$, λ_z, CL/F, V_z/F and $\%AUC_{ex}$ were excluded in the descriptive analysis.

Abbreviations: C_{max} = maximum plasma concentrations; $AUC_{0\text{-}inf}$ = area under the plasma drug concentration-time curve from time 0 to infinity.

In addition, the pairwise comparisons among the three treatment groups showed that the 90% CIs for GMR of the secondary PK parameters $AUC_{0\text{-}t}$, $AUC_{0\text{-}672h}$ and $AUC_{Tmax-inf}$ were all within the equivalence interval (80.00-125.00%).

Clinical study in adult patients with moderate to severe plaque psoriasis (BAT-2206-002-CR)

The PK endpoint was the serum concentration of ustekinumab at pre-dose (C_{trough}) on Day 0 and Weeks 4, 16, 28, and 40 over the course of the study and post-dose at Weeks 2, 8, 12, 32, 44 and 52.

PK results

Of 556 randomised subjects, 548 subjects were included in the PK set (PKS), i.e., subjects who had at least 1 administration (full or partial) of study treatment and at least 1 blood sample providing evaluable PK data for TP1/through the study. Eight (1.4%) subjects were excluded from the PKS because they missed dose at baseline (2 subjects [0.4%]); missed 1 injection (should have received 2 injections) at baseline (1 subject [0.2%]); no evaluable PK assessment postbaseline (1 subject [0.2%]); no evaluable PK samples collected postbaseline before and at Week 4 and with missing dose at Week 4 (3 subjects [0.5%]); or did not receive any treatment with the study drug (1 subject [0.2%]).

Of 528 subjects, 505 subjects were included, and 23 subjects (4.4%) were excluded from the PK set for treatment period 2 (PKS2), i.e., subjects who had at least 1 administration (full or partial) of study treatment at Week 28 or later and at least 1 blood sample providing evaluable PK data during TP2. Subjects were excluded from the PKS2 because they missed dose at Week 16 (8 subjects [1.5%]); missed dose at Week 4 (7 subjects [1.3%]); missed dose at Week 28 (1 subject [0.2%]); missed dose at Week 4, received last dose on Week 28, and received first evaluable TP2 PK assessment on Week 52 (1 subject [0.2%]); missed dose at baseline (2 subjects [0.4%]); missed 1 injection (should have received 2 injections) at baseline (1 subject [0.2%]); had no evaluable PK assessment during TP2 (1 subject [0.2%]); had no evaluable PK assessment during TP2, and missed dose at Week 4 (1 subject [0.2%]); or received the last dose on Week 28, and received the first evaluable TP2 PK assessment on Week 48 (1 subject [0.2%]).

TP1

In TP1, overall, the geometric means of ustekinumab serum concentrations between the Stelara and BAT2206 groups were comparable (see Table 6). When stratified by region (Europe or China), geometric mean ustekinumab serum concentrations were generally similar for subjects from the China region compared with European subjects from baseline to Week 28 (TP1). During TP1 the percentage of values below quantification limit, excluded from the calculations of geometric mean and CV, ranged from 0% at Week 2 to 8.4% at Week 28, and were generally similar across treatment groups and regions.

Table 6. Serum PK concentrations (ng/mL) of ustekinumab during TP1 by scheduled *visit (PKS for TP1)*

Region	Visit	Statistic	Stelara N=276	BAT2206 N=272
Overall	Week 2 (Postdose)	n	275	269
		Geo Mean	3506.8752	3538.6816
		Geo CV%	39.0	39.0
	Week 4 (Predose)	n	270	271
		Geo Mean	2120.7792	2158.8873
		Geo CV%	47.2	46.4
	Week 8 (Postdose)	n	262	266
		Geo Mean	2854.4711	3012.7039
		Geo CV%	54.3	55.8
	Week 16 (Predose)	n	261	268
		Geo Mean	419.2142	416.4181
		Geo CV%	93.5	91.3
	Week 28 (Predose)	n	252	261
		Geo Mean	349.2605	346.8649
		Geo CV%	85.0	93.9
Europe	Week 2 (Postdose)	n	184	179
		Geo Mean	3473.6852	3662.8035
		Geo CV%	39.8	39.5
	Week 4 (Predose)	n	184	180
		Geo Mean	2101.6478	2209.6547
		Geo CV%	48.8	46.4
	Week 8 (Postdose)	n	183	180
		Geo Mean	2789.3888	2997.9842
		Geo CV%	59.0	60.5
	Week 16 (Predose)	n	182	181
		Geo Mean	434.5719	434.5826
		Geo CV%	89.0	90.8
	Week 28 (Predose)	n	179	174
		Geo Mean	356.9752	354.1445
		Geo CV%	86.0	89.6
China	Week 2 (Postdose)	n	91	90
		Geo Mean	3574.9566	3304.1791
		Geo CV%	37.4	37.3
	Week 4 (Predose)	n	86	91
		Geo Mean	2161.3873	2061.8777
		Geo CV%	44.1	46.1
	Week 8 (Postdose)	n	79	86

	Geo Mean	3011.1239	3043.7469
	Geo CV%	42.1	45.5
Week 16 (Predose)	n	79	87
	Geo Mean	386.7087	381.5299
	Geo CV%	103.6	92.0
Week 28 (Predose)	n	73	87
	Geo Mean	330.6952	332.0343
	Geo CV%	82.9	103.5

Abbreviations: BLQ, below the limit of quantification; CV, coefficient of variance; Geo, Geometric; N, number of subjects; n, number of subjects in the specified category.
Note: Concentration values BLQ were treated as 0 in the summary statistics and were not included in the calculation of Geo mean and Geo CV%. Other BLQ values were set to missing.
Note: For subjects that discontinue the study treatment early, pharmacokinetic samples after the next dosing visit were excluded from summaries.

TP2

In TP2, no major difference was observed between the overall geometric means of ustekinumab serum concentrations for the group of Stelara-Stelara or Stelara-BAT2206 compared with BAT2206 alone in TP2 (see Table 7). Geometric means of quantifiable ustekinumab trough concentrations were above 300 ng/mL (0.3 µg/mL) for all combinations of treatment as seen in TP1 for each treatment group. The percentage of concentrations below quantification limit were highest at timepoints 12 weeks after previous treatment administration (8.0% and 6.8% at Weeks 40 and 52, respectively). Ustekinumab serum post-dose concentrations were slightly lower in TP2 compared to the ones quantified in TP1. This was probably due to loading dose at Weeks 0 and 4 (12 weeks dosing interval after Week 4 until the end of treatment i.e., Week 40). These levels are in line with the documented steady-state serum concentrations of ustekinumab achieved by Week 28 after initial SC doses at Weeks 0 and 4 followed by doses every 12 weeks of Stelara in patients with psoriasis. Based on the results of the current study, steady-state was achieved at Week 28 and maintained at steady state from Week 28 through Week 52 for all treatment groups. Mean ustekinumab serum concentrations were generally similar for subjects from China region compared with European subjects in TP2 (Week 32 to Week 52) with no marked difference between the combination of treatments overall (Stelara-Stelara, Stelara- BAT2206, or BAT2206-BAT2206).

Table 7. Serum PK concentrations (ng/mL) of ustekinumab during TP2 by scheduled visit (PKS for TP2)

Region	Visit	Statistic	Stelara -> Stelara N=127	Stelara -> BAT2206 N=122	BAT2206 -> BAT2206 N=256
Overall	Week 32 (Postdose)	n	127	121	247
		Geo Mean	2133.7608	2077.4085	2165.4706
		Geo CV%	61.8	70.0	56.8
	Week 40 (Predose)	n	126	122	253
		Geo Mean	338.2984	354.2995	325.1973
		Geo CV%	91.8	85.9	85.6
	Week 44 (Postdose)	n	122	116	245
		Geo Mean	2211.8466	2054.1026	2111.3469
		Geo CV%	58.5	76.4	69.0
	Week 52 (Postdose)	n	114	108	237
		Geo Mean	368.7813	377.9002	326.6725
		Geo CV%	92.8	82.5	89.5
Europe	Week 32 (Postdose)	n	91	86	172
		Geo Mean	2126.5510	2150.4682	2157.7819
		Geo CV%	69.1	58.5	61.5
	Week 40 (Predose)	n	90	87	172
		Geo Mean	344.3992	357.8946	334.7836
		Geo CV%	89.0	89.2	86.3
	Week 44 (Postdose)	n	89	83	172
		Geo Mean	2232.1568	2159.0788	2114.2296
		Geo CV%	62.6	67.2	74.4
	Week 52 (Postdose)	n	79	81	161
		Geo Mean	396.3691	379.5810	338.4174
		Geo CV%	90.0	85.2	88.0
China	Week 32 (Postdose)	n	36	35	75
		Geo Mean	2152.0948	1908.2596	2183.2069
		Geo CV%	41.6	96.9	45.6

Week 40 (Predose)	n	36	35	81
	Geo Mean	323.0490	344.8506	305.1585
	Geo CV%	100.9	78.4	84.4
Week 44 (Postdose)	n	33	33	73
	Geo Mean	2157.9873	1812.0837	2104.5702
	Geo CV%	47.4	98.0	56.1
Week 52 (Postdose)	n	35	27	76
	Geo Mean	313.3652	372.9022	303.1209
	Geo CV%	97.3	75.9	92.4

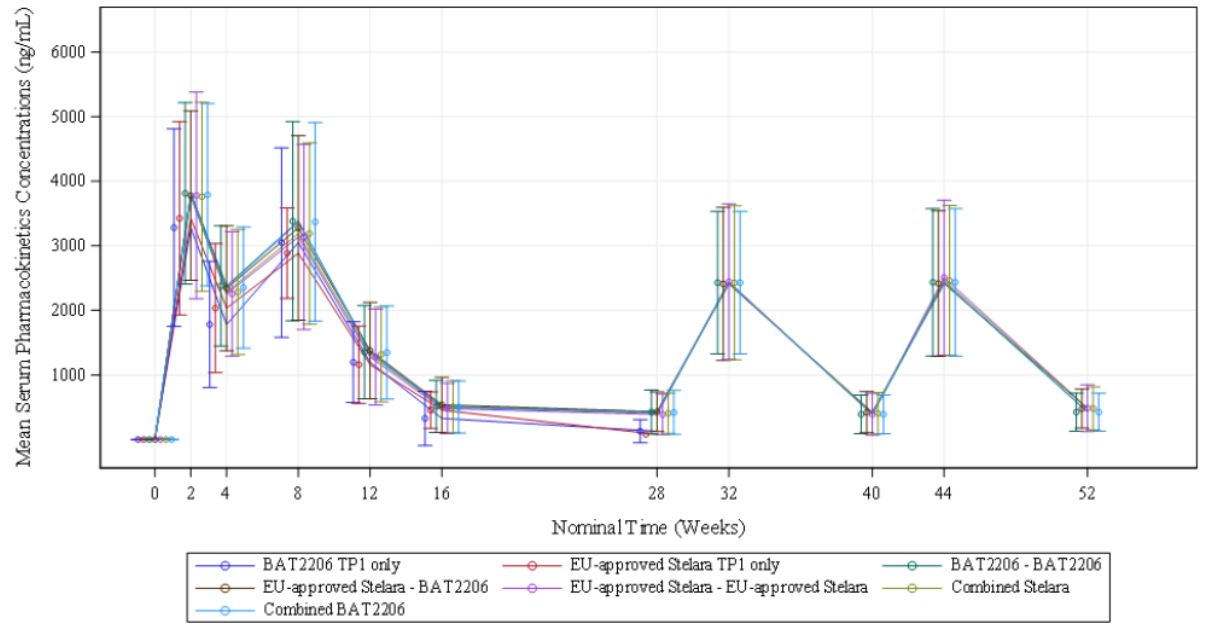
Abbreviations: BLQ, below the limit of quantification; CV, coefficient of variance; Geo, Geometric; N, number of subjects; n, number of subjects in the specified category.

Note: Concentration values BLQ were treated as 0 in the summary statistics and were not included in the calculation of Geo mean and Geo CV%. Other BLQ values were set to missing.

Note: For subjects that discontinue the study treatment early, pharmacokinetic samples after the next dosing visit were excluded from
summaries.

Overall, serum concentrations of ustekinumab were very similar among groups over the studied period (see Figure 2). With long dosing intervals, few pre-dose samples were found to have concentration values below the lower limit of quantification, consistent with the previous report for Stelara.

Figure 2. Linear mean (±SD) serum Ctrough concentrations (ng/mL) of ustekinumab (PKS)



Abbreviation: EU, European Union; TP, treatment period.

PK modelling

The goal of the population PK analysis was to assess the biosimilarity of BAT2206 and Stelara.

Population PK analysis was based on PK data from 2 studies, one in healthy male volunteers (BAT-2206-001-CR) and one in patients with moderate to severe plaque psoriasis (BAT-2206-002-CR). In each study, BAT2206 or ustekinumab was administrated as a SC injection.

Serum concentration-time data of Stelara and BAT2206 were analysed using a nonlinear mixed-effects modelling approach using NONMEM 7.4 (Icon Development Solutions, Ellicott City, MD). The minimisation algorithm of the First-Order Conditional Estimation with Interaction (FOCE-I) was the method used for model parameter estimation.

The evaluation of the BSV models included possible addition of BSV terms (ETAs) to the model parameters, evaluation of the most appropriate form of the ETAs, and evaluation of pair-wise plots of the ETAs for any correlations. Covariate analysis was performed in a stepwise process. Covariates of interest were first screened using visual inspection. Exploratory figures were created to screen potential sources of variability in PK parameters of BAT2206 or Stelara. The most relevant covariates were formally evaluated within the population PK model using a stepwise forward additive approach with a p-value of 0.05 and a backward elimination with a p-value of 0.01. Treatment type (test or reference) was considered a covariate.

The goal of the analysis was to investigate whether BAT2206 is similar in terms of PK to the reference product (Stelara) based on data from the phase 3 study at the administered starting dose of 45 mg for patients with body weight ≤ 100 kg at baseline and 90 mg for patients with body weight > 100 kg at baseline. Therefore, only the PK parameters from the phase 3 study were included in the graphical (Vmax and V2) and statistical ($AUC_{Week\ 16\text{-}28}$ or $AUC_{Week\ 40\text{-}Last}$) comparison of BAT2206 and Stelara.

Post-hoc (individual) estimates of principal PK parameters (clearance and central volume of distribution) of exclusively the phase 3 study were extracted and compared graphically between BAT2206 and Stelara. The population estimates of the final population PK model were used to predict (simulate) the PK profile following the last dose in TP1 (week 16), as well as the last dose in TP2 (Week 40) in the same subjects who were recruited in the phase 3 study, and with the same study design (identical dose, and dosing intervals as used in the phase 3 study).

To assess PK-similarity, model-predicted AUCs were calculated for weeks 16 and 40 (AUC_{tau} from week 16 to week 28, and $AUC_{Week\ 40\text{-}Last}$ from Week 40 to the end of the study) to compare BAT2206 and Stelara.

The GMR (Test/Ref) and the 90% CIs for prediction-based AUCs were calculated. Formulations were to be considered bioequivalent, if the GMR (Test/Ref) and the 90% CIs were contained completely within the 80.00 to 125.00% interval.

The population PK modelling results do not provide relevant support for the PK biosimilarity exercise. Results are not reported, for further detail please see discussion on Clinical pharmacology.

2.6.2.2. Pharmacodynamics

Mechanism of action

Ustekinumab functions by effectively blocking the interaction between IL-12 and IL-23 with the IL-12Rβ1 receptor. It achieves this by binding with high affinity and specificity to the p40 subunit, which is shared by

both IL-12 and IL-23, thereby disrupting the signalling and cytokine cascade mediated by these two molecules.

Primary and Secondary pharmacology

Validated PD markers do not exist for the efficacy of interleukin-23 (IL-23) and interleukin-12 (IL-12) antagonists and therefore, no PD data were evaluated in the clinical studies, nor have they been required according to the EMA guideline on similar biological medicinal products containing monoclonal antibodies (EMA/CHMP/BMWP/403543/2010).

2.6.3. Discussion on clinical pharmacology

The PK of BAT2206 was investigated in two clinical studies (i.e., a pivotal PK study in adult, healthy Chinese male subjects [study BAT-2206-001-CR] and a comparative clinical study adult in patients with moderate to severe plaque psoriasis (study BAT-2206-002-CR]). In study BAT-2206-001-CR, ustekinumab was administered as a single SC injection of 45 mg. The justification for use 45 mg dose was acceptable and the choice of the dose was recommended by the CHMP in SA. In study BAT-2206-002-CR, the dose was 45 mg (baseline body weight [BW] ≤100 kg) or 90 mg (baseline BW > 100 kg) administered SC on day 0, week 4, and thereafter every 12 weeks until week 40. The CHMP did not advise to include patients > 100 kg, however, the applicant added an upper limit of 120 kg of body weight to the exclusion criteria to increase homogeneity of enrolled population and reduce potential variations in the response to study treatment.

Analytical methods

ECL based assays were used for the determination of ustekinumab concentrations, anti-drug antibodies and neutralising antibodies. The assays were validated according to current guidance.

PK similarity study in healthy adult subjects (BAT-2206-001-CR)

The applicant had requested a CHMP SA (EMA/SA/0000047481) in relation to the analyses (including endpoints and margins) and PK/ADA sampling timepoints. The proposed primary and secondary endpoints and margins were considered acceptable by the CHMP. The CHMP advised that the extrapolated AUC should also be reported and furthermore, partial AUC characterising the elimination phase should also be a secondary PK endpoint. Adding $AUC_{Tmax\text{-}inf}$ with $AUC_{0\text{-}672h}$ is considered adequate to support extrapolation of the SC data to the IV administration route and, consequently, to waive a clinical study using the IV presentation.

Additional PK sampling on Day 12 and Day 14 after administration of study drug to capture the C_{max} better in subjects with slow absorption rate and every week instead of every two weeks after Day 29 until Day 113 (e.g., Days 36, 43, 50 and 57 etc.) was recommended by the CHMP to allow a more precise picture on similarity. This advice was not followed. Nonetheless, no issue is raised, as the range of t_{max} is very large (i.e., from day 2 to day 28). Sampling until Day 113 was endorsed by the CHMP. In relation to the ADA sampling, the CHMP considered it adequate. Notably, sampling between Day 29 and the end of the study was recommended to better capture the incidence of ADAs and Nabs. The applicant added two timepoints (i.e., at days 57 and 85) in the ADA sampling timepoints.

In the SA, the CHMP instructed to adjust the confidence interval so that actual type I error rate is maintained at the one-sided level of 5% and not inflated due to the blinded sample size reassessment. In response to the applicant's proposal to use 91% confidence intervals to maintain type 1 error control, the CHMP stated that

the adequacy of this approach should be proven by simulations (EMA/SA/0000062023) (see below for further details).

None of the subjects had pre-dose ustekinumab concentrations. Almost all subjects' AUC_{0-t} was > 80% of the AUC_{inf} confirming that the duration of the PK sampling was adequate (i.e., long enough). Only two subjects in the Stelara (US-sourced) group had the AUC_{0-t} < 80% of the AUC_{inf}.

The 90% CIs of the GMRs for the primary PK endpoints AUC_{inf} and C_{max} (also for the AUC_{0-t}) were within the BE criteria of 0.80 to 1.25 in all comparisons of BAT2206 vs Stelara (EU-sourced), BAT2206 vs Stelara (US-sourced) and Stelara (US-sourced) vs Stelara (EU-sourced). Also, the secondary PK endpoints (i.e., AUC_{0-672h}, $AUC_{Tmax-inf}$, $\%AUC_{ex}$, t_{max}, $t_{½}$, λz, CL/F and Vz/F) seemed similar between BAT2206, Stelara (EU-sourced) and Stelara (US-sourced).

The $AUC_{Tmax-inf}$ with AUC_{0-672h} were added to support extrapolation of the SC data to the IV administration route and, consequently, to waive a clinical study using the IV presentation. The 90% CIs of the GMRs for the $AUC_{Tmax-inf}$ and AUC_{0-672h} were 0.92-1.04 and 0.90-1.05, respectively, for BAT2206 vs Stelara EU-sourced, thus within the BE criteria of 0.80 to 1.25. Because the partial AUCs are similar between the products, the SC data can be extrapolated to the IV administration route and no clinical study using IV presentation is needed.

Three sensitivity analyses were conducted to examine PK similarity among the three groups after excluding missing data, or comparison-based on body weight stratification (the factors in ANOVA were group and weight stratification), or excluding ADA-positive subjects, respectively.

For all sensitivity analyses, the point estimates and 90% CIs of the GMRs for all pairwise comparisons were fully contained within the prespecified margin of 80.00 to 125.00% for AUC_{inf}, C_{max}, and AUC_{0-t}.

In all comparisons of GMR (three treatment groups compared in pairs) of primary and secondary PK parameters also, the 91% CIs of GMRs were within the BE range 80.00-125.00.

