25 April 2024
EMA/228742/2024
Committee for Medicinal Products for Human Use (CHMP)

Assessment report

Wezenla

International non-proprietary name: ustekinumab

Procedure No. EMEA/H/C/006132/0000

Note

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

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Administrative information

Name of the medicinal product:	Wezenla
Applicant:	Amgen Technology (Ireland) Unlimited Company Pottery Road Dun Laoghaire A96 F2A8 IRELAND
Active substance:	Ustekinumab
International Non-proprietary Name/Common Name:	Ustekinumab
Pharmaco-therapeutic group (ATC Code):	immunosuppressants, interleukin inhibitors (L04AC05)
Therapeutic indication(s):	Plaque psoriasis WEZENLA 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 WEZENLA 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) WEZENLA, 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 WEZENLA is indicated for the treatment of adult patients with moderately to severely active Crohn's disease who have had an inadequate response with, lost response to, or were intolerant to either conventional therapy or a TNFα antagonist or have medical contraindications to such therapies.
Pharmaceutical form(s):	Concentrate for solution for infusion; Solution for injection
Strength(s):	45 mg, 90 mg and 130 mg
Route(s) of administration:	Intravenous use and subcutaneous use
Packaging:	pre-filled syringe (glass) and vial (glass)
Package size(s):	1 pre-filled syringe and 1 vial

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List of abbreviations

ADA/ADAs	Antidrug antibody/antidrug antibodies
1gG1κ	Immunoglobulin isotype class G subclass 1 kappa
AAA	Amino acid analysis
ABP 654	Laboratory name for Amgen biosimilar candidate to Stelara (ustekinumab)
ACTB	Actin beta
ADA	Anti-drug antibodies
ADCC	Antibody-dependent cell-mediated cytotoxicity
ADCP	Antibody-dependent cell-mediated phagocytosis
ADL	Amgen Technology Ireland Unlimited Company
adL	Adenovirus tripartite leader
ADM	Animal-derived materials
ADME	Absorption, distribution, metabolism, excretion
α-gal	galactose-α-1,3-galactose
AHU	Air handling units
Alpha	Amplified luminescent proximity homogeneous assay
ALT	alanine aminotransferase
AmpR	Ampicillin resistance
ANCOVA	analysis of covariance
ANG	Automatic needle guard
ANG+	Automatic needle guard plus
anti-HLA	Anti-human leukocyte antigen
AQL	Acceptance quality limit
AR	Aspect ratio
ARI	Immunex Rhode Island Corporation (Amgen Rhode Island)
Asn	Asparagine
ASP	Acceptance sampling plan
ASTM	American Society for Testing and Materials
AU	Absorbance units
AUC	Area under the concentration-time curve
AUC_{inf}	AUC from time 0 extrapolated to infinity
AUC_{last}	AUC from time 0 to the last quantifiable concentration
B	Beginning
BD	Becton Dickinson Pharmaceutical Systems
BI	Biological indicators
BSA	body surface area
BSE	Bovine spongiform encephalopathy
C1q	First sub-component of complement
CCI	Container closure integrity
CD	Crohn’s disease
CD	Cluster of differentiation
CDC	Complement dependent cytotoxicity
cDNA	Complementary deoxyribonucleic acid