While CHMP's concerns were not prospectively addressed regarding whether the use of 91% CI for GMR actually accounts for the possible type 1 error inflation due to the blinded sample size reassessment, the study results were not borderline with respect to meeting the equivalence criteria: It can be deduced from the descriptive statistics that, e.g., for GMR of BAT2206/Stelara (EU-sourced) of C_{max}, even the nominal 99% confidence interval (87.0%, 112.5%) would fall fairly within the acceptable range. Given the clear-cut results observed, the possibility of a false conclusion due to a type 1 error is therefore considered to be negligible in this study.

Clinical study in adult patients with moderate to severe plaque psoriasis (BAT-2206-002-CR)

No additional PK parameters (i.e., C_{max}, T_{max}, Vd, $t_{1/2}$ and partial AUCS after the first dose) were measured although they were recommended by the CHMP in SA. The applicant has selected pre- and post-dose concentrations as PK parameters in this study and they can be considered sufficient, because in the study BAT-2206-001-CR, the PK of the BAT2206 and Stelara products has been studied in detail.

The overall geometric means of serum concentrations of ustekinumab in Stelara and BAT2206 groups in TP1, and for the Stelara-Stelara or Stelara-BAT2206 groups compared with BAT2206 alone in TP2 were comparable.

Steady-state was achieved at Week 28 and maintained from Week 28 through Week 52 for all treatment groups.

PK modelling

A population PK model has been used to generate a biosimilarity comparison for the sparse phase 3 data, for which traditional noncompartmental analysis could not be applied due to data sparsity. The model has been trained using both phase 1 and phase 3 PK data. However, the population PK model has been developed with an assumption that each PK parameter is equal between products, unless proven otherwise; and with an assumption that no between-subject variability exists unless it leads to improvement in model goodness-of-fit. Thus, from a regulatory point of view, the modelling methodology is biased towards concluding biosimilarity. Moreover, the model-building steps have been dependent on the expert judgement of the modelling analyst. It cannot be indisputably ruled out that the model-building steps would have been affected by a conscious or unconscious desire to have the final population PK model demonstrate biosimilarity.

The currently reported population PK modelling results do not provide relevant support for the PK biosimilarity exercise. Nevertheless, there is no need to request modifications to the population PK analysis because the currently established phase 1 PK biosimilarity based on non-compartmental methods, together with supporting PK information from the phase 3 study, are sufficient to establish PK biosimilarity. Although the population PK model is not considered fit for purpose, the issue was not further pursued.

2.6.4. Conclusions on clinical pharmacology

Based on the data submitted, the CHMP concludes that from a clinical pharmacology perspective, Usymro is biosimilar to EU-Stelara.

2.6.5. Clinical efficacy

2.6.5.1. Dose response study

N/A.

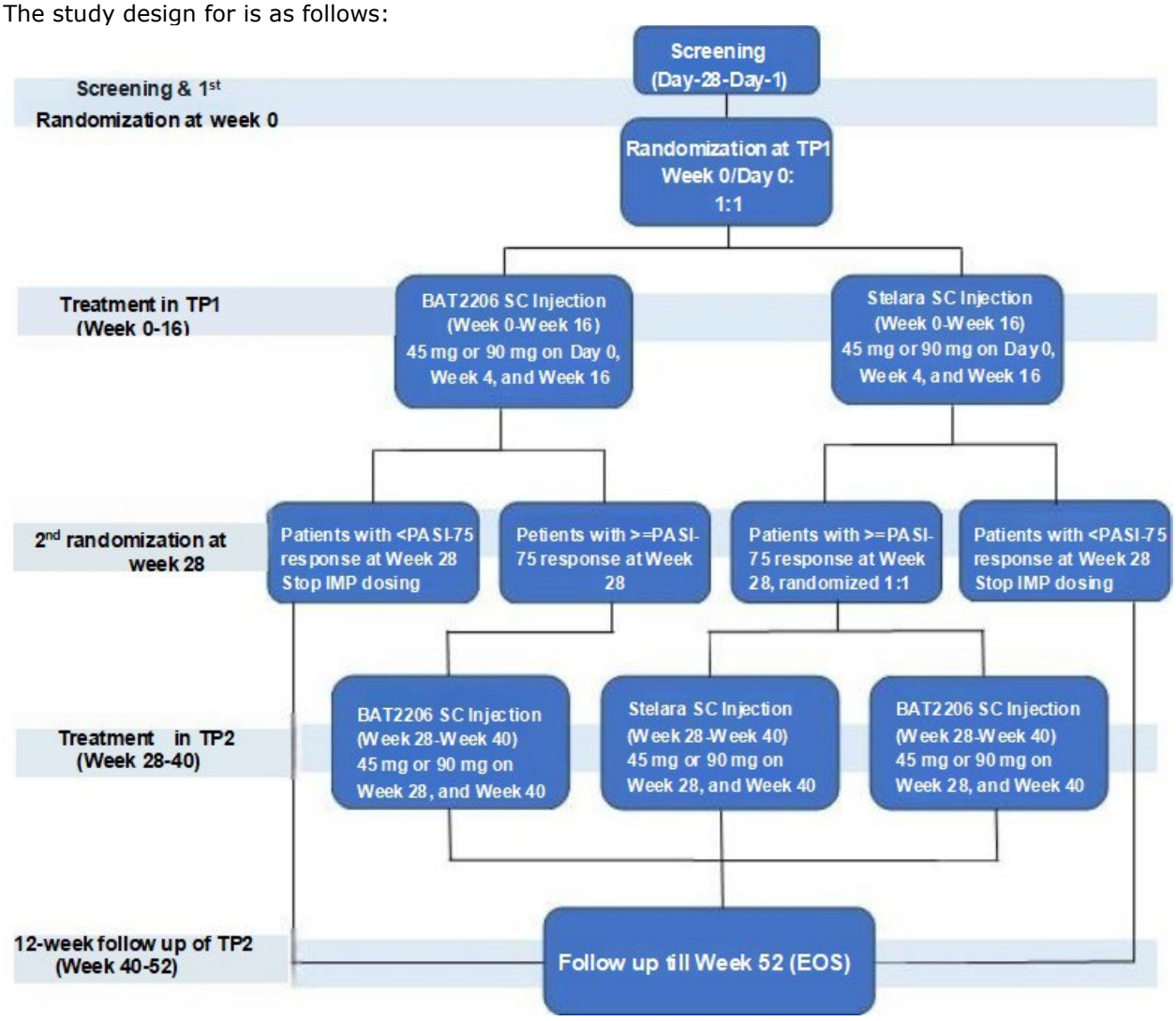
2.6.5.2. Main study

BAT-2206-002-CR

Methods

The Phase 3 study (BAT-2206-002-CR) is a multicenter, randomised, double-blind trial with parallel arms, aiming to compare the efficacy, safety, immunogenicity, and PK of BAT2206 and EU-Stelara in patients with moderate to severe psoriasis.

The study design for is as follows:



Abbreviations: EOS, end of study; IMP, investigational medicinal product; PASI, Psoriasis Area and Severity Index; SC, subcutaneous; TP1, Treatment Period 1; TP2, Treatment Period 2.

- **Study Participants**

The study aimed to screen an adequate number of patients with moderate to severe plaque psoriasis and randomise a total of 556 patients across approximately 41 sites in five countries: China, Poland, Bulgaria, Georgia and Russia.

To be eligible for participation in the study, individuals had to satisfy all of the following criteria:

1. Male or female subjects aged ≥18 years with a diagnosis of plaque-type psoriasis at least 24 weeks before screening.
2. Had moderate to severe plaque-type psoriasis as defined at screening and baseline by:
    a. PASI ≥12,
    b. Static Physician's Global Assessment (sPGA) ≥3, and

c. Body surface area (BSA) affected by chronic plaque-type psoriasis ≥10%

3. Failed to respond to, had a contraindication to, or was intolerant to other systemic therapies including cyclosporine, methotrexate, or PUVA.
4. Females able to conceive and men with female partners who can conceive must use effective contraception during the study and continue these measures for at least 15 weeks after the final dose of the study drug.
5. Had to be willing to provide written consent and to comply with the requirements of the study protocol.

Individuals who met any of the following criteria at screening or baseline was deemed ineligible for participation in the study (only main criteria listed):

1. They have forms of psoriasis other than plaque-type (e.g., erythrodermic psoriasis, pustular psoriasis) or other skin conditions (e.g., eczema) that could interfere with the assessment of the study drug's impact on psoriasis.
2. They have previously received ustekinumab, a biosimilar of ustekinumab, or drugs targeting IL-12, IL-17, or IL-23.
3. They have received monoclonal or non-monoclonal antibody-based biologic drugs for psoriasis or psoriatic arthritis within a certain time frame before the screening visit.
4. They have used topical therapies for psoriasis within 2 weeks before the baseline visit.
5. They have undergone treatments such as phototherapy or received certain medications for psoriasis or psoriatic arthritis within a defined time frame before the baseline visit.
6. They have used herbal remedies or traditional medicines for psoriasis within a certain time frame before the baseline visit.
7. They have concurrent or chronic inflammatory or autoimmune diseases other than plaque psoriasis, except for those with concurrent psoriatic arthritis.

- **Treatments**

All eligible subjects were randomly assigned in a 1:1 ratio to either BAT2206 or Stelara. Throughout TP1 and TP2, patients received either 45 mg or 90 mg of BAT2206 or EU-sourced Stelara through subcutaneous injection using prefilled syringes (PFS).

Subjects with a body weight ≤100 kg at baseline were to receive 45 mg, and subjects weighing >100 kg at baseline were to receive 90 mg of the study treatment in accordance with the approved dosing recommendations of Stelara. An upper limit of 120 kg of body weight was added to the exclusion criteria to increase homogeneity of enrolled subject population and reduce potential variations in the response to study treatment.

BAT2206 or Stelara was administered on Day 0, 4 weeks later, and thereafter every 12 weeks until Week 40. Subjects from either of the treatment groups were discontinued from the study treatment if the improvement in PASI score at Week 28 was <75%. Subjects who were discontinued due to lack of efficacy were followed up for safety throughout the study.

A subject who discontinued study treatment during TP1 (by Week 28) was required to attend the scheduled visit for efficacy assessment until Week 28. A subject who discontinued study treatment during TP2 (from Week 28 with re-randomisation) was required to attend the scheduled visit for efficacy assessment until Week 52.

Re-randomisation

Subjects who achieved a ≥PASI-75 response at Week 28 entered into TP2 of the study to continue treatment.

Subjects randomised to receive BAT2206 during TP1 continued to receive the same drug during TP2. Subjects randomised to receive Stelara during TP1 received either BAT2206 or Stelara in TP2 on the basis of the randomisation performed at the beginning of TP2 (Week 28 visit).

Eligible subjects with body weight ≤100 kg at baseline received a dose of 45 mg (45 mg/0.5 mL) of BAT2206 or Stelara throughout the study. Eligible subjects with body weight >100 kg at baseline received 90 mg (2 PFS of 45 mg/0.5 mL) of BAT2206 or Stelara throughout the study.

Mild moisturizers or lubricants were allowed at any time during the study except within 24 hours before PASI assessment at screening and other study visits.

For the rescue medication in this study, low- to mid-potency (American Academy of Dermatology class 6 to 7) topical corticosteroids on scalp, face, axillae, groin, or genitalia area were allowed except within 24 hours before PASI assessment at screening and other study visits.

- **Objectives**

The primary objective of the study was to demonstrate equivalent efficacy of BAT2206 and Stelara in subjects with moderate to severe psoriasis. Equivalent efficacy was to be concluded if the mean difference between BAT2206 and Stelara in PASI percent improvement from baseline was shown to be within an equivalence margin of (-13, 13) at week 8 (for EMA).

- **Outcomes/endpoints**

The primary endpoint was percent change from baseline (CfB) in PASI score at week 8 (EMA) or week 12 (other agencies).

The secondary efficacy endpoints were as follows:

- Percent CfB in PASI score to Weeks 4, 16, 20, 28, 32, 40, 44, and 52.
- Proportion of subjects who achieved at least 50%/75%/90%/100% improvement from baseline in PASI (PASI-50/75/90/100) at Weeks 4, 8, 12, 16, 20, 28, 32, 40, 44, and 52.
- AUEC for PASI from baseline to Weeks 8, 12, and 28.
- CfB in sPGA score to Weeks 4, 8, 12, 16, 20, 28, 32, 40, 44, and 52.
- Proportion of subjects with sPGA score on a 6-item scale of cleared (0) or minimal (1) at Weeks 4, 8, 12, 16, 20, 28, 32, 40, 44, and 52.
- CfB in affected BSA (%) at Weeks 4, 8, 12, 16, 20, 28, 32, 40, 44, and 52.
- CfB in DLQI score to Weeks 8, 12, 28, 40, and 52.

- **Sample size**

Approximately 556 patients were to be enrolled and randomly assigned to one of the 2 treatment groups in a 1:1 ratio (278 patients in the BAT2206 group and 278 patients in the EU-sourced Stelara group). The sample size was justified as follows:

For EMA, assuming an SD of 25% (allowing for the highest SD observed in the meta-analysis of Week 8 data), true hypothesised mean difference of 0, 2 one-sided tests at alpha (type 1 error) = 0.025 (i.e., 2-sided 95% CI for ascertaining equivalence), and equivalence margin of [-13%, +13%], this number of evaluable subjects provided 99% power.

The overall number of subjects to be randomised was calculated based on both the expected dropout rate and on the requirement from EMA to have at least 100 subjects completing treatment with Stelara after re-randomisation. For TP1, an overall dropout rate of 26% was anticipated, including both an expected dropout of 5% up to Week 28, and an additional 21% at Week 28 due to withdrawal of subjects not achieving PASI75 response. A further 2% dropout rate during TP2 was additionally expected.

Given the requirement for 400 subjects completing TP2 (to allow for a minimum of 200 subjects continuing on BAT2206, 100 subjects continuing on Stelara and 100 subjects switching from Stelara to BAT2206), and factoring in the dropout rates discussed above, a total of 556 subjects (278 subjects per treatment arm) were to be randomised.

- **Randomisation and Blinding (masking)**

On Day 0, all eligible subjects were randomly assigned (using a permuted block design) in a 1:1 ratio to either BAT2206 or Stelara for TP1. To promote balanced allocation, randomisation was stratified by region (China/Europe), body weight (≤100 kg versus >100 kg), PsA (yes/no), and previous biologic use for either psoriasis or PsA treatment (yes/no). There was a separate re-randomisation for TP2 at the Week 28 visit. Subjects assigned to the Stelara group in TP1 were re-randomised in a 1:1 ratio to receive either BAT2206 or Stelara during TP2.

Randomisation of these subjects for TP2 was stratified using the same baseline stratification factors as defined for randomisation in TP1. Subjects assigned to the BT2206 group in TP1 continued to receive BAT2206 during TP2. Any subject with an improvement in PASI score of <75% at Week 28 did not enter TP2 and was discontinued early. To maintain the blind, all subjects were entered into the RAVE electronic data capture at the Week 28 visit, but only those continuing subjects randomised to Stelara in TP1 were re-randomised for TP2.

- **Statistical methods**

Analysis sets

The following analysis sets were considered for efficacy analyses during TP1 (i.e., before re-randomisation at Week 28 for treatment switch) or across the whole study, as applicable:

- ITT Set: All TP1 randomised subjects. The ITT set was used for all primary analyses of efficacy endpoints in TP1.
- PPS: Subjects in the ITT set who received at least 1 administration of study treatment during TP1, had at least one postbaseline PASI assessment during TP1, and additionally for whom there were no major protocol deviations significantly affecting primary efficacy at Week 8 or separately at Week 12. The PPSs were used for selected supportive analyses of efficacy endpoints in TP1.

- ITT2: All subjects re-randomised into TP2 at Week 28. The ITT2 Set was used for all primary analyses of efficacy endpoints in TP2.

Subjects were analysed under the treatment group as randomised.

Statistical analysis of the main estimand

The applicant labelled the predefined intercurrent events types as ICE1 to ICE6. Given that no-one died (ICE1) or discontinued due to lack of efficacy (ICE3) by Week 8, the primary time point for EMA, the description of how such cases were to be handled are redacted from the summary of planned analyses. The observed ICEs (along with their labels) are summarised with the efficacy outcomes.

All available data were used in the analysis regardless of treatment discontinuation, deviations of dosing or rescue/prohibited medication. The data that were missing despite the mandate to continue data collection even after study treatment discontinuations were subject to multiple imputation. The multiple imputations were based on a fully conditional specification method where missing data on PASI assessments are imputed iteratively using treatment group, stratification factors, previous PASI values and previously occurred relevant ICEs as predictors. This is referred to as 'treatment policy strategy'.

PASI data captured using remote assessment were set as missing and multiple imputed under a missing-at-random (MAR) assumption. This is referred to 'hypothetical strategy'.

The estimate of the treatment effect in this instance will be influenced by any effects of errors or deviations in study treatment dosing, receipt of rescue medication within 1 day prior to PASI assessment or prohibited medication and/or premature discontinuation. The number of imputations was 20 per MI step.

The main estimand was analysed using the ANCOVA with treatment group (BAT2206 versus Stelara), region (Central Europe, Asia Pacific), body weight at baseline category (≤100 kg, >100 kg), baseline PsA status (yes/no), and previous biologic use (yes/no) as fixed effects. The data on stratification factors were from interactive web response systems.

The LS means of PASI percent improvement from baseline to Week 8/12 in each treatment group, and the corresponding difference between treatments, along with the 2-sided 90% and 95% CIs for the estimated means and difference were presented. For EMA, equivalence was to be concluded if the 2-sided 95% CI at Week 8 fell entirely within the predefined equivalence margin of ±13%.

Statistical analysis of the second and third estimand

The second estimand corresponds to hypothetical absence of dosing deviations. Thus, PASI data impacted by previous dosing deviations were replaced by multiple imputation; the imputation model used only data from subjects who did not experience any relevant dosing deviations. Similarly, for the third estimand that corresponds to hypothetical absence of rescue and prohibited therapies and dosing deviations, all PASI data impacted by these ICEs were replaced by multiple imputation such that the imputation model used only data from subjects who neither experienced any relevant dosing deviations nor used rescue/prohibited medications.

The second and third estimands for the primary efficacy endpoint were analysed with ANCOVA similarly to the main estimand.

The ICEs that are reported together with the efficacy results are those that were determined, by a blinded data review meeting (BDRM), to have an impact on the efficacy analysis in question.

Secondary endpoints

For the secondary endpoints corresponding to the percent change in PASI at different timepoints through Week 28, statistical analysis analogous with that described above for the primary endpoint were performed. The PASI data were evaluated also as Area Under the Effect Curve (AUEC) from baseline through Weeks 8, 12 and 28, respectively, using the linear trapezoidal method. Estimands and analyses analogous with those of the primary endpoint were reported.

Also, for the categorical analyses related to PASI score, i.e., PASI-50, PASI-75, PASI-90, and PASI-100, analogous estimands and analyses were performed. The imputations of PASI score data occurred first followed by derivation of the categorical response status. Logistic regression analysis was performed including factors for treatment group, region, body weight at baseline category, PsA status, and previous biologic use. The marginal proportions of responders in each treatment group and respective difference were then estimated by averaging all subjects' individual predicted probabilities of response. Standard errors and 90% and 95% confidence intervals were estimated using delta method.

In the analyses involving multiple imputation, the results were eventually combined based on Rubin's rule.

The secondary endpoint assessments changes in sPGA, DLQI and body surface area affected by psoriasis up to and including Week 28 were analysed in the ITT set and PPS at the respective timepoint using an ANCOVA model. Analyses occurred as observed (i.e., no imputation) on the main estimand, and the baseline results were included as a covariate for analyses of absolute changes.

Results

- **Participant flow**

Figure 3. Participant flow (Screened Set), BAT-2206-002-CR

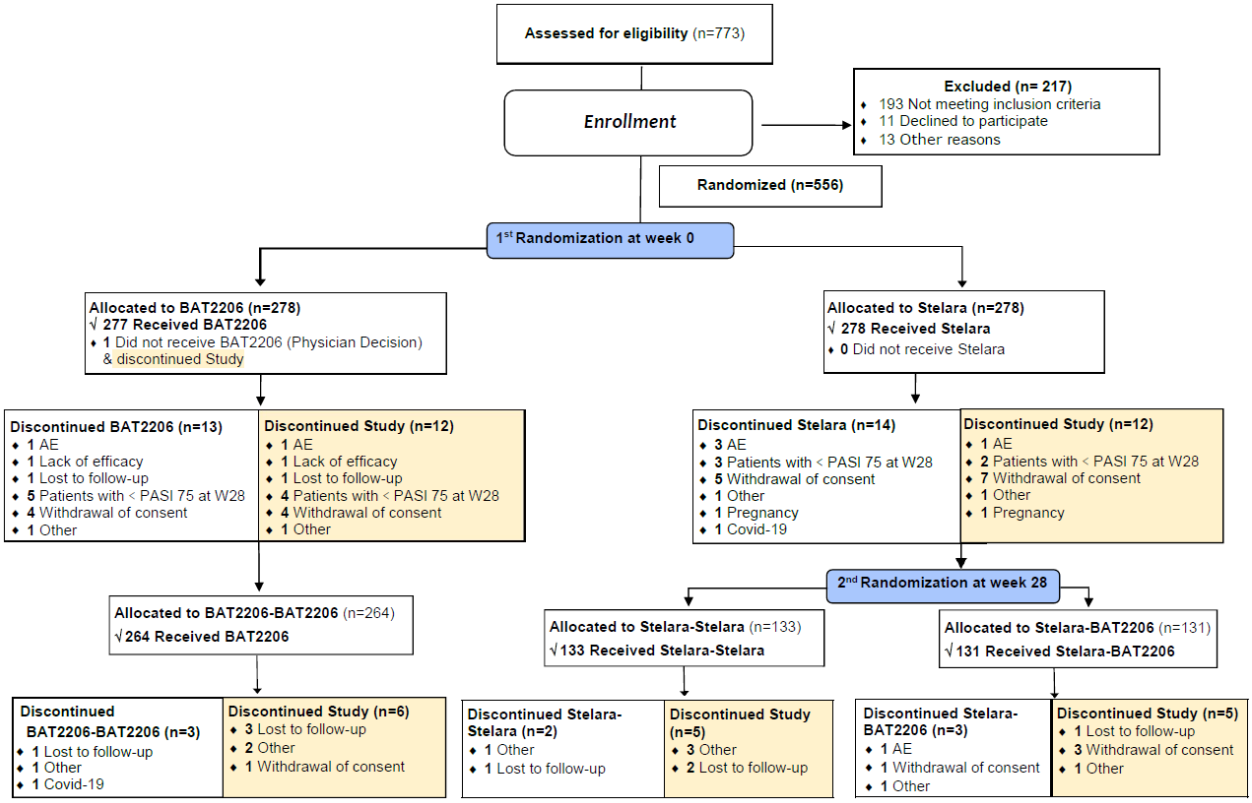


Table 8. Major Protocol Deviations (Intent-to-Treat Set)

	Stelara N=278 n (%)	BAT2206 N=278 n (%)	Total N=556 n (%)
Subjects with at least 1 major protocol deviation	40 (14.4)	49 (17.6)	89 (16.0)
Concomitant medication/administration of prohibited medication	3 (1.1)	5 (1.8)	8 (1.4)
Inclusion or exclusion criteria	3 (1.1)	11 (4.0)	14 (2.5)
Informed consent/other	3 (1.1)	1 (0.4)	4 (0.7)
IP/IP dosing	1 (0.4)	2 (0.7)	3 (0.5)
IP/other	0	4 (1.4)	4 (0.7)
Randomization/other	5 (1.8)	2 (0.7)	7 (1.3)
Randomization/mistratification	5 (1.8)	8 (2.9)	13 (2.3)
SAE not reported or reported late	0	1 (0.4)	1 (0.2)
Study procedure/missed procedure	15 (5.4)	14 (5.0)	29 (5.2)
Study procedure/other	0	1 (0.4)	1 (0.2)
Study procedure/subject compliance	2 (0.7)	0	2 (0.4)
Study procedure/unmasking (not per protocol)	0	2 (0.7)	2 (0.4)
Study procedure/visit missing	8 (2.9)	2 (0.7)	10 (1.8)
Visit window	3 (1.1)	4 (1.4)	7 (1.3)

Abbreviations: IP, investigational product; N, number of subjects; n, number of subjects in the specified category; SAE, serious adverse event.
Note: Percentages were based on the number of subjects in the Intent-to-Treat set.

- **Recruitment**

Date of First Observation: July 06th 2021

Date of Last Observation: July 07th 2023

Unblinding of data: August 21st, 2023

Date of Final Study Report: December 12th, 2023

- **Conduct of the study**

The original protocol (Version 1.0, dated 03 October 2020) was amended 3 times. The key changes (excluding minor editorial and/or administrative changes) in each amendment are summarised below:

Protocol Version 2.0, Amendment 1, dated 23 April 2021

The purpose of this amendment was to revise the protocol after the EMA (29 January 2021) and FDA (29 March 2021) requested clarifications and changes. Several operational and clinical changes were also included in this protocol amendment.

Protocol Version 3.0, Amendment 2, dated 11 January 2022

The purpose of this amendment was to revise the protocol after the EMA (29 January 2021 and 22 July 2021) and FDA (29 March 2021) requested clarifications and changes. The statistical section was modified or clarified where necessary. The status and main results of the BAT-2206-001-CR study were updated. Permitted medications and rescue medications were clarified. Several operational and clinical changes were also included in this protocol amendment.

Protocol Version 4.0, Amendment 3, dated 26 January 2023

In the CHMP SA (dated 29 January 2021), it was recommended to use an earlier timepoint (Week 8) as the primary efficacy endpoint because this may be on a steeper part of the efficacy response curve, leading to a higher sensitivity to detect differences between the biosimilar and the reference product.

Historical data analysing percent CfB in PASI were not available previously for Week 8; upon CHMP's request, Week 8 was added to the protocol.

- **Baseline data**

Table 9. Demographic Demographic and Other Baseline Characteristics (Intent-to-Treat Set), BAT-2206-002-CR

Characteristic	Stelara N=278	BAT2206 N=278	Total N=556
Age (Years)			
n	278	278	556
Mean (SD)	43.1 (12.84)	42.1 (13.04)	42.6 (12.94)
Median	42.0	41.0	41.0
Min, Max	18, 76	18, 82	18, 82
Sex, n (%)			
Male	192(69.1)	182(65.5)	374(67.3)
Female	86(30.9)	96(34.5)	182(32.7)
Region, n (%)			
Central Europe	185(66.5)	184(66.2)	369(66.4)
Asia Pacific	93(33.5)	94(33.8)	187(33.6)
Country, n (%)			
Bulgaria	37(13.3)	36(12.9)	73(13.1)
China	93(33.5)	94(33.8)	187(33.6)
Georgia	25(9.0)	33(11.9)	58(10.4)
Poland	91(32.7)	93(33.5)	184(33.1)
Russia	32(11.5)	22(7.9)	54(9.7)
Race, n (%)			
White	185(66.5)	183(65.8)	368(66.2)
Asian	93(33.5)	95(34.2)	188(33.8)
Ethnicity, n (%)			
Hispanic or Latino	0	1(0.4)	1(0.2)
Not Hispanic or Latino	278(100)	277(99.6)	555(99.8)
Height (cm)			
n	278	277	555
Mean (SD)	172.05 (9.301)	171.15 (8.995)	171.60 (9.152)
Median	172.00	172.00	172.00
Min, Max	150.0, 198.0	150.0, 196.3	150.0, 198.0

Characteristic	Stelara N=278	BAT2206 N=278	Total N=556
Weight (kg)			
n	278	278	556
Mean (SD)	80.58 (17.251)	80.11 (16.553)	80.34 (16.892)
Median	80.00	80.00	80.00
Min, Max	40.0, 120.0	39.5, 120.0	39.5, 120.0
Body mass index (kg/m^2)			
n	278	277	555
Mean (SD)	27.081 (4.8621)	27.249 (4.7153)	27.165 (4.7858)
Median	26.870	26.730	26.770
Min, Max	15.50, 41.14	15.62, 41.52	15.50, 41.52
Psoriatic Arthritis, n (%)			
Yes	35(12.6)	31(11.2)	66(11.9)
No	243(87.4)	247(88.8)	490(88.1)
Previous Biologic use for PsO/PsA, n (%)			
Yes	20(7.2)	17(6.1)	37(6.7)
No	258(92.8)	261(93.9)	519(93.3)

Abbreviations: Max, maximum; Min, minimum; N, number of subjects; n, number of subjects in the specified category; PASI, psoriasis area severity index; PK, pharmacokinetics; PsA, psoriatic arthritis; PsO, psoriasis.
Note: Percentages were based on the number of subjects in ITT set.

Table 10. Summary of Baseline Disease Characteristics (Intent-to-Treat Set)

Characteristic	Stelara N=278	BAT2206 N=278	Total N=556
PASI Score			
n	278	277	555
Mean (SD)	24.40 (9.620)	24.00 (10.060)	24.20 (9.835)
Median	22.30	21.20	21.70
Min, Max	12.0, 65.0	12.0, 66.0	12.0, 66.0
sPGA			
n	278	277	555
Mean (SD)	3.4 (0.61)	3.5 (0.67)	3.5 (0.64)
Median	3.0	3.0	3.0
Min, Max	3, 5	3, 5	3, 5
sPGA[a], n (%)			
3	172 (61.9)	156 (56.1)	328 (59.0)
4	88 (31.7)	94 (33.8)	182 (32.7)
5	18 (6.5)	27 (9.7)	45 (8.1)
Missing	0	1 (0.4)	1 (0.2)
BSA			
n	278	277	555
Mean (SD)	31.66 (15.687)	30.47 (15.776)	31.07 (15.729)
Median	29.00	26.00	28.00
Min, Max	10.0, 86.0	10.0, 85.5	10.0, 86.0
DLQI			
n	278	277	555

Characteristic	Stelara N=278	BAT2206 N=278	Total N=556
Mean (SD)	14.0 (6.95)	14.8 (7.13)	14.4 (7.05)
Median	14.0	15.0	14.0
Min, Max	0, 30	1, 30	0, 30

Abbreviations: BSA, body surface area; DLQI, Dermatology Life Quality Index; Max, maximum; Min, minimum; N, number of subjects; n, number of subjects in the specified category; PASI, psoriasis area severity index; PK, pharmacokinetics; SD, standard deviation; sPGA, static Physician's Global Assessment

Note: Baseline is defined as the last available, valid, non-missing assessment prior to the first dose of study medication.

Note: Percentages were based on the number of subjects in Intent-to-Treat set.

[a] 0 = cleared, 1 = minimal, 2 = mild, 3 = moderate, 4 = marked, 5 = severe

- **Numbers analysed**

A total of 556 subjects underwent randomisation, with 278 subjects assigned to each group (BAT2206 or Stelara) in TP1. In TP1, all 278 subjects in the Stelara group and 277 subjects in the BAT2206 group received at least one dose of the study treatment.

Moving to TP2, a total of 528 subjects entered. Among the 264 subjects randomised to receive Stelara in TP1 and entering TP2, 133 continued with Stelara, while 131 were switched to BAT2206 in TP2 (Stelara-BAT2206). The 264 subjects randomszed to BAT2206 in TP1 continued to receive BAT2206 in TP2.

In total, 92.6% (515/556) of all subjects randomised at screening completed TP2.

Table 11. Number of Subjects Excluded from Analysis Set for Treatment Period 1 (Intent-to-Treat Set)

	Stelara N=278 n (%)	BAT2206 N=278 n (%)	Total N=556 n (%)
Subjects excluded from Per Protocol Set at Week 8	8 (2.9)	6 (2.2)	14 (2.5)
Ineligibility (inclusion/exclusion criterion)	0	1 (0.4)	1 (0.2)
Missed dose at Week 4	6 (2.2)	2 (0.7)	8 (1.4)
Missed dose at Week 4; missing postbaseline PASI data available up to and including Week 8	1 (0.4)	1 (0.4)	2 (0.4)
Missed dose at baseline	1 (0.4)	1 (0.4)	2 (0.4)
No dosing in the study	0	1 (0.4)	1 (0.2)
Subjects excluded from Per Protocol Set at Week 12	8 (2.9)	7 (2.5)	15 (2.7)
Ineligibility (inclusion/exclusion criterion)	0	1 (0.4)	1 (0.2)
Missed dose at Week 4	7 (2.5)	2 (0.7)	9 (1.6)
Missed dose at Week 4; missing postbaseline PASI data available up to and including Week 12	0	1 (0.4)	1 (0.2)
Missed dose at baseline	1 (0.4)	1 (0.4)	2 (0.4)
No dosing in the study	0	1 (0.4)	1 (0.2)
Prohibited medication	0	1 (0.4)	1 (0.2)
Subjects excluded from Safety Analysis Set	0	1 (0.4)	1 (0.2)
Not received any treatment with study drug	0	1 (0.4)	1 (0.2)
Subjects excluded from PK Set	2 (0.7)	6 (2.2)	8 (1.4)
Missed dose at baseline	1 (0.4)	1 (0.4)	2 (0.4)
Missed 1 injection (should have received 2 injections) at baseline	0	1 (0.4)	1 (0.2)
No evaluable PK assessment postbaseline	0	1 (0.4)	1 (0.2)
No evaluable PK samples collected postbaseline before and at Week 4 and with missing dose at Week 4	1 (0.4)	2 (0.7)	3 (0.5)
Not received any treatment with study drug	0	1 (0.4)	1 (0.2)
Subjects excluded from Intent-to-Treat Set for treatment period 2	14 (5.0)	14 (5.0)	28 (5.0)
Not re-randomized	14 (5.0)	14 (5.0)	28 (5.0)

Abbreviations: N, number of subjects; n, number of subjects in the specified category; PASI, psoriasis area severity index; PK, pharmacokinetics.
Note: Percentages were based on the number of subjects in the Intent-to-Treat set.

- **Outcomes and estimation**

Primary endpoint (PASI Score at Week 8)

Table 12 presents a summary of the percentage change from baseline (CfB) in PASI Score at Week 8 for the ITT set designated for the EMA.

Table 12. Percent Change from Baseline in PASI Score at Week 8 (Intent-to-Treat Set), BAT-2206-002-CR

Statistic	Stelara N =278	BAT2206 N =278
Number of subjects evaluable for PASI at Week 8	274 (98.6)	275 (98.9)
Number of subjects experienced[a], n (%):		
ICE2YN - Discontinuation not due to LoE or death	1 (0.4)	2 (0.7)
ICE4YN - Deviations in dosing	8 (2.9)	6 (2.2)
ICE5YN - Rescue and/or prohibited therapy used for treatment of psoriasis	2 (0.7)	3 (1.1)
ICE6 - Data obtained remotely	8 (2.9)	6 (2.2)
Main Estimand:[b]		
LS mean (SE)	-76.507 (2.6526)	-75.543 (2.6847)
LS mean difference (SE)		0.964 (1.8952)
90% CI		(-2.154, 4.081)
95% CI		(-2.751, 4.679)
Secondary Estimand:[c]		
LS mean (SE)	-77.132 (2.5434)	-76.046 (2.5899)
LS mean difference (SE)		1.086 (1.8806)
90% CI		(-2.007, 4.179)
95% CI		(-2.600, 4.772)
Third Estimand:[d]		
LS mean (SE)	-77.125 (2.5769)	-76.092 (2.6341)
LS mean difference (SE)		1.032 (1.9170)
90% CI		(-2.121, 4.186)
95% CI		(-2.725, 4.790)

Abbreviations: ANCOVA, analysis of covariance; CI, confidence interval; ICE, intercurrent event; IWRS, interactive web response system; LoE, lack of efficacy; LS mean, least square mean; N, number of subjects; n, number of subjects in the specified category; PASI, psoriasis area severity index; SE, standard error.
Note: ANCOVA model is applied with treatment group (BAT2206 versus Stelara, reference Stelara), and randomized strata from IWRS (region, body weight at baseline category, baseline psoriatic arthritis status and previous biologic use) as terms in the model.
[a] Percentages were based on the number of subjects in Intent-to-Treat set under each group. All ICEs happened before or on Week 8 and influencing the PASI score at Week 8 were counted.
[b] A composite strategy was applied for ICE1 and ICE3, a treatment policy strategy for ICE2, ICE4 and ICE5 and a hypothetical strategy for ICE6.

Main secondary endpoints

Proportion of Subjects Achieving PASI-75 Improvement

Table 13 and Table 14 present summaries of PASI-75 response up to Week 28 and from post Week 28 through Week 52 for the ITT set. In TP1, the PASI-75 response rate increased until Week 28, with similar rates between treatment groups.

Table 13. Proportion of Subjects Achieving a PASI-75 Response up to Week 28 (Intent-to-Treat Set), BAT-2206-002-CR

Visit	Statistic	Stelara N = 278	BAT2206 N = 278
Week 4	Number of subjects evaluable for PASI response	273	274
	Number of responders, n (%)	44 (15.8)	51 (18.3)
	Main Estimand[a]		
	PASI-75 response rate (%)	16.31	18.82
	% Estimated treatment difference (SE)		2.51 (3.262)
	90% CI		(-2.85, 7.88)
	95% CI		(-3.88, 8.91)
	Secondary Estimand[b]		
	PASI-75 response rate (%)	16.24	18.84

Visit	Statistic	Stelara N = 278	BAT2206 N = 278
	% Estimated treatment difference (SE)		2.60 (3.244)
	90% CI		(-2.73, 7.94)
	95% CI		(-3.76, 8.96)
	Third Estimand[c]		
	PASI-75 response rate (%)	16.11	19.14
	% Estimated treatment difference (SE)		3.03 (3.271)
	90% CI		(-2.35, 8.41)
	95% CI		(-3.38, 9.44)
Week 8	Number of subjects evaluable for PASI response	274	275
	Number of responders, n (%)	153 (55.0)	153 (55.0)
	Main Estimand[a]		
	PASI-75 response rate (%)	55.01	54.66
	% Estimated treatment difference (SE)		-0.35 (4.223)
	90% CI		(-7.30, 6.59)
	95% CI		(-8.63, 7.93)
	Secondary Estimand[b]		
	PASI-75 response rate (%)	55.45	54.50
	% Estimated treatment difference (SE)		-0.95 (4.209)
	90% CI		(-7.87, 5.97)
	95% CI		(-9.20, 7.30)
	Third Estimand[c]		
	PASI-75 response rate (%)	55.09	54.35
	% Estimated treatment difference (SE)		-0.74 (4.231)
	90% CI		(-7.70, 6.22)
	95% CI		(-9.03, 7.55)
Week 12	Number of subjects evaluable for PASI response	275	274
	Number of responders, n (%)	217 (78.1)	211 (75.9)
	Main Estimand[a]		
	PASI-75 response rate (%)	78.36	76.32
	% Estimated treatment difference (SE)		-2.03 (3.620)
	90% CI		(-7.99, 3.92)
	95% CI		(-9.13, 5.06)
	Secondary Estimand[b]		
	PASI-75 response rate (%)	78.23	76.11
	% Estimated treatment difference (SE)		-2.12 (3.639)
	90% CI		(-8.10, 3.87)
	95% CI		(-9.25, 5.01)
	Third Estimand[c]		
	PASI-75 response rate (%)	78.03	76.03
	% Estimated treatment difference (SE)		-2.01 (3.670)
	90% CI		(-8.04, 4.03)
	95% CI		(-9.20, 5.19)
Week 16	Number of subjects evaluable for PASI response	275	275
	Number of responders, n (%)	231 (83.1)	232 (83.5)
	Main Estimand[a]		
	PASI-75 response rate (%)	83.89	83.54
	% Estimated treatment difference (SE)		-0.36 (3.201)
	90% CI		(-5.62, 4.91)
	95% CI		(-6.63, 5.92)
	Secondary Estimand[b]		
	PASI-75 response rate (%)	83.43	83.20
	% Estimated treatment difference (SE)		-0.23 (3.261)
	90% CI		(-5.60, 5.13)
	95% CI		(-6.62, 6.16)
	Third Estimand[c]		
	PASI-75 response rate (%)	83.31	83.51
	% Estimated treatment difference (SE)		0.20 (3.284)
	90% CI		(-5.21, 5.60)
	95% CI		(-6.24, 6.63)
Week 20	Number of subjects evaluable for PASI response	272	274
	Number of responders, n (%)	251 (90.3)	253 (91.0)

Visit	Statistic	Stelara N = 278	BAT2206 N = 278
	Main Estimand[a]		
	PASI-75 response rate (%)	92.22	91.73
	% Estimated treatment difference (SE)		-0.49 (2.360)
	90% CI		(-4.38, 3.39)
	95% CI		(-5.12, 4.13)
	Secondary Estimand[b]		
	PASI-75 response rate (%)	90.84	91.36
	% Estimated treatment difference (SE)		0.52 (2.521)
	90% CI		(-3.63, 4.67)
	95% CI		(-4.42, 5.46)
	Third Estimand[c]		
	PASI-75 response rate (%)	91.43	90.94
	% Estimated treatment difference (SE)		-0.49 (2.526)
	90% CI		(-4.65, 3.66)
	95% CI		(-5.44, 4.46)
Week 28	Number of subjects evaluable for PASI response	269	271
	Number of responders, n (%)	266 (95.7)	266 (95.7)
	Main Estimand[a]		
	PASI-75 response rate (%)	98.09	97.70
	% Estimated treatment difference (SE)		-0.39 (1.236)
	90% CI		(-2.42, 1.64)
	95% CI		(-2.81, 2.03)
	Secondary Estimand[b]		
	PASI-75 response rate (%)	97.47	96.94
	% Estimated treatment difference (SE)		-0.53 (1.547)
	90% CI		(-3.08, 2.01)
	95% CI		(-3.56, 2.50)
	Third Estimand[c]		
	PASI-75 response rate (%)	98.11	96.44
	% Estimated treatment difference (SE)		-1.67 (1.547)
	90% CI		(-4.22, 0.87)
	95% CI		(-4.70, 1.36)

Abbreviations: CI, confidence interval; ICE, intercurrent event; IWRS, interactive web response system; LS mean, least square mean; N, number of subjects; n, number of subjects in the specified category; PASI, psoriasis area severity index; SE, standard error.