cGMP	Current good manufacturing practices
CH	Constant domain, heavy chain
CHMP	Committee for Medicinal Products for Human Use
CHO	Chinese hamster ovary cell line
CI	Confidence interval
cIEF	Capillary isoelectric focusing
CL	Constant domain, light chain
CL/F	Apparent clearance
C_{max}	Maximum observed serum concentration
COVID-19	Coronavirus disease 2019
CPP	Critical process parameter
CQA	Critical quality attribute
CRT	Controlled room temperature
CSR	clinical study report
CTCAE	Common terminology criteria for adverse events
C-terminal	Carboxyl terminal
CTRS	Comparable to reference standard
CTSS	Controlled temperature shipping system
DF	Diafiltration
DHF	Design history file
DHFR	Dihydrofolate reductase
DLS	Dynamic light scattering
DLs	Data loggers
DNA	Deoxyribonucleic acid
DOE	Design of experiments
DP	Drug product
DS	Drug substance
E	End
EAC	Equivalence acceptance criteria
EC	European Commission
EC_{50}	Half maximal effective concentration
ECG	electrocardiogram
EDTA	Disodium edetate
ELISA	Enzyme-linked immunosorbent assay
EM	Environmental monitoring
EMA	European Medicines Agency
EOI	events of interest
EOP	End of production
EOS	end-of-study
ERA	Environmental risk assessment
EU	European Union
EU	Endotoxin units
Fab	Antigen-binding fragment

FAS	full analysis set
Fc	Fragment crystallisable
FC	Flow cell
FcγRIa	Fragment crystallisable gamma receptor type Ia
FcγRIIa	Fragment crystallisable gamma receptor type IIa
FcγRIIIa	Fragment crystallisable gamma receptor type IIIa
FcγRs	Fc gamma receptors
FcRn	Neonatal Fc receptor
FcγR	Fragment crystallisable gamma receptor
FDA	Food and Drug Administration
FFT	Flexible freeze and thaw
FMEA	Failure modes and effects analysis
FTIR	Fourier transform infrared spectroscopy
G	Glycosylation
g/L-r	Grams per litre resin
GMR	geometric mean ratio
HC	Heavy chain
HCCF	Harvest cell culture fluid
HCP	Healthcare professional/provider
HCP	Host cell protein
HF	Human factor
HILIC	Hydrophilic interaction column
HMW	High molecular weight
HTRF	
ICH	International Council for Harmonisation of Technical Requirements for Pharmaceuticals for Human Use
ID	Identity
IFU	Instructions for use
IgG	Immunoglobulin isotype G
IgG1	Immunoglobulin isotype G subclass 1
IgG1κ	IgG subclass 1 kappa
IL	Interleukin
IL-12	Interleukin 12
IL-12/23	interleukin-12/interleukin-23
IL-12R	Interleukin-12 receptor
IL-12Rβ1	IL-12 receptor subunit beta 1
IL-23	Interleukin 23
INN	International non-proprietary name
IPC	In-process control
ISO	International Organization for Standardization
IV	Intravenous
JAK	Janus kinase
JP	Japanese Pharmacopoeia

LC	Light chain
LIVCA	Limit of in vitro cell age
LMW	Low molecular weight
LOCF	last observation carried forward
LOQ	Limit of quantitation
MA	Marketing authorisation
MAA	Marketing authorisation application
MAH	Marketing authorisation holder
MCB	Master cell bank
MedDRA	Medical Dictionary for Regulatory Activities
Met	Methionine
MFI	Micro-flow imaging
MOA	Mechanism of action
mRNA	Messenger RNA
MTX	Methotrexate
N	Production bioreactor
NANA	N-acetylneuraminic acid
NF	United States National Formulary
NGHC	Non-glycosylated heavy chain
NGNA	N-glycolylneuraminic acid
non-CDR	Non-complementarity determining region
NRI	non-responder imputation
O	Occurrence
PASI	Psoriasis area and severity index
PASI 50	ê 50% improvement in PASI
PASI 50/75	50%/75% improvement in PASI
PASI 50/75/100	50%/75%/100% improvement in PASI
PASI 75	ê 75% improvement in PASI
PD	Pharmacodynamic
PDE	Permitted daily exposure
PFS	Pre-filled syringe
PFS-SA	Prefilled syringe subassembly
PhEur	European Pharmacopoeia
PK	pharmacokinetic(s)
PP	per-protocol
ppm	Parts per million
PQA	Product quality attribute
PQRA	Product quality risk assessment
Ps	plaque psoriasis
PS80	Polysorbate 80
PsA	psoriatic arthritis
PV	Process validation