Note: Percentages were based on the number of subjects in Intent-to-Treat set under each group.

Note: Multiple imputation was applied to PASI assessment up to Week 28.

Note: Logistic regression model was applied with treatment group (BAT2206 versus Stelara, reference Stelara), and randomized strata from IWRS (region, body weight at baseline category, baseline psoriatic arthritis status and previous biologic use) as terms in the model.

[a] A composite strategy was applied for ICE1 and ICE3, a treatment policy strategy for ICE2, ICE4 and ICE5 and a hypothetical strategy for ICE6.

[b] A composite strategy was applied for ICE1 and ICE3, a treatment policy strategy for ICE2 and ICE5 and a hypothetical strategy for ICE4, ICE6.

[c] A composite strategy was applied for ICE1 and ICE3, a treatment policy strategy for ICE2 and a hypothetical strategy for ICE4, ICE5, ICE6.

Table 14. Summary of the Proportion of Subjects Achieving a PASI-75 Response Post Week 28 Through Week 52 (Intent-to-Treat Set for TP2), BAT-2206-002-CR

Visit	Statistic	Stelara-> Stelara N = 133	Stelara-> BAT2206 N = 131	BAT2206-> BAT2206 N = 264
Week 32	Number of subjects evaluable for PASI response	133	129	263
	Number of responders, n (%)	131 (98.5)	126 (96.2)	260 (98.5)
Week 40	Number of subjects evaluable for PASI response	132	129	262
	Number of responders, n (%)	126 (94.7)	121 (92.4)	254 (96.2)
Week 44	Number of subjects evaluable for PASI response	132	128	261

Visit	Statistic	Stelara-> Stelara N = 133	Stelara-> BAT2206 N = 131	BAT2206-> BAT2206 N = 264
	Number of responders, n (%)	127 (95.5)	120 (91.6)	253 (95.8)
Week 52	Number of subjects evaluable for PASI response	128	126	258
	Number of responders, n (%)	122 (91.7)	115 (87.8)	246 (93.2)

Abbreviations: N, number of subjects; n, number of subjects in the specified category; PASI, psoriasis area severity index; TP2, treatment period 2.
Note: Percentages were based on the number of subjects in Intent-to-Treat set for TP2 under each group.
Note: For Week 32, 40, 44, and 52 PASI assessment, analysis was based on observed data.

Change from Baseline in static Physician's Global Assessment Score

Table 15. Summary of Change from Baseline in sPGA Score up to Week 28 (Intent-to-Treat Set), BAT-2206-002-CR

Visit	Statistic	Stelara N = 278	BAT2206 N = 278
Week 4	n	273	274
	Mean (SD)	-1.3 (0.88)	-1.4 (0.95)
	Median	-1.0	-1.0
	Min, Max	-4, 0	-4, 0
Week 8	n	274	275
	Mean (SD)	-2.2 (1.01)	-2.3 (1.03)
	Median	-2.0	-2.0
	Min, Max	-5, 0	-5, 0
Week 12	n	275	274
	Mean (SD)	-2.5 (0.94)	-2.6 (1.01)
	Median	-3.0	-3.0
	Min, Max	-5, -1	-5, 1
Week 16	n	275	275
	Mean (SD)	-2.7 (0.94)	-2.7 (1.03)
	Median	-3.0	-3.0
	Min, Max	-5, 0	-5, 1
Week 20	n	272	274
	Mean (SD)	-2.8 (0.91)	-2.9 (0.95)
	Median	-3.0	-3.0
	Min, Max	-5, 0	-5, 1
Week 28	n	269	271
	Mean (SD)	-2.8 (0.87)	-2.9 (0.98)
	Median	-3.0	-3.0
	Min, Max	-5, 0	-5, -1

Abbreviations: Max, maximum; Min, minimum; N, number of subjects; n, number of subjects at the specified timepoint; SD, standard deviation; sPGA, static Physician's Global Assessment.
Note: For sPGA assessment, analysis is based on observed data.

Change From Baseline in Dermatology Life Quality Index Score

Table 16. Summary of Change from Baseline in DLQI Score up to Week 28 (Intent-to-Treat Set), BAT-2206-002-CR

Visit	Statistic	Stelara N = 278	BAT2206 N = 278
Week 8	n	274	275
	Mean (SD)	-9.4(6.83)	-10.4(6.85)
	Median	-8.0	-10.0
	Min, Max	-29, 6	-30, 12
Week 12	n	275	274
	Mean (SD)	-11.1(6.79)	-11.6(7.12)
	Median	-11.0	-11.0
	Min, Max	-29, 3	-30, 3
Week 28	n	269	271
	Mean (SD)	-11.9(6.97)	-12.3(7.22)
	Median	-12.0	-11.0
	Min, Max	-30, 8	-30, 4

Abbreviations: DLQI, Dermatology Life Quality Index; Max, maximum; Min, minimum; N, number of subjects; n, number of subjects at the specified timepoint; SD, standard deviation.

Change From Baseline in Affected Body Surface Area

Table 17. Summary of Change from Baseline in Affected BSA (%) up to Week 28 (Intent-to-Treat Set), BAT-2206-002-CR

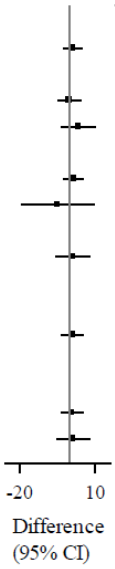
Visit	Statistic	Stelara N = 278	BAT2206 N = 278
Week 4	n	273	274
	Mean (SD)	-8.92(10.888)	-8.73(10.559)
	Median	-6.00	-5.50
	Min, Max	-70.0, 10.5	-79.3, 17.7
Week 8	n	274	275
	Mean (SD)	-19.29(15.083)	-18.43(14.992)
	Median	-15.00	-14.50
	Min, Max	-75.7, 4.2	-84.5, 15.7
Week 12	n	275	274
	Mean (SD)	-24.67(15.290)	-23.04(16.085)
	Median	-21.90	-20.50
	Min, Max	-86.0, 0	-85.5, 22.0
Week 16	n	275	275
	Mean (SD)	-26.12(15.001)	-24.99(16.124)
	Median	-23.00	-22.00
	Min, Max	-83.0, 13.4	-83.8, 22.0
Week 20	n	272	274
	Mean (SD)	-27.93(14.879)	-26.85(15.865)
	Median	-25.00	-23.50
	Min, Max	-83.0, -3.5	-83.6, 9.3
Week 28	n	269	271
	Mean (SD)	-28.64(14.740)	-28.29(15.867)
	Median	-26.50	-25.00
	Min, Max	-79.5, -3.5	-84.5, 9.3

Abbreviations: BSA, body surface area; Max, maximum; Min, minimum; N, number of subjects; n, number of subjects at the specified timepoint; SD, standard deviation.

- **Ancillary analyses**

To evaluate the consistency in the primary efficacy endpoint over demographic and stratification factors (including region), plus by whether subjects were positive for ADA or NAbs as appropriate, exploratory subgroup analyses were performed.

Figure 4. Percent Change from Baseline in PASI Score at Week 8 by Demographic and Baseline Characteristics (Primary Estimand) (Intent-to-Treat Set), BAT-2206-002-CR



	Stelara	BAT2206	Difference (90% CI)	Difference (95% CI)	Interaction p-value
Overall (N=556)	-76.507 (2.6526)	-75.543 (2.6847)	0.964 (-2.154, 4.081)	0.964 (-2.751, 4.679)	
Gender					0.382
Male (N=374)	-76.201 (2.8085)	-76.484 (2.8152)	-0.283 (-4.142, 3.577)	-0.283 (-4.882, 4.317)	
Female (N=182)	-77.331 (3.3345)	-73.895 (3.4644)	3.437 (-2.228, 9.101)	3.437 (-3.314, 10.188)	
Age Group					0.414
< 65 years (N=521)	-77.190 (2.6894)	-75.774 (2.7071)	1.416 (-1.805, 4.637)	1.416 (-2.422, 5.254)	
>= 65 years (N=35)	-68.268 (5.4448)	-73.121 (5.9404)	-4.853 (-17.060, 7.355)	-4.853 (-19.399, 9.693)	
Race					0.959
Asian (N=188)	-78.990 (3.5884)	-77.869 (3.4261)	1.121 (-4.475, 6.718)	1.121 (-5.549, 7.791)	
Black (N=0)	-	-	-	-	
Native Hawaiian or Pacific Islander (N=0)	-	-	-	-	
White (N=368)	-74.014 (2.5692)	-73.104 (2.6489)	0.910 (-2.861, 4.682)	0.910 (-3.583, 5.404)	
Other (N=0)	-	-	-	-	
Region Where the Patient was Enrolled					0.925
Central Europe (N=367)	-73.961 (2.5693)	-73.129 (2.6490)	0.832 (-2.944, 4.608)	0.832 (-3.667, 5.331)	
Asia Pacific (N=189)	-79.122 (3.5781)	-77.902 (3.4264)	1.220 (-4.356, 6.796)	1.220 (-5.426, 7.865)	

	Stelara	BAT2206	Difference (90% CI)	Difference (95% CI)	Interaction p-value
Body Weight (kg)					0.129
<=100 kg (N=478)	-80.415 (2.4991)	-78.303 (2.5306)	2.112 (-1.246, 5.470)	2.112 (-1.890, 6.114)	
>100 kg (N=78)	-70.003 (4.1303)	-76.112 (4.1629)	-6.109 (-14.376, 2.158)	-6.109 (-15.960, 3.741)	
Psoriatic Arthritis (PsA)					0.509
Yes (N=66)	-77.325 (4.0740)	-72.842 (4.8053)	4.483 (-4.818, 13.784)	4.483 (-6.601, 15.567)	
No (N=490)	-76.898 (2.5904)	-76.403 (2.5157)	0.495 (-2.834, 3.824)	0.495 (-3.471, 4.462)	
Baseline PASI score					0.065
< 20 (N=228)	-78.154 (3.3817)	-73.069 (3.2086)	5.085 (0.092, 10.079)	5.085 (-0.866, 11.036)	
>= 20 (N=327)	-75.536 (2.7450)	-77.687 (2.8547)	-2.151 (-6.176, 1.874)	-2.151 (-6.947, 2.645)	
Previous Biologic Use					0.784
Yes (N=36)	-78.987 (5.2340)	-80.033 (5.8278)	-1.045 (-13.531, 11.440)	-1.045 (-15.923, 13.833)	
No (N=520)	-73.274 (2.2400)	-72.174 (2.2249)	1.100 (-2.122, 4.322)	1.100 (-2.739, 4.939)	

Abbreviations: CI, confidence interval; N, number of subjects; PASI, psoriasis area severity index.
Notes:

- A composite strategy was applied for ICE1 and ICE3, a treatment policy strategy for ICE2, ICE4 and ICE5 and a hypothetical strategy for ICE6.
- Proportion difference as well as corresponding confidence interval, and interaction p-values were based on ANCOVA model.
- For randomized strata subgroups (region, body weight at baseline category, baseline psoriatic arthritis status and previous biologic use), the randomized strata from IWRS were used.

- **Summary of main efficacy results**

The following table summarises the efficacy results from the main study 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 18. Summary of efficacy for trial BAT-2206-002-CR

Title: *a multicenter, randomised, double-blind,pParallel-arm, Phase 3 study to compare efficacy and safety of BAT2206 with Stelara in patients with moderate to severe plaque psoriasis*		
Study identifier	BAT-2206-002-CR EudraCT Number: 2020-004504-33	
Design	Multicenter, randomised, double-blind, parallel-arm, Phase 3 study designed to compare the efficacy, safety, immunogenicity, and pharmacokinetics of BAT2206 with Stelara in subjects with moderate to severe psoriasis. Subjects with a ≥PASI-75 response at Week 28 entered into TP2 of the study to continue treatment. Qualified subjects in the Stelara group in TP1 were re-randomised 1:1 at TP2 (during Week 28 visit) to receive either BAT2206 or Stelara in TP2. Randomisation of these subjects for TP2 was stratified using the same baseline stratification factors as defined for randomisation in TP1. Qualified subjects in the BAT2206 group in TP1 continued treatment with BAT2206 in TP2.	
	Duration of main phase (TP1): Duration of TP2: Duration of Run-in phase: Duration of	28 weeks of treatment 24 weeks (weeks 28-52, last treatment at week 40) not applicable not applicable
Primary objective	The primary objective of the study was to demonstrate equivalent efficacy of BAT2206 and Stelara in subjects with moderate to severe psoriasis.	
Treatments groups	BAT2206	278 subjects randomised 45 mg (1 injection or 90 mg (2 injections) injections based on body weight at Day 0, 4 weeks later, and thereafter every 12 weeks until Week 40 Only subjects with PASI ≥75 continued treatment with BAT2206 after Week 28 for TP2.
	Stelara Ustekinumab	278 subjects randomised 45 mg (1 injection) or 90 mg (2 injections) injections based on body weight at Day 0, 4 weeks later, and thereafter every 12 weeks until Week 40. Subjects with PASI≥75 at Week 28 were re-randomised to BAT2206 or Stelara for TP2.

Endpoints and definitions	Primary endpoint	PASI CfB at week 8 (Intention-to-treat set [ITT])	Percent change from baseline (CfB) in PASI score at Week 8 (EMA) based on the ITT. The 95% CIs for the LS mean difference between the BAT2206 and Stelara groups had to be within the equivalence margin of -13.0% to +13.0% to prove that BAT2206 is biosimilar to Stelara.

	Primary endpoint, sensitivity and supportive analyses	PASI CfB at week 8 (ITT) [1)]	• Repeated Measures Mixed Model without Imputation • Repeated Measures Mixed Model • LOCF Imputation • Ignoring ICE6 • Using EDC Random Stratification Factor • Using Combined Strata • Tipping point analysis
	Secondary endpoints	PASI CfB over time	Percent CfB in PASI score at weeks 4, 16, 20, 28, 32, 40, 44, and 52 (ITT, PPS)
		Rates of PASI improvement over time	Proportion of subjects who achieved at least 50%/75%/90%/100% improvement from baseline in PASI (PASI-50/75/90/100) at Weeks 4, 8, 12, 16, 20, 28, 32, 40, 44, and 52
		PASI AUEC	Area-under-the effect-curve (AUEC) for PASI from baseline to Weeks 8, 12, and 28
		sPGA CfB over time	CfB in static Physician's Global Assessment score (sPGA) at Weeks 4, 8, 12, 16, 20, 28, 32, 40, 44, and 52
		Rates of sPGA response over time	Proportion of subjects with sPGA on a 6-item Scale of Cleared (0) or Minimal (1) at Weeks 4, 8, 12, 16, 20, 28, 32, 40, 44, and 52
		CfB in affected BSA over time	CfB in affected body surface area (BSA) at Weeks 4, 8, 12, 16, 20, 28, 32, 40, 44, and 52
		CfB in DLQI score over time	CfB in Dermatology Life Quality Index (DLQI) score at Weeks 8, 12, 28, 40, and 52
Database lock	21 August 2023		
Results and Analysis			
Analysis description	**Primary analysis of primary endpoint**		
Analysis population Time point description	Intention-to-treat set (ITT): includes all TP1 randomised subjects Week 8 (EMA)		
Descriptive statistics and estimate variability	Treatment group	**Stelara**	**BAT2206**
	Number of subjects (ITT)	278	278
	Number of subjects	274	275
	PASI CfB at week 8 Least square mean (LSM) (SE)	-76.507 (2.6526)	-75.543 (2.6847)

Effect estimate per comparison			Comparison groups		Stelara BAT2206
			LSM difference (BAT2206 *minus* Stelara)		0.964
			Standard error (SE)		1.8952
			95% confidence interval (CI)		(-2.751, 4.679)
Sensitivity and Supportive Analyses of PASI at Week 8 (EMA), Main Results					
PASI percent CfB at Week 8 (ITT):	• Repeated Measures Mixed Model without Imputation		LSM difference (95% CI) (BAT2206 *minus* Stelara)		0.901 (-2.775, 4.577)
	• Repeated Measures Mixed Model				0.995 (-2.767, 4.758)
	• LOCF Imputation				-0.201 (-4.223, 3.822)
	• Ignoring ICE6				0.643 (-2.995, 4.280)
	• Using EDC Random Stratification Factor[1)]				0.991 (-2.721, 4.704)
	• Using Combined Strata [1)]				1.024 (-2.682, 4.730)
	• Tipping point analysis		Since equivalence was observed in the analysis of the main estimand, a 2-dimensional tipping point analysis was conducted based on the different levels of delta shift for the imputation in each treatment group, gradually increasing the severity of imputation involved for the BAT2206 and/or Stelara treatment until the resulting 90%/95% CI tipped to nonequivalence. The EMA nonequivalence met with delta shift leave = 27 for the imputation in the BAT2206 group or delta shift leave = 36 for the imputation in the Stelara group.		
	Secondary endpoints, TP1 main results				
Parameter:	**Analysis set**		**Stelara (N=278)**	**BAT2206 (N=278)**	**Statistic**
PASI Percent CfB over time, LSM %CfB [1)]	ITT	Week 4	-49.80	-50.39	LSM difference (95% CI): -0.59 (-4.87, 3.69)
		Week 16	-87.46	-86.38	LSM difference (95% CI): 1.08 (-1.81, 3.96)
		Week 20	-89.56	-88.76	LSM difference (95% CI): 0.80 (-1.80, 3.40)
		Week 28	-91.13	-90.54	LSM difference (95% CI): 0.59 (-1.25, 2.43)

PASI-75 response rate % of subjects [1)]	ITT	Week 4	16.31	18.82	ET difference (95% CI): 2.51 (-3.88, 8.91)
		Week 8	55.01	54.66	ET difference (95% CI): -0.35 (-8.63, 7.93)
		Week 12	78.36	76.32	ET difference (95% CI): -2.03 (-9.13, 5.06)
		Week 16	83.89	83.54	ET difference (95% CI): -0.36 (-6.63, 5.92)
		Week 20	92.22	91.73	ET difference (95% CI): -0.49 (-5.12, 4.13)
		Week 28	98.09	97.70	ET difference (95% CI): -0.39 (-2.81, 2.03)
PASI AUEC from Baseline to Weeks 8, 12, and 28 LSM [1)]	ITT	Week 8	847.11	818.95	LSM difference (95% CI): -28.16 (-92.10, 35.79)
		Week 12	990.23	961.12	LSM difference (95% CI): -29.11 (-110.18, 51.96)
		Week 28	1317.35	1294.80	LSM difference (95% CI): -22.56 (-154.80, 109.69)
sPGA CfB to Weeks 8, 12, 20 and 28 Mean ± SD	ITT	Week 8	-2.2 ± 1.01	-2.3 ± 1.03	---
		Week 12	-2.5 ± 0.94	-2.6 ± 1.01	
		Week 20	-2.8 ± 0.91	-2.9 ± 0.95	
		Week 28	-2.8 ± 0.87	-2.9 ± 0.98	
CfB in affected BSA over time LS mean	ITT	Week 8	-17.898	-17.662	LSM difference (95% CI): 0.236 (-1.584, 2.056)
		Week 12	-23.346	-22.756	LSM difference (95% CI): 0.591 (-0.996, 2.177)
		Week 20	-26.786	-26.657	LSM difference (95% CI): 0.129 (-0.992, 1.250)
		Week 28	-27.676	-27.934	LSM difference (95% CI): -0.258 (-1.075, 0.560)
CfB in DLQI score over time Mean ± SD	ITT	Week 8	-9.4 ± 6.83	-10.4 ± 6.85	---
		Week 12	-11.1 ± 6.79	-11.6 ± 7.12	
		Week 28	-11.9 ± 6.97	-12.3 ± 7.22	
Notes		Of the 278 subjects randomised to Stelara for TP1, 273 subjects completed TP1 and 264/273 subjects entered into TP2 and 254/273 subjects completed TP2 (10 withdrawals [5 of the withdrawals had switched to BAT2206 for TP2]). Of the 278 subjects randomised to BAT2206 for TP1, 271 subjects completed TP1 and 264/271 subjects entered into TP2 and 258 subjects completed TP2 (6 withdrawn from the study).			

Abbreviations: AS = analysis set; CfB = change from baseline; AEUC = Area-under-the effect-curve; BSA = body surface area; CI = confidence interval; DLQI = Dermatology Life Quality Index Score; EDC = electronic data capture; ET difference= estimated treatment difference; ICE = intercurrent event; ITT = intension-to-treat set; LOCF = last observation carried forward; n' = number of evaluable subjects; PASI = Psoriasis Area and Severity Index score; sPGA = static Physician's Global Assessment score; SE = standard error; TP = treatment period

1) Main estimand = a composite strategy was applied for ICE1 and ICE3, a treatment policy strategy for ICE2, ICE4 and ICE5 and a hypothetical strategy for ICE6

2) PASI percent CfB at Week 12 is the primary endpoint for the FDA and NMPA (but for EMA it was Week 8):

- For the EMA at Week 8, the equivalence margin 95% CI (α = 0.025) was [-13.0%, +13.0%]
- For the FDA at Week 12, the equivalence margin 90% CI (α = 0.05) was [-10.0%, +10.0%]
- For NMPA and other agencies at Week 12, the equivalence margin 95% CI (α = 0.025) was [-13.0%, +13.0%]

2.6.5.3. Clinical studies in special populations

Not applicable.

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

Usability of the PFS

BAT2206 is supplied in PFS with automatic needle guard and single-use vial presentations. With regard to the PFS, the applicant refers to the identicality between the BAT2206 PFS with a needle safety device (NSD) and Stelara PFS with NSD. To support the usability of the PFS with NSD, the applicant has conducted a use-related risk analysis (URRA) including detailed information on known use related problems and an evaluation of risks and critical tasks for BAT2206 PFS with NSD. In addition, a threshold analysis to identify design differences in the user interface of the biosimilar and reference product device was performed. The threshold analysis included a comparative labelling analysis, comparative task analysis, and physical comparison of the delivery device constituent parts. The submitted data support the usability of BAT2206 PFS with NSD in the intended target population and use environment.

2.6.6. Discussion on clinical efficacy

Design and conduct of clinical studies

Design and treatment

The clinical development programme to compare clinical efficacy, safety and immunogenicity between BAT2206 and EU-Stelara comprised one single phase III study (BAT-2206-002-CR) in patients with moderate to severe plaque-type psoriasis (Ps).

Study BAT-2206-002-CR was a multicentre, randomised, double-blind trial with parallel arms. Eligible subjects received either 45 mg (bw ≤100kg) or 90 mg (bw >100kg) of BAT2206 or EU-sourced Stelara by SC injection via PFS. The study was composed of a 28-week initial treatment period (TP1), and a 24-week secondary treatment period (TP2) including a 12-week efficacy and safety follow-up period after the last dose at Week 40 up to the EOS visit at Week 52. Subjects from either of the treatment groups were discontinued from the study treatment if the improvement in PASI score at Week 28 was <75%. This is in line with the originator SmPC recommendation to discontinue treatment in patients who have shown no response up to 28 weeks of treatment.

At Week 28, responders who continued in the study were re-randomised. Subjects randomised to receive BAT2206 during TP1 continued to receive BAT2206 during TP2. Subjects randomised to receive Stelara during TP1 were re-randomised to receive BAT2206 or Stelara in TP2.

The study was conducted at 39 sites in five countries: China, Poland, Bulgaria, Georgia and Russia. However, the comparator used at all centres was EU approved Stelara.

The study design was adequate to demonstrate similarity between BAT2206 and EU-approved Stelara. The design is in accordance with the EMA Guideline on similar biological medicinal products (CHMP/437/04 Rev 1, October 2014) and with the EMA Guideline on clinical investigation of medicinal products indicated for the treatment of psoriasis (CHMP/EWP/2454/02 corr). The switching regimen is not required by EMA but was conducted by request of other regulatory agencies.

Participants

The study was conducted in men and women ≥ 18 years of age with a diagnosis of plaque-type psoriasis at least 24 weeks before screening, who had failed to respond to, had a contraindication to, or were intolerant to other systemic therapies. Subjects were to have baseline score of Psoriasis Area and Severity Index (PASI) ≥ 12, involvement of ≥ 10% body surface area (BSA), and Static Physician's Global Assessment (sPGA) ≥ 3 at screening and at baseline.

The CHMP SA pointed out that a clinical biosimilarity study should include the most homogeneous and sensitive population. However, the applicant did not follow entirely the SA as further discussed below.

Overall, the inclusion and exclusion criteria were adequate, and the study population is representative of the target population in plaque-type psoriasis. However, patients with concurrent psoriatic arthritis who had a worse prognosis were allowed to participate in the study, although the CHMP SA advised against because of the unwanted heterogeneity which this can introduce. Instead, the randomisation was stratified by presence of psoriatic arthritis at Day 0 and at the Week 28 visit (separate randomisation for TP2).

In addition, the study was a multicentre study conducted in European countries and China and as mentioned in the SA, inclusion of an ethnically diverse study population is not considered an ideal choice for a biosimilar exercise and a more homogeneous population would have been preferred. However, according to the SmPC of Stelara, the PK of ustekinumab were generally comparable between Asian and non-Asian patients with psoriasis. In addition, the study randomisation was stratified by region (China/Europe) at Day 0 and at the Week 28 visit (separate randomisation for TP2) and subgroup analysis has been performed, which is considered acceptable.

The study included patients with a body weight up to 120 kg, which led to different dosing regimens for different subjects, i.e., patients ≤ 100 kg at baseline received 45 mg of ustekinumab (1 injection of 45 mg/0.5 mL) throughout the study whereas patients > 100 kg at baseline received 90 mg of ustekinumab (2 injections of 45 mg/0.5 mL each) throughout the study, although the CHMP SA advised against because this could introduce non-product-related variability. Instead, the applicant preferred to apply a study randomisation stratified by body weight (≤100 kg versus >100 kg) at Day 0 and at the Week 28 visit (separate randomisation for TP2) and a subgroups analysis was performed.

Apart from the issues discussed above, the eligibility criteria were overall in line with the given CHMP SA. The study population is representative of the target population in plaque-type psoriasis and baseline characteristics were generally balanced between study arms. It is noted that the pivotal trials for Stelara, which the equivalence margins were based on, included a larger proportion of patients with PsA as compared with the current study. Therefore, inclusion of PsA patients is acceptable, in principle. If the proportion of PsA patients would have greatly exceeded the corresponding proportion in the pivotal trials for Stelara, this could have had implications to the applicable equivalence margin, but this was not the case.

Conduct and methods of analysis

The primary endpoint was percent change from baseline (CfB) in PASI score at week 8. Equivalence was to be concluded if the 2-sided 95% CI of the estimate fell entirely within the predefined equivalence margin of ±13%. CfB in PASI is considered sufficiently sensitive to detect potential clinically meaningful differences in efficacy. Assessment of efficacy, including primary and secondary endpoints, time of assessment, and duration of follow up is in line with the EMA Guideline on clinical investigation of medicinal products indicated for the treatment of psoriasis (CHMP/EWP/2454/02 corr) and with the given CHMP SA. The equivalence margin of ±13% was not clinically justified by the applicant but is acceptable as it was endorsed by the CHMP in the SA.

Three estimands were formulated with different approaches to intercurrent events (ICEs: study treatment discontinuation, rescue/prohibited medications and deviations of dosing and death). The main estimand corresponds to intent-to-treat analysis which is also focal in the assessment of efficacy for CHMP. The other two estimands represent steps toward an estimand corresponding to a hypothetical scenario where ICEs did not take place. A hypothetical estimand corresponding to complete absence of ICEs was not defined, however, given the small number of relevant ICEs observed, such an analysis could not lead to a different conclusion. Notably, as no-one discontinued study treatment due to lack of efficacy during the first few months, this ICE hasn't got any impact on the outcome.

The data that were missing – either not obtained or set as missing in each estimand's ICE strategy – were subject to multiple imputation using fully conditional specification that accounted to treatment group, stratification factors, previous PASI values and previously occurred ICEs as the predictors. This approach is appropriate, and, given the low incidence of ICE and otherwise missing data, further scrutiny of data imputation models is not worthwhile.

The ANCOVA model that was used to estimate treatment effect from each of the multiple imputed datasets is a conventional method estimating treatment difference while also accounting for stratification factors. Covariate adjustment to baseline PASI was not done; a crude adjustment to baseline level is part of the percent change calculation. The reported treatment group specific LSmeans (corresponding to a hypothetical target population with 50-50 (%) split with respect to levels of each binary stratification factor) may not be accurate and precise estimators of the mean response overall. However, in the current study the consequent lack of accuracy/precision in the results is clinically irrelevant. Importantly, this concern does not impact the estimated difference between treatments.

A logistic regression model was fitted to estimate between-treatment differences in the proportion of subjects achieving different levels of PASI response. The estimands and strategies to cope with ICEs were analogous to those adopted with percent change PASI as continuous endpoint. The method used to estimate the marginal proportions of responders from the subject-specific predicted response probabilities is endorsed.

In principle, concluding equivalent efficacy based on 95% confidence interval of the mean change in percent CfB in PASI, corresponding to two 1-sided hypothesis tests at 2.5% significance level to exclude relevant difference between treatments, is in accordance with CHMP's expectations. Overall, the planned statistical analyses are fit for purpose. Their specification is detailed and comprehensive.

No uncertainties regarding data quality or study conduct arose during assessment.

Efficacy data and additional analyses

A total of 556 subjects were randomised, 278 subjects received Stelara, 277 subjects received BAT2206 and 92.6% (515/556) of all subjects randomised at screening completed the 52-week study.

Demographic and disease characteristics at baseline were well balanced across the BAT2206 and Stelara groups. The studied population is representative of patients with moderate to severe plaque psoriasis.

At Week 8, The LS mean difference in PASI percent CfB for BAT2206 versus Stelara was 0.964 and the 95% CI was -2.751 to 4.679. Thus, the primary objective of the study was achieved.

Sensitivity analyses were supportive of the results as all 95% CI were entirely contained within the predefined equivalence margins regardless of which estimand, imputation method or analysis set was used.

To evaluate the consistency in the primary efficacy endpoint over demographic and stratification factors (including region), exploratory subgroup analyses were performed. The percent CfB in PASI score at Week 8 was comparable between BAT2206 and Stelara groups for all subgroups.

Based on the narrow CI of the primary endpoint, the sensitivity analyses and the subgroup analyses, the presumed heterogeneity of the study population (inclusion of subjects >100 kg and PsA patients) does not preclude conclusions on similarity.

The outcome of the secondary endpoints are consistent with the primary results and support similarity between EU Stelara and BAT2206.

The mean percent CfB in PASI score and the PASI-50/75/90/100 response rates were generally similar across all treatment groups throughout the whole study with no important differences, including for the subjects who continued to receive Stelara and subjects who switched from Stelara to BAT2206.

The PASI-75 response rate at week 28 was unexpectedly high, 98.1% and 97.7% for the Stelara and BAT2206 groups, respectively. According to the Stelara SmPC, approximately 70-79% of patients reach PASI-75 by week 28. This difference could possibly be caused by different baseline characteristics and/or different handling of missing data but these details have not been further explored. Although, the sensitivity to detect differences might not be optimal with such high response rates, the issue of unusually high response rates is not pursued further because the overall results are considered to be consistent and robust by the CHMP.

For the descriptive analyses of the CfB in sPGA score, CfB in DLQI score and CfB in affected BSA, no important differences between the groups were seen throughout the study.

Overall, the efficacy of BAT2206 is similar to that of EU-Stelara in subjects with moderate to severe psoriasis. The results are consistent over different analysis sets and subgroups and over all secondary measures of efficacy.

2.6.7. Conclusions on the clinical efficacy

The presented efficacy data supports clinical equivalence of Usymro to EU-Stelara.

2.6.8. Clinical safety

2.6.8.1. Patient exposure

In the Phase 1 PK study, 269 healthy Chinese male subjects aged 18-55 years received one 45 mg dose of treatment, including 90 subjects in the BAT2206 injection group and 89 subjects in the Stelara (EU-sourced) group and 90 subjects in the Stelara (US-sourced) group.

In the Phase 3 study, 555 patients with moderate to severe plaque psoriasis received weight-based dosing for one year. Exposure in the target population is described in Table 19.

Table 19. Exposure to Study Treatment - During TP1, TP2 and Through the Study (Safety Analysis Set) in BAT-2206-002-CR

	Treatment Period 1		
Statistics	**Stelara N = 278**	**BAT2206 N = 277**	**Total N = 555**
Number of doses administered			
n	278	277	555
Mean (SD)	2.9 (0.25)	3.0 (0.22)	2.9 (0.23)
Median	3.0	3.0	3.0
Min, Max	2, 3	1, 3	1, 3
Cumulative dose administered (mg)			
n	278	277	555
Mean (SD)	151.3 (49.29)	151.9 (48.22)	151.6 (48.72)
Median	135.0	135.0	135.0
Min, Max	90, 270	45, 270	45, 270

	Treatment Period 2			
Statistics	**Stelara ->Stelara N = 133**	**Stelara ->BAT2206 N = 131**	**BAT2206 ->BAT2206 N = 264**	**Total N = 528 n (%)**
Number of doses administered				
n	133	131	264	528
Mean (SD)	2.0 (0.12)	2.0 (0.17)	2.0 (0.11)	2.0 (0.13)
Median	2.0	2.0	2.0	2.0
Min, Max	1, 2	1, 2	1, 2	1, 2
Cumulative dose administered (mg)				
n	133	131	264	528
Mean (SD)	103.5 (33.69)	100.6 (31.49)	101.4 (31.15)	101.8 (31.85)
Median	90.0	90.0	90.0	90.0
Min, Max	45, 180	45, 180	45, 180	45, 180

	Through the Study							
	Stelara				**BAT2206**			
Statistics	**Stelara TP1 only N = 14**	**Stelara ->Stelara N = 133**	**Stelara ->BAT2206 N = 131**	**Combined N = 278**	**BAT2206 TP1 only N = 13**	**BAT2206 -> BAT2206 N = 264**	**Combined N = 277**	**Total N = 555**
Number of doses administered								
n	14	133	131	278	13	264	277	555
Mean (SD)	2.6 (0.51)	4.9 (0.22)	4.9 (0.33)	4.8 (0.60)	2.8 (0.60)	5.0 (0.21)	4.9 (0.52)	4.8 (0.56)
Median	3.0	5.0	5.0	5.0	3.0	5.0	5.0	5.0
Min, Max	2, 3	4, 5	3, 5	2, 5	1, 3	3, 5	1, 5	1, 5
Cumulative dose administered (mg)								
n	14	133	131	278	13	264	277	555
Mean (SD)	125.4 (47.29)	258.2 (83.99)	251.5 (78.12)	248.3 (84.53)	155.8 (70.23)	253.1 (77.69)	248.6 (79.95)	248.4 (82.20)
Median	135.0	225.0	225.0	225.0	135.0	225.0	225.0	225.0
Min, Max	90, 270	180, 450	135, 450	90, 450	45, 270	135, 450	45, 450	45, 450

Abbreviations: Max, maximum; Min, minimum; N, number of subjects; n, number of subjects in the specified category; SD, standard deviation; TP1, treatment period 1.

2.6.8.2. Adverse events

Phase 1 PK study (BAT-2206-001-CR)

Table 20 lists the TEAE's classified by the investigator to be at least possibly related to the study drug.

Table 20. Incidence of TRAEs by System Organ Class and Preferred Terms (SAS) in Study BAT-2206-001-CR

System Organ Class Preferred Term [1]	BAT2206 Injection (N=90) n (%)/Cases	STELARA(EU-sourced) (N=89) n (%)/Cases	STELARA(US-sourced) (N=90) n (%)/Cases	Total (N=269) n (%)/Cases
TEAE Related to Study Drug (TRAE)	40 (44.4)/98	46 (51.7)/79	38 (42.2)/70	124 (46.1)/247
Blood and lymphatic system disorders	0/0	0/0	1 (1.1)/1	1 (0.4)/1
Anaemia	0/0	0/0	1 (1.1)/1	1 (0.4)/1
Cardiac disorders	2 (2.2)/2	2 (2.2)/2	1 (1.1)/1	5 (1.9)/5
Arrhythmia supraventricular	1 (1.1)/1	0/0	0/0	1 (0.4)/1
Atrioventricular block second degree	1 (1.1)/1	0/0	0/0	1 (0.4)/1
Palpitations	0/0	1 (1.1)/1	0/0	1 (0.4)/1
Supraventricular extrasystoles	0/0	1 (1.1)/1	1 (1.1)/1	2 (0.7)/2
Gastrointestinal disorders	1 (1.1)/1	2 (2.2)/2	4 (4.4)/4	7 (2.6)/7
Mouth ulceration	1 (1.1)/1	0/0	0/0	1 (0.4)/1
Abdominal pain upper	0/0	1 (1.1)/1	0/0	1 (0.4)/1
Toothache	0/0	1 (1.1)/1	3 (3.3)/3	4 (1.5)/4
Vomiting	0/0	0/0	1 (1.1)/1	1 (0.4)/1
General disorders and administration site conditions	0/0	1 (1.1)/1	1 (1.1)/1	2 (0.7)/2
Asthenia	0/0	0/0	1 (1.1)/1	1 (0.4)/1
Injection site pain	0/0	1 (1.1)/1	0/0	1 (0.4)/1
Infections and infestations	4 (4.4)/6	5 (5.6)/5	3 (3.3)/3	12 (4.5)/14
Upper respiratory tract infection	2 (2.2)/2	3 (3.4)/3	2 (2.2)/2	7 (2.6)/7
Urinary tract infection	2 (2.2)/3	2 (2.2)/2	1 (1.1)/1	5 (1.9)/6
Body tinea	1 (1.1)/1	0/0	0/0	1 (0.4)/1
Investigations	23 (25.6)/53	24 (27.0)/42	20 (22.2)/37	67 (24.9)/132
Alanine aminotransferase increased	7 (7.8)/9	5 (5.6)/5	6 (6.7)/7	18 (6.7)/21
Blood bilirubin increased	5 (5.6)/5	11 (12.4)/14	5 (5.6)/6	21 (7.8)/25
Neutrophil count decreased	5 (5.6)/9	2 (2.2)/2	3 (3.3)/5	10 (3.7)/16
Neutrophil count increased	5 (5.6)/5	3 (3.4)/3	4 (4.4)/4	12 (4.5)/12
White blood cell count increased	5 (5.6)/5	3 (3.4)/3	4 (4.4)/4	12 (4.5)/12
Aspartate aminotransferase increased	4 (4.4)/5	3 (3.4)/3	4 (4.4)/4	11 (4.1)/12
Blood creatinine increased	2 (2.2)/3	3 (3.4)/5	1 (1.1)/1	6 (2.2)/9
Gamma-glutamyltransferase increased	2 (2.2)/2	1 (1.1)/1	1 (1.1)/1	4 (1.5)/4

System Organ Class Preferred Term [1]	BAT2206 Injection (N=90) n (%)/Cases	STELARA(EU-sourced) (N=89) n (%)/Cases	STELARA(US-sourced) (N=90) n (%)/Cases	Total (N=269) n (%)/Cases
Total bile acids increased	2 (2.2)/3	2 (2.2)/3	1 (1.1)/1	5 (1.9)/7
White blood cell count decreased	2 (2.2)/4	2 (2.2)/2	2 (2.2)/4	6 (2.2)/10
Amylase increased	1 (1.1)/1	0/0	0/0	1 (0.4)/1
Lipase increased	1 (1.1)/1	0/0	0/0	1 (0.4)/1
Urinary casts present	1 (1.1)/1	1 (1.1)/1	0/0	2 (0.7)/2
Metabolism and nutrition disorders	18 (20.0)/22	15 (16.9)/17	11 (12.2)/13	44 (16.4)/52
Hypertriglyceridaemia	10 (11.1)/11	10 (11.2)/10	7 (7.8)/8	27 (10.0)/29
Hyperglycaemia	5 (5.6)/6	3 (3.4)/3	4 (4.4)/4	12 (4.5)/13
Hyperuricaemia	4 (4.4)/4	3 (3.4)/3	1 (1.1)/1	8 (3.0)/8
Hyperkalaemia	1 (1.1)/1	0/0	0/0	1 (0.4)/1
Hypercholesterolaemia	0/0	1 (1.1)/1	0/0	1 (0.4)/1
Musculoskeletal and connective tissue disorders	0/0	0/0	2 (2.2)/2	2 (0.7)/2
Myalgia	0/0	0/0	2 (2.2)/2	2 (0.7)/2
Nervous system disorders	0/0	1 (1.1)/1	1 (1.1)/1	2 (0.7)/2
Headache	0/0	1 (1.1)/1	1 (1.1)/1	2 (0.7)/2
Renal and urinary disorders	10 (11.1)/12	3 (3.4)/5	5 (5.6)/5	18 (6.7)/22
Haematuria	7 (7.8)/8	1 (1.1)/3	2 (2.2)/2	10 (3.7)/13
Proteinuria	4 (4.4)/4	2 (2.2)/2	3 (3.3)/3	9 (3.3)/9
Respiratory, thoracic and mediastinal disorders	2 (2.2)/2	3 (3.4)/3	0/0	5 (1.9)/5
Cough	1 (1.1)/1	0/0	0/0	1 (0.4)/1
Oropharyngeal pain	1 (1.1)/1	3 (3.4)/3	0/0	4 (1.5)/4
Skin and subcutaneous tissue disorders	0/0	1 (1.1)/1	2 (2.2)/2	3 (1.1)/3
Alopecia	0/0	0/0	1 (1.1)/1	1 (0.4)/1
Pruritus	0/0	1 (1.1)/1	1 (1.1)/1	2 (0.7)/2

[1] AEs were coded using MedDRA version 24.0. A subject with multiple occurrences of a TEAE was counted only once under each system organ classification and preferred term.

The incidences of TEAEs with CTCAE Grade ≥3 among the three administration groups were similar. TRAEs with CTCAE Grade ≥3 occurred in 2 (0.7%) subjects, including 1 (1.1%, hypertriglyceridemia) subject in the BAT2206 injection group and 1 (1.1%, hypertriglyceridemia) subject in the Stelara (EU-sourced) group. All other TRAEs were Grade 1 or 2.