rCE-SDS	Reduced capillary electrophoresis-sodium dodecyl sulfate
RMP	Reference medicinal product
RNA	Ribonucleic acid
RP	Reference product
RPLS	reversible posterior leukoencephalopathy syndrome
S	Severity
SA	Sialic acid
SAP	statistical analysis plan
SC	subcutaneous
SD	Standard deviation
SDS	Sodium dodecyl sulfate
SE-HPLC-LS	Size exclusion high-performance liquid chromatography with light scattering
SE-UHPLC	Size exclusion ultra-high performance liquid chromatography
SmPC	Summary of Product Characteristics
SMQ	Standardized MedDRA queries
SOP	Standard operating procedure
Sp2/0	Murine myeloma cell line
sPGA	Static Physician’s Global Assessment
SPR	Surface plasmon resonance
SS	Stainless steel
TSE	Transmissible spongiform encephalopathy
UC	ulcerative colitis
UF/DF	Ultrafiltration/diafiltration
URRA	Use-related risk analysis
US	United States
USP	United States Pharmacopoeia
UV	Ultraviolet
UV CD	Ultraviolet circular dichroism
WCB	Working cell bank
WFI	Water for injection

1. Background information on the procedure

1.1. Submission of the dossier

The applicant Amgen Technology (Ireland) Unlimited Company submitted on 20 April 2023 an application for marketing authorisation to the European Medicines Agency (EMA) for WEZENLA, 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

TRADENAME 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

TRADENAME 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)

TRADENAME, 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

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

Ulcerative colitis

TRADENAME is indicated for the treatment of adult patients with moderately to severely active ulcerative colitis who have had an inadequate response with, lost response to, or were intolerant to either conventional therapy or a biologic or have medical contraindications to such therapies (see section 5.1).

The applicant withdrew the ulcerative colitis indication during the procedure.

1.2. Legal basis, dossier content and multiples

The legal basis for this application refers to:

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

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

This application was submitted as a multiple of Upstelda which was subsequently withdrawn during the procedure.

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; 90 mg/mL (45 mg per PFS), Solution for injection in pre-filled syringe; 90 mg/mL (90 mg per PFS), Solution for injection in pre-filled syringe; 5 mg/mL (130 mg per vial), Concentrate for solution for infusion
- Marketing authorisation holder: Janssen-Cilag International NV
- Date of authorisation: 15 January 2009
- Marketing authorisation granted by:
  - Union
- Marketing authorisation number: 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; 90 mg/mL (45 mg per PFS), Solution for injection in pre-filled syringe; 90 mg/mL (90 mg per PFS), Solution for injection in pre-filled syringe; 5 mg/mL (130 mg per vial), Concentrate for solution for infusion
- Marketing authorisation holder: Janssen-Cilag International NV
- Date of authorisation: 15 January 2009
- Marketing authorisation granted by:
  - Union
- Marketing authorisation number: EU/1/08/494/001, EU/1/08/494/003, EU/1/08/494/004, EU/1/08/494/005

Medicinal product which is or has been authorised in accordance with Union provisions in force and to which bioequivalence has been demonstrated by appropriate bioavailability studies:

- Product name, strength, pharmaceutical form: Stelara 90 mg/mL (45 mg per vial) Solution for injection in vial; 90 mg/mL (45 mg per PFS), Solution for injection in pre-filled syringe; 90 mg/mL (90 mg per PFS), Solution for injection in pre-filled syringe; 5 mg/mL (130 mg per vial), Concentrate for solution for infusion
- Marketing authorisation holder: Janssen-Cilag International NV
- Date of authorisation: 15 January 2009
- Marketing authorisation granted by:
  - Union Marketing authorisation number(s): EU/1/08/494/001, EU/1/08/494/003, EU/1/08/494/004, EU/1/08/494/005
- Bioavailability study number(s): Study 20190230