Phase 3 study (BAT-2206-002-CR)

TRAEs reported for 1% or more of subjects in any group are detailed in Table 21.

Table 21. Treatment-Related Treatment Emergent Adverse Events in ≥1% of Subjects in Either Treatment Group by System Organ Class and Preferred Term (Safety Analysis Set), BAT-2206-002-CR

Treatment Period 1[a]			
System Organ Class (in bold) Preferred Term	**Stelara N =278 n (%) E**	**BAT2206 N =277 n (%) E**	**Total N =555 n (%) E**
At least one treatment-related TEAE	50 (18.0) 83	45 (16.2) 73	95 (17.1) 156
Infections and infestations	27 (9.7) 38	22 (7.9) 28	49 (8.8) 66
Upper respiratory tract infection	15 (5.4) 19	14 (5.1) 16	29 (5.2) 35
Nasopharyngitis	2 (0.7) 2	3 (1.1) 4	5 (0.9) 6
Tonsillitis	3 (1.1) 3	1 (0.4) 1	4 (0.7) 4
Investigations	4 (1.4) 4	7 (2.5) 9	11 (2.0) 13
Alanine aminotransferase increased	0	3 (1.1) 3	3 (0.5) 3
Metabolism and nutrition disorders	5 (1.8) 6	8 (2.9) 9	13 (2.3) 15
Hyperlipidaemia	4 (1.4) 4	6 (2.2) 6	10 (1.8) 10

Treatment Period 2[b]				
System Organ Class (in bold) Preferred Term	**Stelara ->Stelara N =133 n (%) E**	**Stelara ->BAT2206 N =131 n (%) E**	**BAT2206 ->BAT2206 N =264 n (%) E**	**Total N =528 n (%) E**
At least one treatment-related TEAE	17 (12.8) 24	14 (10.7) 19	25 (9.5) 35	56 (10.6) 78
Infections and infestations	9 (6.8) 11	8 (6.1) 10	17 (6.4) 18	34 (6.4) 39
Upper respiratory tract infection	7 (5.3) 9	5 (3.8) 5	9 (3.4) 9	21 (4.0) 23
Hepatobiliary disorders	2 (1.5) 2	1 (0.8) 1	0	3 (0.6) 3
Hepatic function abnormal	2 (1.5) 2	1 (0.8) 1	0	3 (0.6) 3

Through the Study[a]						
System Organ Class (in bold) Preferred Term	**Stelara TP1 Only N =14 n (%) E**	**Stelara ->Stelara N =133 n (%) E**	**Stelara ->BAT2206 N =131 n (%) E**	**BAT2206 TP1 Only N =13 n (%) E**	**BAT2206 ->BAT2206 N =264 n (%) E**	**Total N =555 n (%) E**
At least one treatment-related TEAE	5 (35.7) 8	31 (23.3) 59	26 (19.8) 59	2 (15.4) 2	56 (21.2) 106	120 (21.6) 234
Infections and infestations	1 (7.1) 1	16 (12.0) 27	20 (15.3) 31	0	33 (12.5) 46	70 (12.6) 105
Upper respiratory tract infection	1 (7.1) 1	11 (8.3) 18	11 (8.4) 14	0	20 (7.6) 25	43 (7.7) 58
Nasopharyngitis	0	1 (0.8) 1	1 (0.8) 1	0	3 (1.1) 5	5 (0.9) 7
Tonsillitis	0	1 (0.8) 1	2 (1.5) 2	0	1 (0.4) 1	4 (0.7) 4
Bronchitis	0	0	2 (1.5) 2	0	1 (0.4) 1	3 (0.5) 3

Pharyngitis	0	0	2 (1.5) 4	0	1 (0.4) 1	3 (0.5) 5
Urinary tract infection	0	0	0	0	3 (1.1) 3	3 (0.5) 3
Investigations	1 (7.1) 1	6 (4.5) 6	3 (2.3) 6	0	9 (3.4) 13	19 (3.4) 26
Alanine aminotransferase increased	0	1 (0.8) 1	0	0	3 (1.1) 3	4 (0.7) 4
Urinary occult blood positive	0	1 (0.8) 1	2 (1.5) 2	0	0	3 (0.5) 3
Weight increased	1 (7.1) 1	0	0	0	0	1 (0.2) 1
Metabolism and nutrition disorders	2 (14.3) 3	3 (2.3) 3	3 (2.3) 3	0	9 (3.4) 10	17 (3.1) 19
Hyperlipidaemia	2 (14.3) 2	3 (2.3) 3	1 (0.8) 1	0	7 (2.7) 7	13 (2.3) 13
Hyperuricaemia	1 (7.1) 1	0	1 (0.8) 1	0	2 (0.8) 2	4 (0.7) 4
Skin and subcutaneous tissue disorders	1 (7.1) 2	4 (3.0) 4	2 (1.5) 2	1 (7.7) 1	8 (3.0) 14	16 (2.9) 23
Psoriasis	0	0	0	1 (7.7) 1	1 (0.4) 1	2 (0.4) 2
Dermatomyositis	1 (7.1) 2	0	0	0	0	1 (0.2) 2
Hepatobiliary disorders	0	3 (2.3) 3	3 (2.3) 3	1 (7.7) 1	1 (0.4) 2	8 (1.4) 9
Hepatic function abnormal	0	3 (2.3) 3	2 (1.5) 2	1 (7.7) 1	0	6 (1.1) 6
Cardiac disorders	0	1 (0.8) 1	3 (2.3) 4	0	2 (0.8) 2	6 (1.1) 7
Bundle branch block right	0	0	2 (1.5) 2	0	0	2 (0.4) 2
Respiratory, thoracic and mediastinal disorders	0	0	1 (0.8) 1	0	5 (1.9) 5	6 (1.1) 6
Cough	0	0	0	0	3 (1.1) 3	3 (0.5) 3
Musculoskeletal and connective tissue disorders	0	1 (0.8) 2	3 (2.3) 3	0	1 (0.4) 1	5 (0.9) 6
Arthralgia	0	0	2 (1.5) 2	0	0	2 (0.4) 2
Nervous system disorders	0	3 (2.3) 7	0	0	2 (0.8) 4	5 (0.9) 11
Dizziness	0	2 (1.5) 3	0	0	2 (0.8) 3	4 (0.7) 6
Somnolence	0	2 (1.5) 4	0	0	1 (0.4) 1	3 (0.5) 5
Neoplasms benign, malignant and unspecified (incl cysts and polyps)	1 (7.1) 1	0	0	0	0	1 (0.2) 1
Breast cancer	1 (7.1) 1	0	0	0	0	1 (0.2) 1

Abbreviations: E, number of events; N, number of subjects; n, number of subjects in the specified category; TEAE, treatment-emergent adverse event; TP1, Treatment Period 1.
Note: Missing causality or causality of "possible", "probable" or "definite" was considered as related to study drug.
[a] Percentages were based on the number of subjects in Safety Analysis Set.
[b] Percentages were based on the number of subjects in Safety Analysis Set for TP2.

2.6.8.3. Serious adverse event/deaths/other significant events

In the Phase 1 PK study (BAT-2206-001-CR) no death, other SAE or AE leading to drug discontinuation occurred.

No deaths occurred during the conduct of the Phase 3 study (BAT-2206-002-CR CSR). During TP1, 15 subjects (2.7%) experienced 19 serious TEAEs, with no specific serious TEAE occurring in more than one subject. Of these 15 subjects, 4 subjects (0.7%) had 4 treatment-related serious TEAEs.

Serious TEAEs are summarised in Table 22.

Table 22. Serious Treatment Emergent Adverse Events by System Organ Class and Preferred Term, BAT-2206-002-CR

Treatment Period 1[a]

System Organ Class (in bold) Preferred Term	Stelara N=278 n (%) E	BAT2206 N=277 n (%) E	Total N=555 n (%) E
At least 1 serious TEAE	4 (1.4) 4	5 (1.8) 6	9 (1.6) 10
Injury, poisoning and procedural complications	1 (0.4) 1	2 (0.7) 2	3 (0.5) 3
Forearm fracture	0	1 (0.4) 1	1 (0.2) 1
Humerus fracture	1 (0.4) 1	0	1 (0.2) 1
Spinal cord injury lumbar	0	1 (0.4) 1	1 (0.2) 1
Neoplasms benign, malignant and unspecified (incl cysts and polyps)	1 (0.4) 1	1 (0.4) 1	2 (0.4) 2
Breast cancer	1 (0.4) 1	0	1 (0.2) 1
Polycythaemia vera	0	1 (0.4) 1	1 (0.2) 1
Hepatobiliary disorders	1 (0.4) 1	0	1 (0.2) 1
Cholecystitis chronic	1 (0.4) 1	0	1 (0.2) 1
Infections and infestations	1 (0.4) 1	1 (0.4) 1	2 (0.4) 2
Epiglottitis	1 (0.4) 1	0	1 (0.2) 1
Respiratory tract infection viral	0	1 (0.4) 1	1 (0.2) 1
Immune system disorders	0	1 (0.4) 1	1 (0.2) 1
Anaphylactic shock	0	1 (0.4) 1	1 (0.2) 1
Respiratory, thoracic and mediastinal disorders	0	1 (0.4) 1	1 (0.2) 1
Interstitial lung disease	0	1 (0.4) 1	1 (0.2) 1

Treatment Period 2[b]

System Organ Class (in bold) Preferred Term	Stelara ->Stelara N=133 n (%) E	Stelara ->BAT2206 N=131 n (%) E	BAT2206 ->BAT2206 N=264 n (%) E	Total N=528 n (%) E
At least 1 serious TEAE	1 (0.8) 1	1 (0.8) 1	5 (1.9) 7	7 (1.3) 9
Injury, poisoning and procedural complications	0	1 (0.8) 1	1 (0.4) 1	2 (0.4) 2
Foot fracture	0	0	1 (0.4) 1	1 (0.2) 1
Spinal compression fracture	0	1 (0.8) 1	0	1 (0.2) 1
Cardiac disorders	0	0	1 (0.4) 1	1 (0.2) 1
Coronary artery disease	0	0	1 (0.4) 1	1 (0.2) 1
Hepatobiliary disorders	0	0	1 (0.4) 2	1 (0.2) 2
Cholangitis	0	0	1 (0.4) 1	1 (0.2) 1
Cholelithiasis	0	0	1 (0.4) 1	1 (0.2) 1
Metabolism and nutrition disorders	0	0	1 (0.4) 1	1 (0.2) 1
Hypokalaemia	0	0	1 (0.4) 1	1 (0.2) 1
Neoplasms benign, malignant, and unspecified (incl cysts and polyps)	1 (0.8) 1	0	0	1 (0.2) 1
Lipoma	1 (0.8) 1	0	0	1 (0.2) 1
Skin and subcutaneous tissue disorders	0	0	1 (0.4) 1	1 (0.2) 1
Eczema	0	0	1 (0.4) 1	1 (0.2) 1
Vascular disorders	0	0	1 (0.4) 1	1 (0.2) 1
Aortic aneurysm	0	0	1 (0.4) 1	1 (0.2) 1

Through the Study[a]						
System Organ Class (in bold) Preferred Term	**Stelara TP1 Only N=14 n (%) E**	**Stelara -> Stelara N=133 n (%) E**	**Stelara -> BAT2206 N=131 n (%) E**	**BAT2206 TP1 Only N=13 n (%) E**	**BAT2206 -> BAT2206 N=264 n (%) E**	**Total N=555 n (%) E**
At least 1 serious TEAE	1 (7.1) 1	1 (0.8) 1	4 (3.1) 4	0	9 (3.4) 13	15 (2.7) 19
Injury, poisoning and procedural complications	0	0	2 (1.5) 2	0	3 (1.1) 3	5 (0.9) 5
Foot fracture	0	0	0	0	1 (0.4) 1	1 (0.2) 1
Forearm fracture	0	0	0	0	1 (0.4) 1	1 (0.2) 1
Humerus fracture	0	0	1 (0.8) 1	0	0	1 (0.2) 1
Spinal compression fracture	0	0	1 (0.8) 1	0	0	1 (0.2) 1
Spinal cord injury lumbar	0	0	0	0	1 (0.4) 1	1 (0.2) 1
Neoplasms benign, malignant and unspecified (incl cysts and polyps)	1 (7.1) 1	1 (0.8) 1	0	0	1 (0.4) 1	3 (0.5) 3
Breast cancer	1 (7.1) 1	0	0	0	0	1 (0.2) 1
Lipoma	0	1 (0.8) 1	0	0	0	1 (0.2) 1
Polycythaemia vera	0	0	0	0	1 (0.4) 1	1 (0.2) 1
Hepatobiliary disorders	0	0	1 (0.8) 1	0	1 (0.4) 2	2 (0.4) 3
Cholangitis	0	0	0	0	1 (0.4) 1	1 (0.2) 1
Cholecystitis chronic	0	0	1 (0.8) 1	0	0	1 (0.2) 1
Cholelithiasis	0	0	0	0	1 (0.4) 1	1 (0.2) 1
Infections and infestations	0	0	1 (0.8) 1	0	1 (0.4) 1	2 (0.4) 2
Epiglottitis	0	0	1 (0.8) 1	0	0	1 (0.2) 1
Respiratory tract infection viral	0	0	0	0	1 (0.4) 1	1 (0.2) 1
Cardiac disorders	0	0	0	0	1 (0.4) 1	1 (0.2) 1
Coronary artery disease	0	0	0	0	1 (0.4) 1	1 (0.2) 1
Immune system disorders	0	0	0	0	1 (0.4) 1	1 (0.2) 1
Anaphylactic shock	0	0	0	0	1 (0.4) 1	1 (0.2) 1
Metabolism and nutrition disorders	0	0	0	0	1 (0.4) 1	1 (0.2) 1
Hypokalaemia	0	0	0	0	1 (0.4) 1	1 (0.2) 1
Respiratory, thoracic and mediastinal disorders	0	0	0	0	1 (0.4) 1	1 (0.2) 1
Interstitial lung disease	0	0	0	0	1 (0.4) 1	1 (0.2) 1
Skin and subcutaneous tissue disorders	0	0	0	0	1 (0.4) 1	1 (0.2) 1
Eczema	0	0	0	0	1 (0.4) 1	1 (0.2) 1
Vascular disorders	0	0	0	0	1 (0.4) 1	1 (0.2) 1
Aortic aneurysm	0	0	0	0	1 (0.4) 1	1 (0.2) 1

Abbreviations: E, number of events; N, number of subjects; n, number of subjects in the specified category; TEAE, treatment-emergent adverse event.

[a] Percentages were based on the number of subjects in the Safety Analysis Set.

[b] Percentages were based on the number of subjects in the Safety Analysis Set for TP2.

Hypersensitivity and/or injection-site reactions

In the Phase 1 PK study, one subject in the Stelara (EU-sourced) group had mild pain without redness, swelling or induration at the injection site 1h post-dose. No other hypersensitivity reactions were observed.

In the Phase 3 study, 8 TEAEs of hypersensitivity and/or injection-site reactions were reported in 4 subjects (0.7%). All these subjects tested negative for ADA.

2.6.8.4. Laboratory findings

Throughout the two studies, no notable trends or differences were observed among treatment groups in haematology, chemistry, and urinalysis parameters in terms of abnormal laboratory results.

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

ADA frequencies

In the PK study BAT-2206-001-CR, the number of ADA-positive subjects throughout the study were 24 (26.7%) and 13 (14.8%) in the BAT2206 and Stelara (EU-sourced) groups, respectively.

In the Phase 3 study BAT-2206-002-CR, there was a higher incidence of ADA positivity (and correspondingly, NAb positivity) in the Stelara combined group than in the BAT2206 combined group. A summary of the results is provided in Table 23.

Table 23. Incidence rates of antidrug antibody and neutralising antidrug antibody, Safety Analysis Set, BAT-2206-002-CR

	Stelara				BAT2206		
	Stelara TP1 only N=14 n (%)	Stelara -> Stelara N=133 n (%)	Stelara -> BAT2206 N=131 n (%)	Combined N=278 n (%)	BAT2206 TP1 only N=13 n (%)	BAT2206 -> BAT2206 N=264 n (%)	Combined N=277 n (%)
Overall (postbaseline)							
ADA positive at any point	4 (28.6)	45 (33.8)	38 (29.0)	87 (31.3)	3 (23.1)	66 (25.0)	69 (24.9)
ADA negative	10 (71.4)	88 (66.2)	93 (71.0)	191 (68.7)	9 (69.2)	198 (75.0)	207 (74.7)
NAb positive	0	31 (23.3)	19 (14.5)	50 (18.0)	3 (23.1)	38 (14.4)	41 (14.8)
NAb negative	4 (28.6)	14 (10.5)	19 (14.5)	37 (13.3)	0	28 (10.6)	28 (10.1)
Postbaseline Through Week 8							
ADA positive at any point	2 (14.3)	15 (11.3)	12 (9.2)	29 (10.4)	2 (15.4)	27 (10.2)	29 (10.5)
ADA negative	12 (85.7)	118 (88.7)	119 (90.8)	249 (89.6)	10 (76.9)	235 (89.0)	245 (88.4)
NAb positive	0	7 (5.3)	3 (2.3)	10 (3.6)	2 (15.4)	5 (1.9)	7 (2.5)
NAb negative	2 (14.3)	8 (6.0)	9 (6.9)	19 (6.8)	0	22 (8.3)	22 (7.9)
Postbaseline Through Week 12							

ADA positive at any point	4 (28.6)	27 (20.3)	17 (13.0)	48 (17.3)	3 (23.1)	37 (14.0)	40 (14.4)
ADA negative	10 (71.4)	106 (79.7)	114 (87.0)	230 (82.7)	9 (69.2)	225 (85.2)	234 (84.5)
NAb positive	0	16 (12.0)	6 (4.6)	22 (7.9)	3 (23.1)	12 (4.5)	15 (5.4)
NAb negative	4 (28.6)	11 (8.3)	11 (8.4)	26 (9.4)	0	25 (9.5)	25 (9.0)
Postbaseline Through TP1							
ADA positive at any point	4 (28.6)	40 (30.1)	26 (19.8)	70 (25.2)	3 (23.1)	57 (21.6)	60 (21.7)
ADA negative	10 (71.4)	93 (69.9)	105 (80.2)	208 (74.8)	9 (69.2)	207 (78.4)	216 (78.0)
NAb positive	0	27 (20.3)	12 (9.2)	39 (14.0)	3 (23.1)	30 (11.4)	33 (11.9)
NAb negative	4 (28.6)	13 (9.8)	14 (10.7)	31 (11.2)	0	27 (10.2)	27 (9.7)
Through TP2							
Subjects entered TP2	3	133	129	N/A	1	264	N/A
ADA positive at any point	0	29 (21.8)	26 (19.8)		0	40 (15.2)	
ADA negative	3 (21.4)	104 (78.2)	103 (78.6)		1 (7.7)	224 (84.8)	
NAb positive	0	19 (14.3)	15 (11.5)		0	29 (11.0)	
NAb negative	0	10 (7.5)	11 (8.4)		0	11 (4.2)	

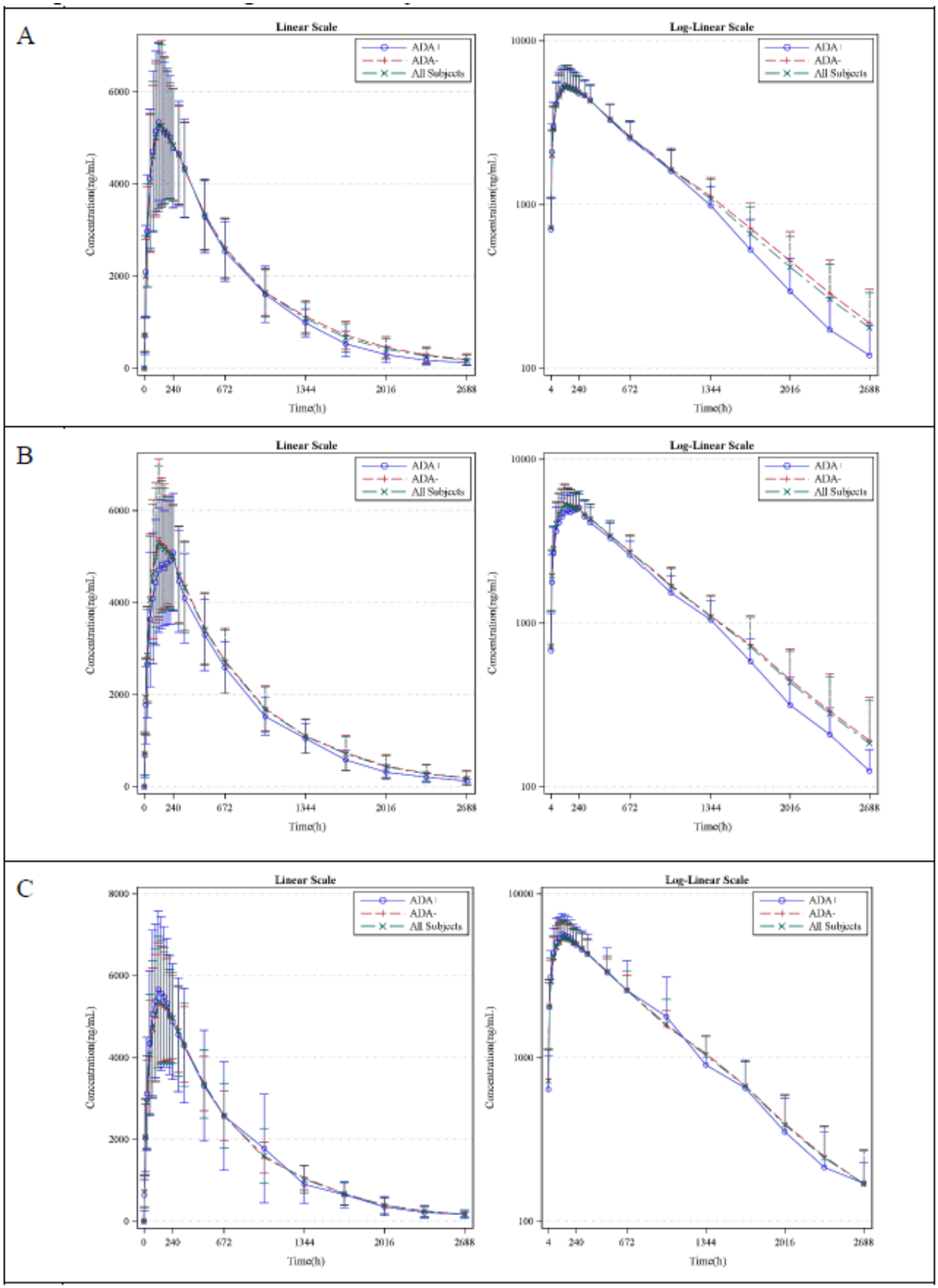
Abbreviations: ADA = antidrug antibody; N = number of subjects; n = number of subjects in the specified category; N/A, not applicable; NAb = neutralizing antibody; TP1 = treatment period 1; TP2 = treatment period 2.

Impact of ADAs on PK

Clinical study BAT-2206-001-CR

Overall, the mean plasma concentration-time curves of ADA-positive, ADA-negative and all subjects were highly similar in any of the three treatment groups (see Figure *5*). In addition, at the end of curves, plasma concentrations of ADA-positive subjects tended to be slightly lower than that of ADA-negative and all subjects in any of the three treatment groups.

Figure 5. Arithmetic mean plasma concentration (Mean ± SD)-time curves in ADA-positive/ADA-negative/all subjects



A: BAT2206 injection, B: Stelara® (EU-sourced), C: Stelara® (US-sourced), linear scale on the left, semi-logarithmic scale on the right.

The PK parameters C_{max}, AUC_{0-inf} and AUC_{0-t} were comparable in each treatment group, and AUC_{0-inf} of ADA-positive subjects was slightly lower than that of ADA-negative and all subjects in the same group (see Table 24).

Table 24. Descriptive summary of effects of positive ADA on PK parameters (Immunogenicity Analysis Set/PKPS)

PK Parameters (Unit)	ADA+	ADA-	All Subjects
BAT2206 Injection			
C_{max} (μg/mL)	5.630 ± 1.676 (29.76)	5.595 ± 1.735 (31.00)	5.604 ± 1.710 (30.51)
	5.379 (32.48)	5.345 (31.62)	5.354 (31.66)
AUC_{0-inf} (h*μg/mL)	4346 ± 1139 (26.22)	4730 ± 1290 (27.27)	4627 ± 1257 (27.16)
	4208 (26.28)	4555 (28.72)	4460 (28.17)
AUC_{0-t} (h*μg/mL)	4258 ± 1137 (26.70)	4586 ± 1214 (26.47)	4499 ± 1197 (26.60)
	4116 (27.09)	4424 (28.17)	4340 (27.93)
Stelara® (EU-sourced)			
C_{max} (μg/mL)	5.492 ± 1.243 (22.64)	5.737 ± 1.629 (28.40)	5.701 ± 1.574 (27.61)
	5.361 (23.28)	5.520 (28.74)	5.496 (27.89)
AUC_{0-inf} (h*μg/mL)	4327 ± 1097 (25.36)	4781 ± 1380 (28.86)	4714 ± 1346 (28.55)
	4196 (26.61)	4621 (26.08)	4556 (26.24)
AUC_{0-t} (h*μg/mL)	4263 ± 1078 (25.30)	4631 ± 1229 (26.54)	4576 ± 1209 (26.42)
	4134 (26.57)	4493 (24.76)	4438 (25.05)
Stelara® (US-sourced)			
C_{max} (μg/mL)	5.865 ± 1.937 (33.02)	5.768 ± 1.424 (24.68)	5.786 ± 1.522 (26.30)
	5.526 (38.41)	5.593 (25.66)	5.581 (28.17)
AUC_{0-inf} (h*μg/mL)	4492 ± 1689 (37.59)	4589 ± 1005 (21.89)	4570 ± 1157 (25.31)
	4201 (39.48)	4483 (22.10)	4427 (26.05)
AUC_{0-t} (h*μg/mL)	4413 ± 1674 (37.94)	4399 ± 1031 (23.44)	4402 ± 1168 (26.54)
	4126 (39.56)	4264 (27.02)	4238 (29.47)

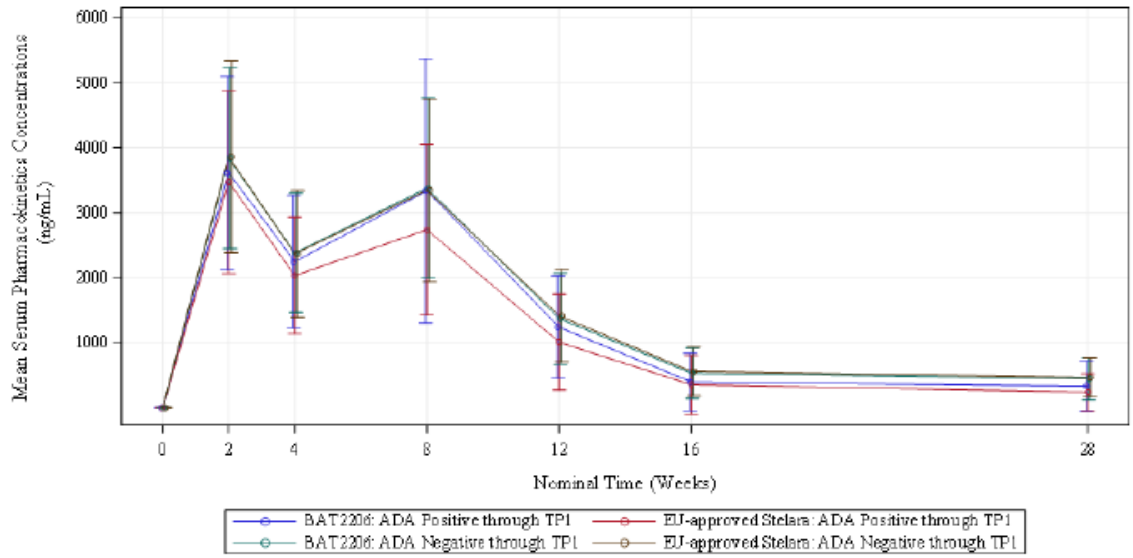
Note: PK parameters are shown as Mean ± SD (%CV) and Geomean (%CV_b). For subjects with %AUC_{ex} >20%, PK parameters AUC_{0-inf} was excluded in the descriptive analysis.

Abbreviations: C_{max} = maximum plasma concentrations; AUC_{0-inf} = area under the plasma drug concentration-time curve from time 0 to infinity; AUC_{0-t} = area under the plasma drug concentration-time curve from time 0 to the last quantifiable concentration; %CV = coefficient of variation; Geomean = geometric mean; %CV_b = geometric coefficient of variation.

Clinical study BAT-2206-002-CR

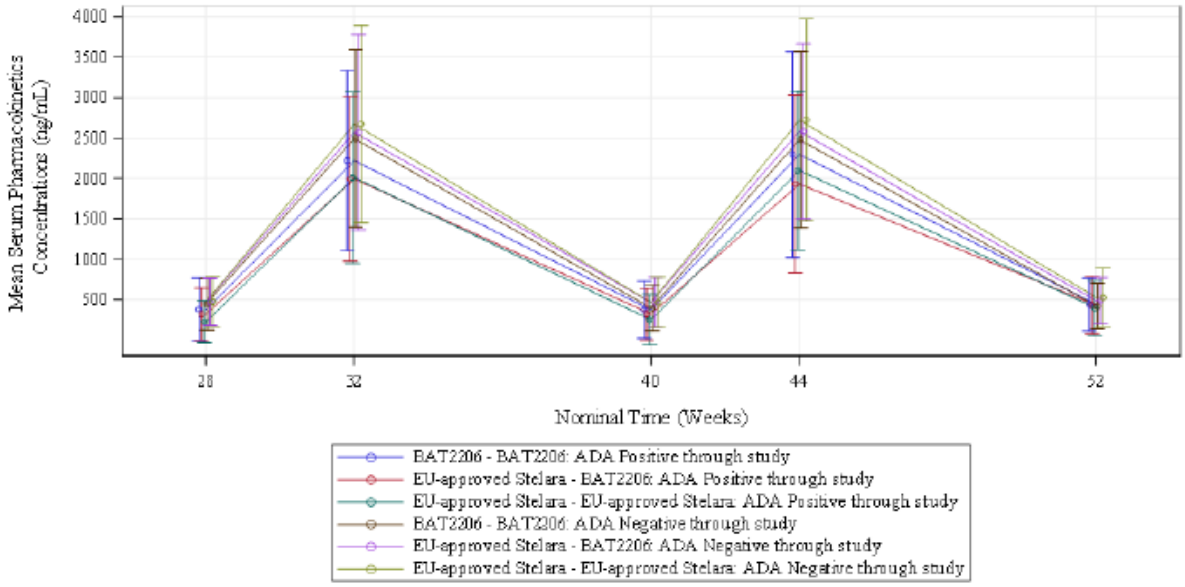
Lower serum concentrations were observed in ADA positive subjects compared with ADA negative subjects. Ustekinumab serum levels for subjects with ADA positive status were slightly lower for Stelara group (TP1) and Stelara-BAT2206 group (TP2), but overall, no major differences are observed in serum concentrations between the treatment groups (see Figure *6* and Figure 7). There was no observed difference between the different treatment arms for the ADA-related PK analyses.

Figure 6. Linear mean (±SD) serum PK concentrations (ng/mL) of ustekinumab during TP1 by ADA incidence through TP1 (PKS)



Abbreviation: ADA, antidrug antibody; EU, European Union; TP, treatment period

Figure 7. Linear mean (±SD) serum PK concentrations (ng/mL) of ustekinumab from week 28 through week 52 by ADA incidence through the study (PKS for TP2)



Abbreviation: ADA, antidrug antibody, EU, European Union; TP, treatment period.

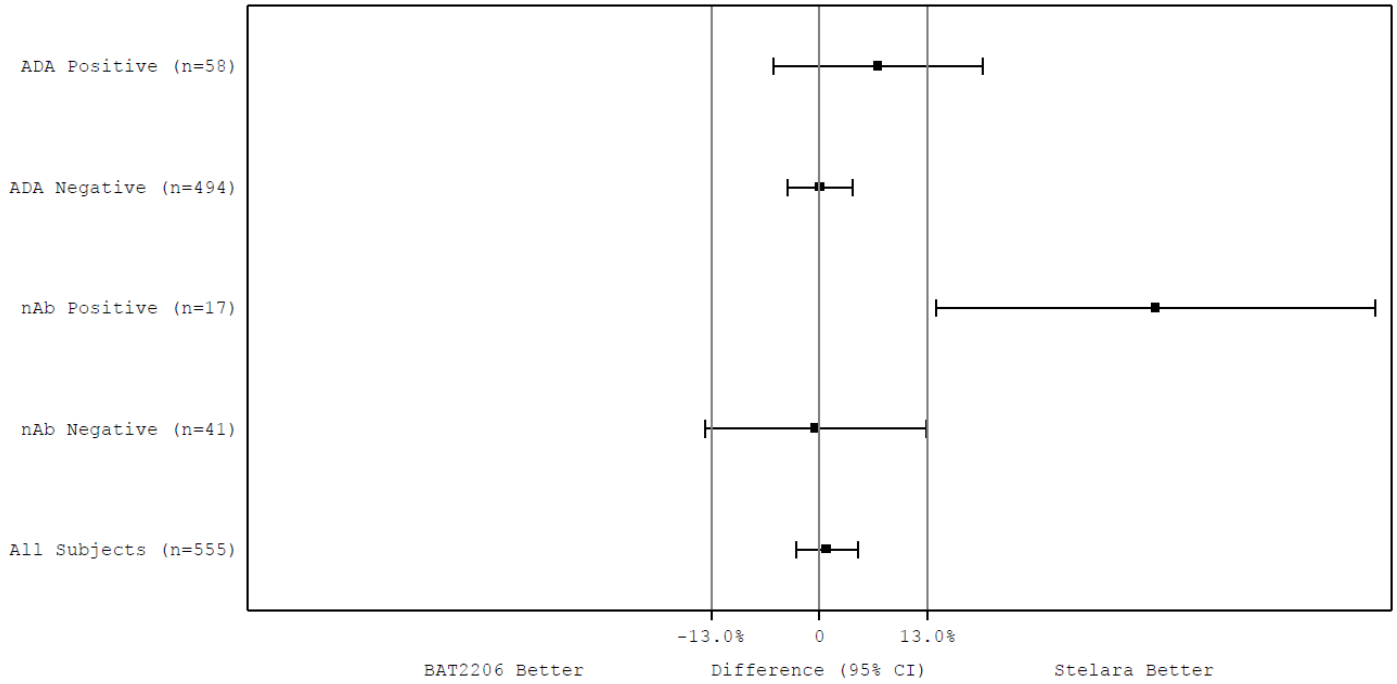
Effect of ADA on Efficacy (Clinical study BAT-2206-002-CR)

A forest plot of percent CfB in PASI score at Week 8 by ADA is provided in Figure 8. PASI improvement was essentially similar between ADA positive and ADA negative subjects at weeks 8 and 12 in both treatment arms. At week 8, the LS mean difference (SE) in PASI percent CfB for ADA negative vs ADA positive

subgroups were 3.635 (4.1557) and -1.723 (4.5006) for Stelara and BAT2206, respectively. The 95% CI were (-4.510, 11.781) for Stelara and (-10.545, 7.099) for BAT2206.

At week 12, the LS mean difference (SE) in PASI percent CfB for ADA negative vs ADA positive subgroups were 2.528 (2.4952) and -6.196 (3.2242) for Stelara and BAT2206, respectively. The 95% CI were (-2.362, 7.419) for Stelara and (-12.516, 0.123) for BAT2206, all within the equivalence margin of -13.0% to +13.0%.

Figure 8. Forest Plot of Percent Change from Baseline in PASI Score at Week 8 (Main Estimand) by ADA Incidence (Safety Analysis Set), BAT-2206-002-CR



Abbreviations: ADA, antidrug antibody; CI, confidence interval; n, number of subjects at the specified timepoint; NAb, neutralizing antibody; PASI, psoriasis area severity index.

Effect of ADA on Safety

There were no formal analyses of TEAEs stratified by ADA or NAb status in the single dose Phase 1 study BAT-2206-001-CR. No TEAEs led to treatment discontinuation in the study.

Overall, ADA had no significant influence on safety, and no subject with a positive ADA status had a TEAE suggestive of hypersensitivity, rapid allergic reaction, or injection site reaction at any time during the study.

In the clinical Phase 3 study BAT-2206-002-CR, twenty-two (7.9%) subjects in the Stelara group and 19 (6.8%) subjects in the BAT2206 group experienced premature withdrawal from the study. No trend was observed in terms of number of treatment-related TEAEs among the ADA positive patients, especially those leading to discontinuation.

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

Not applicable.

2.6.8.9. Discontinuation due to adverse events

No AE leading to drug discontinuation occurred in the PK study.

In the Phase 3 study, a total of 36 subjects (6.5%) discontinued the study treatment.

Four subjects had temporary treatment interruption due to AEs not related to study drug. Five subjects discontinued treatment due to treatment related AEs. There was no difference between groups in frequency or nature of TEAEs leading to treatment discontinuation.

2.6.8.10. Post marketing experience

Not applicable.

2.6.9. Discussion on clinical safety

The safety of BAT2206 injection was evaluated in a single-dose Phase 1 study (BAT-2206-001-CR) in healthy volunteers and a Phase 3 similarity study (BAT-2206-002-CR) in patients with moderate to severe plaque psoriasis.

In the Phase 1 PK study, 269 healthy Chinese male subjects aged 18-55 years received one 45 mg dose of BAT2206, US-Stelara or EU-Stelara, including 90 subjects in the BAT2206 injection group.

In the Phase 3 study, 555 patients with moderate to severe plaque psoriasis received weight-based dosing of BAT2206 or EU-Stelara for one year. Subjects who achieved a ≥PASI-75 response at Week 28 entered into TP2 of the study and were re-randomised. Subjects randomised to receive Stelara during TP1 received either BAT2206 or Stelara in TP2 while subjects randomised to receive BAT2206 during TP1 continued to receive the same drug during TP2.

In total, 92.6% (515/556) of all subjects in the Phase 3 study randomised at screening completed the one-year follow-up, 258 of them received BAT2206. It is not clear whether all subjects who completed the study received all treatment doses. However, the total number of subjects who discontinued treatment or had protocol deviations in terms of missed doses is small and the uncertainty about absolute numbers has no consequence for the conclusions on similarity as there were no notable differences in exposure between the treatment groups in terms of total number of doses or cumulative dose in milligrams.

The size of the safety database is considered sufficient to enable a reasonable analysis of comparability and the follow-up of one year is aligned with the EMA Guideline on similar biological medicinal products (CHMP/437/04 Rev 1, October 2014). The safety data has not been pooled, which is acceptable in light of the different study populations. Overall, the applicant's approach to the safety analyses is endorsed and aligned with the CHMP SA (EMA/SA/0000047481, January 2021 and EMA/SA/0000062023, July 2021).

While the switch from Stelara to BAT2206 at week 28 decreased the sample size for the Stelara group and thereby decreased the discriminatory power of the study to evaluate potential differences at later stages, it is noted that 128 subjects in the unswitched Stelara arm completed the study and thereby had continuous exposure to EU-Stelara for the full duration of the study. This is considered sufficient in the biosimilar setting and aligned with the CHMP SA.

The BAT2206 clinical development programme and design of the studies is considered adequate to evaluate the comparability of BAT2206 with its reference product EU-Stelara in terms of safety and immunogenicity.

Key safety data are derived from the clinical phase 3 study in patients with moderate to severe plaque psoriasis, with additional safety data from the clinical phase I study in healthy Chinese male subjects.

Safety evaluation included adverse events (AEs), serious AEs (SAEs), treatment-related adverse events (TRAEs), treatment emergent adverse events (TEAEs), local tolerability, vital signs, and laboratory evaluations as well as immunogenicity.

Adverse events

Overall, the incidence and severity of TEAEs was balanced across treatment arms in both studies. Most TEAEs were mild or moderate in severity.

In the Phase 1 study, the incidence of TEAE's related to the study drug (TRAE) were generally balanced between treatment arms.

In the Phase 3 study, the incidence of at least one TRAE was 18.0% and 16.2% in the Stelara and BAT2206 groups respectively during TP1. In TP2, the proportion of subjects with at least one TRAE remained similar across groups at both SOC and PT level. No significant differences were noted in subjects transitioning from Stelara to BAT2206 in TP2 compared to those who continued to receive Stelara.

The most common TRAE were in the Infections and infestations SOC. The large majority of TRAEs were mild. Severe TRAEs were reported for a total of 4 (0.7%) patients throughout the study with no imbalance between treatment groups.

No deaths occurred in either of the studies and no other SAE occurred in the PK study. In the Phase 3 study, serious adverse events were overall infrequent, and the nature, severity and frequency of such events was comparable between the treatment groups. Most events were single occurrences, with no clustering discernible.

Hypersensitivity and injection-site reactions were rare, and no significant differences were observed across the treatment groups. Hypersensitivity was unrelated to formation of ADA. There was no difference between groups in frequency or nature of TEAEs leading to treatment discontinuation.

Overall, the adverse event profiles of BAT2206 and EU-Stelara were comparable in both the single dose PK study and the Phase 3 study in psoriasis patients in terms of nature, frequency and severity of TRAEs. Most reported TRAEs were mild or moderate in severity and no unexpected clustering of events was seen. Both products seemed to be generally well tolerated with a safety profile comparable to that previously reported for EU-Stelara.

Immunogenicity

In the PK study, the number of ADA-positive subjects throughout the study were 24 (26.7%) and 13 (14.8%) in the BAT2206 and Stelara (EU-sourced) groups, respectively. In the Phase 3 study, overall, 24.9% of subjects were ADA positive at any time post baseline with no meaningful differences between study arms in either treatment period.