1.3. Information on paediatric requirements

Not applicable

1.4. Information relating to orphan market exclusivity

1.4.1. Similarity

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

1.5. Scientific advice

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

Date	Reference	SAWP co-ordinators
12 December 2019	EMEA/H/SA/4328/1/2019/III	Brigitte Schwarzer-Daum, Sheila Killalea
24 June 2021	EMA/SA/0000060816	Carin Bergquist, Andreas Kirisits, Kerstin Wickstroem

The applicant received Scientific Advice on the development of ustekinumab biosimilar (ABP 654) for the treatment in the same indications as the reference medicinal product Stelara from the CHMP on 12 December 2019 (EMEA/H/SA/4328/1/2019/III). The scientific advice pertained to the following quality, non-clinical, and clinical aspects:

- Analytical similarity testing plans including structural and functional tests and assays to demonstrate analytical similarity between ABP 654, EU Stelara, and US Stelara, analytical similarity testing strategy to encompass all approved Stelara presentations.
- Appropriateness of the non-clinical development programme including in vitro pharmacology studies.
- Design of a randomised, double-blind, single-dose, 3-arm, parallel-group study to determine the pharmacokinetic equivalence of ABP 654 and Stelara in healthy adult subjects including route of administration, dose, study population, endpoints, equivalence margins.
- Design of a Phase 3, multicentre, randomised, double-blind study evaluating the efficacy and safety of ABP 654 compared with Stelara in subjects with moderate to severe plaque psoriasis including study population, endpoints, timing of assessments, efficacy equivalence margins, sample size, PK evaluation, study duration.
- Bridging from s.c. route of administration to i.v. route of administration for ABP 654 and Stelara.
- Extrapolation of the results of the clinical development programme to all authorised indication of Stelara.

The applicant received scientific advice on the development of ustekinumab biosimilar (ABP 654) for the treatment in the same indications as the reference medicinal product Stelara from the CHMP on 24 June 2021 (EMA/SA/0000060816). The Scientific Advice pertained to the following Quality and Clinical aspects:

- Protein concentration and deliverable volume targets.
- Pharmacokinetics comparability study (including choice of study population, choice of dose, primary and secondary endpoints, and sample size).

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: Robert Porszasz

The application was received by the EMA on	20 April 2023
The procedure started on	18 May 2023
The CHMP Rapporteur's first Assessment Report was circulated to all CHMP and PRAC members on	7 August 2023
The CHMP Co-Rapporteur's first Assessment Report was circulated to all CHMP and PRAC members on	n/a
The PRAC Rapporteur's first Assessment Report was circulated to all PRAC and CHMP members on	21 August 2023
The CHMP agreed on the consolidated List of Questions to be sent to the applicant during the meeting on	14 September 2023
The applicant submitted the responses to the CHMP consolidated List of Questions on	13 December 2023
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	29 January 2024
The PRAC agreed on the PRAC Assessment Overview and Advice to CHMP during the meeting on	08 February 2024
The CHMP agreed on a list of outstanding issues in writing to be sent to the applicant on	22 February 2024
The applicant submitted the responses to the CHMP List of Outstanding Issues on	26 March 2024
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	10 April 2024
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 Wezenla on	25 April 2024

2. Scientific discussion

2.1. Problem statement

Not applicable for biosimilars.

2.2. About the product

Wezenla (ustekinumab also referred to as ABP 654) is recombinant human immunoglobulin isotype class G subclass 1 kappa monoclonal antibody that belongs to the pharmacologic class of interleukin 23 (IL 23) and interleukin 12 (IL 12) antagonists. Ustekinumab binds with specificity to the p40 protein subunit of the IL-23 and IL-12 cytokines to neutralise IL-23 and IL 12 mediated signalling. Interleukin-23 and IL-12 are naturally occurring cytokines that are involved in inflammatory and immune responses. Interleukin-12 stimulates natural killer cells and drives the differentiation of cluster of differentiation 4 positive T cells toward the T helper 1 phenotype; IL-23 induces the T helper 17 pathway.

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

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

2.3. Type of application and aspects on development

The applicant is seeking marketing authorisation for ABP 654 in accordance with Article 10(4) of Directive 2001/83/EC, as amended. The reference biological medicinal product Stelara was originally approved in the EU in January 2009 (EMEA/H/C/000958).

The marketing authorisation application (MAA) presents the totality of data to demonstrate biosimilarity of ABP 654 to Stelara (ustekinumab) based on results of analytical, nonclinical, and clinical studies comparing ABP 654 and ustekinumab.

The clinical evidence supporting the similarity of ABP 654 to Stelara (ustekinumab) includes a randomised, double-blind, single-dose, 3-arm, parallel-group PK similarity study in healthy adult subjects comparing ABP 654 to ustekinumab (Study 20190230); and a randomised, double-blind, active controlled clinical study in adult subjects with moderate to severe Ps (Study 20190232).

2.4. Quality aspects

2.4.1. Introduction

The finished product intended for subcutaneous (SC) injection is presented in a prefilled syringe (PFS) or a vial as a sterile, single-use, preservative-free solution containing 90 mg (1.0 mL, PFS only) or 45 mg (0.5 mL, PFS and vial) of ABP 654 (ustekinumab) formulated in sucrose, L histidine and L-histidine hydrochloride monohydrate, polysorbate 80, pH 6.0. One finished product presentation is intended for intravenous (IV) infusion and it's presented as a sterile concentrate for solution in a single-use vial containing 26 mL deliverable volume of 130 mg of ABP 654 formulated in sucrose, L-histidine and L-histidine hydrochloride monohydrate, L methionine, polysorbate 80, sodium hydroxide and EDTA at pH 6.0. The 130 mg vial presentation is intended for dilution in 0.9% saline.

ABP 654 is being developed as a biosimilar candidate to Stelara (ustekinumab). ABP 654 is expressed in a Chinese hamster ovary (CHO) cell expression system and Stelara is expressed in a murine (Sp2/0) cell line.

ABP 654 is a human immunoglobulin G1 (IgG1) kappa monoclonal antibody, composed of two identical heavy chains (449 amino acid residues each with 4 intrachain disulfides) and two identical light chains (214 amino acid residues with 2 intrachain disulfides), belonging to the pharmacological class of IL-23 and IL-12 antagonists. ABP 654 binds to the commonly shared p40 subunit of IL-23 and IL-12 cytokines.

ABP 654 has the same formulation, route of administration, dosage form, and product strength as Stelara.

In summary, the finished product is supplied in 4 presentations as follows:

- 45 mg (0.5 mL) PFS presentation for SC injection
- 90 mg (1.0 mL) PFS presentation for SC injection
- 45 mg (0.5 mL) vial presentation for SC injection
- 130 mg (26 mL) vial presentation intended for dilution prior IV infusion.

Each PFS consists of a 1 mL Type I glass syringe with fixed stainless steel needle and a needle cap. The syringe is fitted with an automatic needle guard which is activated after drug delivery to cover the needle.

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

2.4.2. Active Substance

2.4.2.1. General Information

ABP 654 (ustekinumab) is a human IgG1 monoclonal antibody composed of two identical heavy chains and two identical light chains of the kappa subclass. ABP 654 contains 32 cysteine residues involved in both intrachain and interchain disulfide bonds. Each heavy chain contains 449 amino acids with 4 intrachain disulfides. Each light chain contains 214 amino acids with 2 intrachain disulfides. Each heavy chain contains an N-linked glycan at a consensus glycosylation site on asparagine 299, the predominant glycan moiety being A2G1F. Details of antibody structure and the amino acid sequence has been provided in the dossier.