Although the incidence of ADA was higher with BAT2206 than with Stelara in the PK study, the finding was not replicated in the Phase 3 study. On the contrary, there, the finding was reversed, if anything. Median ADA titres and time to onset of ADA formation was comparable between the treatment arms. Hence, no consistent difference in the overall immunogenicity was detected.

The PK differences between ADA-positive and ADA-negative subjects were very small in study BAT-2206-001-CR. For ADA-positive, ADA-negative and all subjects in any of the three treatment groups, the mean plasma concentration-time curves were highly similar and the primary PK parameters were comparable.

There were slight differences in serum concentrations by ADA incidences between the different treatment arms in the study BAT-2206-002-CR. The ustekinumab serum levels for ADA-positive subjects were slightly lower for Stelara group (TP1) (the biggest differences at weeks 4 and 8) and Stelara-BAT2206 group (TP2). A few patients reached very high ADA titres at an early stage in the Stelara group. These high titres might explain the slightly lower mean drug concentrations seen in the Stelara ADA-positive subjects in TP1.

In the primary analyses the difference in PASI improvement between ADA positive and ADA negative patients was very small in the Stelara group but approximately 8%-points in the BAT2206 group. A clarification was requested whereupon the applicant provided a more robust analysis. The updated analysis showed no significant difference in PASI improvement between ADA positive and ADA negative subjects in either treatment group. Likewise, there was no significant difference in PASI improvement between Stelara and BAT2206 treatment arms in either ADA positive or ADA negative subjects.

No subject with a positive ADA status had a TEAE suggestive of hypersensitivity, rapid allergic reaction, or injection site reaction at any time during any of the studies. Data on patients with early treatment discontinuation did not show any trends in terms of ADA incidence or titre and no difference between treatment groups. Overall, ADA had no significant influence on safety in either of the two clinical studies.

Minor uncertainties regarding ADA detection in the PK study are not considered detrimental for conclusions on similarity in terms of immunogenicity as immunogenicity in the target population, with multiple dosing and a long follow-up is much more relevant.

2.6.10. Conclusions on the clinical safety

Overall, a comprehensive analysis of safety data from the Usymro development programme has been provided. The size of the safety database is considered sufficient to enable a reasonable analysis of comparability between BAT2206 and EU-Stelara. No important difference in ADA incidence or titres was seen between the products. Based on the data submitted, the CHMP concludes that Usymro and EU-Stelara are biosimilar from a safety perspective.

2.7. Risk Management Plan

2.7.1. Safety concerns

Summary of safety concerns	
Important identified risks	• None
Important potential risks	• Serious infections (including mycobacterial and salmonella infections) • Malignancy • Cardiovascular events • Serious depression including suicidality • Venous thromboembolism
Missing information	• Long-term safety in pediatric psoriasis patients 6 years and older • Long-term impact on growth and development in pediatric psoriasis patients 6 years and older • Long-term safety in adult patients with moderately to severely active Crohn's disease • Long-term safety in paediatric patients weighing at least 40 kg with moderately to severely active Crohn's disease

2.7.2. Pharmacovigilance plan

No additional pharmacovigilance activities.

2.7.3. Risk minimisation measures

None.

2.7.4. Conclusion

The CHMP considers that the risk management plan version 0.3 is acceptable.

2.8. Pharmacovigilance

2.8.1. Pharmacovigilance system

The CHMP 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

The results of the user consultation with target patient groups on the package leaflet submitted by the applicant show that the package leaflet meets the criteria for readability as set out in the *Guideline on the readability of the label and package leaflet of medicinal products for human use.*

2.9.2. Labelling exemptions

A request to omit certain particulars from the labelling as per Art.63.3 of Directive 2001/83/EC has been submitted by the applicant and has been found acceptable by the QRD Group for the following reasons:

The group agreed with the proposed approach to apply the minimum particulars on the vial label due to space constraints and because the product is not intended to be self-administered by the patient.

2.9.3. Additional monitoring

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

The proposed indications for BAT2206 are in:

Adult patients with:

- moderate to severe plaque psoriasis who failed to respond to, or who have a contraindication to, or are intolerant to other systemic therapies including ciclosporin, methotrexate (MTX) or PUVA (psoralen and ultraviolet A).
- active psoriatic arthritis when the response to previous non-biological disease-modifying anti-rheumatic drug (DMARD) therapy has been inadequate.
- 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 .

Paediatric patients with:

- 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.

- moderately to severely active Crohn's disease in paediatric patients weighing at least 40 kg, who have had an inadequate response to, or were intolerant to either conventional or biologic therapy.

Except for the treatment of ulcerative colitis, which is not sought for BAT2206, the proposed indications of BAT2206 are the same as those currently authorised for the reference product, Stelara in EU. The strengths of BAT2206 match those of Stelara.

Summary of quality data

A comprehensive similarity exercise following the general principles outlined in the guideline on similar biological medicinal products containing biotechnology-derived proteins as active substance; Quality issues (EMA/CHMP/BWP/247713/2012) has been performed between the proposed biosimilar BAT2206 and the reference product Stelara (ustekinumab). The analytical similarity of BAT2206 is assessed compared to EU-Stelara. Received CHMP scientific advice has been only partly followed in the presented similarity exercise.

45mg/0.5ml (i.e. 90 mg/ml) PFS presentations of BAT2206 and EU-Stelara were used in clinical studies (PK and Phase 3). The primary comparative analytical assessment for biosimilarity has been made with the three 90 mg/ml presentations and a targeted similarity evaluation for 130mg/26ml vial has been performed. Comparability between all four DP presentations has been adequately demonstrated and thus it can be concluded that the material used in the analytical biosimilarity studies is considered representative of the material used in clinical trials.

The QAs included in the comparative assessment cover all relevant attributes of the products. The comparative testing included analysis of primary structure, higher order structure, particles and aggregates, purity and product-related substances, general properties, biological and functional activities and thermal stability and degradation studies. All methods used in the similarity assessment were appropriately qualified or validated to confirm suitability of use.

Summary of non-clinical data

The non-clinical comparative assessment included a battery of *in vitro* functional activity studies which were also presented under the Quality section. In addition, several *in vivo* studies were performed, including two PD studies in mice models, PK study in mouse model and two repeat-dose toxicity studies in Cynomolgus monkeys. None of these studies was GLP-compliant as study sites were located in non-OECD member state.

Summary of clinical data

The clinical development programme comprised one single-dose PK study and one 52-week Phase III study in patients with moderate to severe plaque-type psoriasis. The development programme is overall in accordance with EMA guidelines on development of biosimilar products (EMEA/CHMP/42832/2005 Rev. 1 and EMA/CHMP/BMWP/403543/2010) and with the given CHMP scientific advice.

3.2. Results supporting biosimilarity

Quality

Similarity between BAT2206 and EU-Stelara has been demonstrated for the following physicochemical and biological properties:

- Primary structure
- Higher order structure
- Thermal stability and degradation studies
- General properties including protein concentration
- Biological and functional activity including Fab- and Fc-mediated activities:
    - Binding to p40 antigen
    - Binding to IL-12 antigen
    - Binding to IL-23 antigen
    - Binding kinetics to IL-12
    - Binding kinetics to IL-23
    - Lack of binding to receptor bound IL-12 on the cell surface
    - Lack of binding to receptor bound IL-23 on the cell surface
    - Competitive Inhibition Activity of IL-12Rβ1 Binding to p40
    - Neutralizing activity against IL-12
    - FcRn binding
    - FcγRIa, FcγRIIa (131H/R), FcγRIIb, FcγRIIIa (158V/F) and FcγRIIIb Binding
    - Binding to C1q
    - Lack of ADCC /ADCP /CDC activity

Non-clinical

The supportive *in vivo* studies did not reveal significant differences between the BAT2206 and EU-Stelara in the pharmacology, pharmacokinetic, toxicokinetic or toxicology endpoints.

Clinical

Pharmacokinetics

In the comparison of PK data (pivotal PK study BAT-2206-001-CR), the 90% CIs of the GMRs for the primary PK endpoints AUC_{inf} and C_{max} were within the BE criteria of 0.80 to 1.25 in all comparisons of BAT2206 vs Stelara (EU-sourced), BAT-2206 vs Stelara (US-sourced) and Stelara (EU-sourced) vs Stelara (US-sourced): ratio of LS geometric means (90% CI) of BAT2206 vs Stelara (EU-sourced) was 0.9789 [0.9161, 1.0460] for AUC_{inf} and 0.9741 [0.9060, 1.0472] for C_{max}.

Also, the secondary PK endpoints (i.e., AUC_{0-t}, AUC_{0-672h}, $AUC_{Tmax-inf}$, $\%AUX_{ex}$, t_{max}, $t_{1/2}$, λz, CL/F and Vz/F) seemed to be similar between BAT2206, Stelara (EU-sourced) and Stelara (US-sourced). The 90%CIs of the GMRs for the $AUC_{Tmax-inf}$ and AUC_{0-672h} were in comparison of BAT2206 vs Stelara (EU-sourced) 0.92-1.04 and 0.90-1.05, respectively. The 90%CIs of the GMRs for the $AUC_{Tmax-inf}$ and AUC_{0-672h} in comparisons of BAT2206

vs Stelara (US-sourced) and Stelara (EU-Sourced) vs Stelara (US-sourced) were within the BE criteria of 0.80 to 1.25. Consequently, the SC data can be extrapolated to the IV administration route and no clinical study using an IV presentation is needed.

Three sensitivity analyses were conducted (excluded missing data, comparison based on body weight stratification and excluding ADA-positive subjects). For all sensitivity analyses, the point estimates and 90%CIs of the GMRs for all pairwise comparisons were fully contained within the prespecified margin of 0.80 to 1.25 for AUC_{inf} and $C_{max.}$

In the comparative efficacy and safety study (i.e., BAT-2206-002-CR) in patients with moderate to severe plaque psoriasis, the overall geometric means of serum concentrations of ustekinumab were very similar between BAT2206 and Stelara (EU-sourced) groups over the studied period.

Efficacy

In the Phase 3 study (BAT-2206-002-CR) a total of 278 subjects received Stelara, 277 subjects received BAT2206 and 92.6% (515/556) of all subjects randomised at screening completed the 52-week study.

At Week 8, The LS mean difference in PASI percent CfB for BAT2206 versus Stelara was 0.964 and the 95% CI was -2.751 to 4.679. Thus, the primary objective of the study was achieved.

Sensitivity analyses were supportive of the results as all 95% CI were entirely contained within the predefined equivalence margins regardless of which estimand, imputation method or analysis set was used.

Analysis of subgroups and secondary endpoints were consistent with the primary results and support similarity between Stelara and BAT2206.

Safety

In the Phase 3 study, the incidence of at least one treatment related adverse event (TRAE) was 18.0% and 16.2% in the Stelara and BAT2206 groups, respectively during treatment period 1 (TP1). In TP2, the proportion of subjects with at least one TRAE remained similar across groups at both SOC and PT level. The most common TRAE were in the Infections and infestations SOC with 27 (9.7%) and 22 (7.9%) subjects in the Stelara and BAT2206 group, respectively in TP1. Severe TRAEs were reported for a total of 4 (0.7%) patients throughout the study with no imbalance between treatment groups.

Overall, the adverse event profiles of BAT2206 and EU-Stelara were comparable in both the single dose PK study and the Phase 3 study in psoriasis patients in terms of nature, frequency and severity of TRAEs. Most reported TRAEs were mild or moderate in severity and no unexpected clustering of events was seen. Both products seemed to be generally well tolerated with a safety profile comparable to that previously reported for Stelara.

Immunogenicity

In the single dose Phase 1 study, the overall incidence of ADA formation was 14.8% in the EU-Stelara group and 26.7% in the BAT2206 group.

Although the incidence of ADA was higher with BAT2206 than with Stelara in the PK study, the finding was not replicated in the Phase 3 study. In the Phase 3 study, the overall incidence of ADA formation was 31.3% in the Stelara group and 24.9% in the BAT2206 group. Median ADA titres and time to onset of ADA formation was comparable between the treatment arms.

The PK differences between ADA-positive and ADA-negative subjects were very small in the PK study and not meaningful in the Phase 3 study. PASI improvement was essentially similar between ADA positive and ADA negative subjects at weeks 8 and 12 in both treatment arms.

ADA had no significant influence on safety in either of the two clinical studies. No subject with a positive ADA status had a TEAE suggestive of hypersensitivity or injection site reaction at any time during the study.

3.3. Uncertainties and limitations about biosimilarity

Quality

None

Non-clinical

None.

Clinical

Pharmacokinetics

None.

Efficacy

None.

Safety

The size of the safety database is limited and effectively precludes the detection of any rare adverse effects. No other uncertainties were identified. Nevertheless, considering the extensive experience already available with the reference product and the overall evidence regarding similarity, the size can overall be considered sufficient in the context of a biosimilar application

3.4. Discussion on biosimilarity

Quality

The totality of the presented biological and physiochemical data support the claim of biosimilarity for BAT2206 and EU-Stelara. All biological activities relevant to the primary mechanism of action, including binding to p40, IL-12 and IL-23 antigens, binding kinetics to IL-12 and IL-23, lack of binding to receptor bound IL-12 or IL-23 on the cell surface, competitive inhibition activity of IL-12Rβ1 binding to p40, neutralizing activity against IL-12, and FcRn binding, are similar. A significantly lower sialylation level in BAT2206 compared to EU-Stelara did not result in differences in binding studies or PK-profiles. Differences were also observed in charge variant levels analysed with IEC-HPLC. The level of both acidic and basic peaks in BAT2206 was lower than in EU-Stelara. The differences between BAT2206 and EU-Stelara in the levels of acidic and basic peaks are not considered clinically meaningful, based on charge variant characterisation studies. Furthermore, minor differences were observed in aggregate profiles and size variant profiles. These differences are not likely to be clinically meaningful and are adequately discussed and justified. Overall, the presented quality data support the biosimilarity of BAT2206 and EU-Stelara.

Non-clinical

From the non-clinical point of view, *in vitro* PD studies did not suggest significant differences in Fab or FcRn medicated functional activities and additional *in vivo* studies comparing the pharmacology, PK, TK and toxicology of BAT2206 and EU-Stelara supported the claim that there are no significant clinically relevant differences between the biosimilar and the reference medicinal product.

Clinical

Pharmacokinetics

The PK similarity in the pivotal PK study BAT-2206-001-CR using healthy Chinese male adult subjects has been formally demonstrated between BAT2206 and Stelara (EU-sourced) and Stelara (US-sourced) as for the primary PK parameters AUC_{inf} and C_{max}, the 90%CIs for the ratio of test-to-reference/comparator fell within the acceptance range of 0.80-1.25 (including 1.0). Also, secondary PK parameters were comparable between studied treatments and for all sensitivity analyses, the point estimates and 90% CIs of the GMRs for pairwise comparisons were fully contained within the equivalence range of 0.80-1.25.

The partial AUCs ($AUC_{0\text{-}672h}$ and $AUC_{Tmax\text{-}inf}$) support the extrapolation of the SC data to the IV administration route.

The additional PK data obtained from the efficacy/safety study BAT-2206-002-CR support the PK similarity.

Efficacy

Results from the pivotal study on efficacy and safety (BAT-2206-002-CR) support comparability of efficacy of BAT2206 and EU-Stelara. The primary endpoint, PASI percent improvement from baseline to week 8, was similar between the treatment arms as the 95% CI for the difference was well contained within the predefined equivalence margins. No relevant difference was seen between treatment arms in PASI improvement up to week 52. Secondary endpoints, subgroup analyses and sensitivity analyses confirmed the robustness of the result. Switching from EU-Stelara to BAT2206 at week 28 did not lead to a change in efficacy or safety. As the study was well designed and no major flaws in conduct were detected, it can be concluded that the efficacy of BAT2206 is similar to that of EU-Stelara in subjects with moderate to severe psoriasis.

Safety

The reported adverse event profiles of BAT2206 and Stelara seem similar in terms of nature, frequency and severity and no unexpected events or clustering was seen. Both products seemed to be generally well tolerated with a safety profile comparable to that previously reported for Stelara.

As stated above, the size of the safety database is limited and effectively precludes the detection of any rare adverse effects. Nevertheless, considering the extensive experience already available with the reference product and the overall evidence regarding similarity, the size can be considered sufficient in the context of a biosimilar application. To conclude, safety data from both the clinical PK study in healthy volunteers and the pivotal clinical study in Psoriasis patients can overall be considered to support a determination of biosimilarity.

Immunogenicity

No important difference in ADA incidence or titres was seen between the products. Although, the ADA detection method was not optimal in the PK study, this issue is not considered relevant as immunogenicity is better assessed in a Phase 3 study.

While the incidence of ADA was somewhat higher with BAT2206 than with Stelara in the PK study, the finding was not replicated in the Phase 3 study. In the Phase 3 study, the overall incidence of ADA formation was somewhat higher in the Stelara group than in the BAT2206 group. This was methodologically a more reliable finding and clinically more relevant as it was from the long-term multiple dose study in the target population. According to the EMA guideline (EMA/CHMP/BMWP/403543/2010), a lower immunogenicity for the biosimilar mAb is a scenario that does not preclude biosimilarity. Hence, no meaningful difference in the overall immunogenicity was detected.

3.5. Extrapolation of safety and efficacy

The applicant is seeking approval for BAT2206 for the same indications as approved for the reference medicinal product Stelara, except for the UC indication which was not applied for. Approval is sought for all the same dosage forms and strengths as approved for Stelara in the EU. In this application, only the 45 mg/0.5 mL and 90 mg/1.0 mL prefilled syringe (PFS) presentations were included in the clinical studies and only adults with Ps were studied. Hence, extrapolation is needed

a) from SC to IV presentation

b) from Ps to other indications

c) from adult to paediatric use.

In general, factors that should be considered for scientifically justifying extrapolation include mechanism of action (MoA), PK, expected toxicities, and any other factor that may affect safety and efficacy.

No PK data is available for IV administration and no plans have been presented to generate data on IV administration. Extrapolation of data generated with SC administration to IV administration could be acceptable if the applicant can demonstrate comparability in both absorption and elimination for the SC route. The 90%CIs of the GMRs for the $AUC_{Tmax\text{-}inf}$ and $AUC_{0\text{-}672h}$ were within the BE criteria of 0.80 to 1.25. Because the partial AUCs are similar between the products, the SC data can be extrapolated to the IV administration route and no clinical study using IV presentation is needed.

The MoA is the same across the approved indications for Stelara (ustekinumab). Ustekinumab binds to the p40 subunit of the heterodimeric cytokines IL-23 (consisting of p19 and p40 subunits) and IL-12 (consisting of p35 and p40 subunits) via the Fab region of the antibody and prevents the interaction of IL-23 and IL-12 with the shared cell-surface receptor, IL-12Rb1, which results in the inhibition of downstream signalling that leads to immune modulation. Comparative analytical *in vitro* biological and functional assay results along with results from supplementary *in vitro* pharmacology studies show that BAT2206 and Stelara (ustekinumab) have the same MoA, which is common for each of the originator indications (Ps, paediatric Ps, PsA, CD, paediatric CD).

Comprehensive analytical similarity testing of SC and IV formulations of BAT2206 and Stelara have been conducted, and the results showed that BAT2206 and Stelara are analytically similar. Similar physicochemical analytical quality results and the similar biological activity results for the biological properties involved in the

MoA of ustekinumab support extrapolation from the results obtained in the comparative clinical efficacy and safety study in patients with Ps to all other approved indications of Stelara not studied in the clinical program of BAT2206.

Stelara (ustekinumab) prescribing information supports the conclusion that, aside from body weight, there is no impact of intrinsic and extrinsic factors on the PK, safety or effectiveness of Stelara (ustekinumab) in children compared to adults. Measures to account for the impact of body weight (ie, weight-based dosing) are provided in the Stelara (ustekinumab) and Usymro (ustekinumab) product information.

A 45 mg vial will be available for paediatric patients who need to receive less than the full 45 mg dose (in line with the reference product).

Hence, the totality of evidence presented in this application is supportive of the conclusion that BAT2206 is structurally and functionally similar to Stelara (ustekinumab) and that there are no clinically meaningful differences between the products. These data, combined with previous findings of safety and efficacy for the approved indications of Stelara (ustekinumab) and current knowledge of the product in each approved condition of use, form the scientific justification for extrapolation of the studied formulations and indications to all conditions of use approved for Stelara (ustekinumab) for which MA is sought.

3.6. Additional considerations

Not applicable.

3.7. Conclusions on biosimilarity and benefit risk balance

Based on the review of the submitted data, Usymro is considered biosimilar to Stelara. Therefore, a benefit/risk balance comparable to the reference product can be concluded. The overall benefit/risk balance of Usymro 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 Usymro is favourable in the following indications:

Plaque psoriasis

Usymro 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

Usymro 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

Usymro, 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

Usymro 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.

Paediatric Crohn's disease

Usymro is indicated for the treatment of moderately to severely active Crohn's disease in paediatric patients weighting at least 40 kg, who have had an inadequate response to, or were intolerant to either conventional or biologic therapy.
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.