2.4.2.2. Manufacture, characterisation and process controls

ABP 654 active substance is manufactured and release tested at Immunex Rhode Island (ARI), 40 Technology Way, West Greenwich, RI, 02817-1700, USA, in accordance with Good Manufacturing Practice (GMP).

All the facilities involved in the manufacturing and testing of the active substance comply with EU GMP.

Description of manufacturing process and process controls

The ABP 654 (ustekinumab) active substance manufacturing process has been adequately described. In contrast to the reference medicinal product, which is produced in Sp2/0 murine cells, ABP 654 AS is expressed in Chinese hamster ovary (CHO) cells. The manufacturing process follows a standard monoclonal antibody production process, and it is divided into an upstream and a downstream manufacturing process. The upstream process begins with a working cell bank (WCB) vial and includes cell expansion steps, a bioreactor step, and a harvest step leading to a harvest cell culture fluid (HCCF).

In the downstream process HCCF is purified using a series of chromatography purification steps. Reprocessing is currently not proposed. The manufacturing steps have been adequately described and the ranges of critical process parameters and the routine in-process controls (IPCs) along with acceptance criteria, are described for each step. The active substance manufacturing process is considered acceptable.

Each lot of ABP 654 receives a unique batch number which provides traceability to the manufacture, packaging, and distribution history.

Control of materials

Sufficient information on raw materials used in the active substance manufacturing process has been submitted. A detailed list of compendial (Ph.Eur., USP) and non-compendial materials used in the upstream process for cell culture media and the downstream process for buffers and purification materials was provided. The specifications were provided for non-compendial materials, and examples of certificates of analysis (CoAs) from suppliers were included for both compendial and non-compendial materials. Compositions for the cell culture media and feeds, as well as buffers and solutions used in the harvest and purification of ABP 654 active substance have been described in detail. The Water For Injection (WFI) used meets the requirements of Ph.Eur.

No animal-derived raw materials or excipients are used in ABP 654 manufacturing. One material obtained from a fermentation process including materials of animal origin, was used as a media additive in master cell bank (MCB) and working cell bank (WCB) generation and considered appropriate. transmissible spongiform encephalopathy (TSE) issues have been assessed in section R.4. An assessment of the raw and starting materials of animal origin for TSE and adventitious viral agents has determined the risk for transmission of adventitious agents by ABP 654 is negligible.

Overall, the section of raw materials was well addressed.

Generation of cell substrate and cell line history

History of the parental CHO cell line and selection of the host cell substrate has been provided. The amino acid sequence of ustekinumab was determined from a commercial batch of Stelara by appropriate characterisation tests. The verified amino acid sequence was used for the construction of the ABP 654 expression vectors. Both nucleotide and amino acid sequences of the ABP 654 LC and HC have been provided.

Cell banking system, characterisation, and testing

A two-tiered cell bank system consisting of MCB and WCB is used. Certificates of analysis (CoAs) were provided for MCB and for WCB. Reagents and materials used for generation of cell banks contain no animal derived material, except one material. Cells banks are stored at multiple locations for risk mitigation. In general, creation of the MCB and WCB was described briefly, but at sufficient level.

The MCB and WCB have been characterised for identity and purity. Viral safety of cell banks was assessed. The expected ABP 654 cDNA sequence was verified, and results were provided in the genetic stability section. Stability of the MCB and WCB during storage is studied by measuring the cell viability.

Genetic stability of MCB and WCB was demonstrated through the end of production (EOP) culture and limit of in vitro cell age (LIVCA) studies. According to the data provided, genetic stability of the ABP 654 LC and HC nucleotide sequences, gene integrity, gene transcripts (mRNA), and integration sites were comparable in MCB, WCB, EOP and LIVCA. A decrease was observed in gene copy numbers of both LC and HC between MCW/WCB and EOP/LIVCA. The applicant provided a justification for this observed decrease with no impact to productivity or product quality. This was agreed based on the batch data provided.

Overall, the cell line development, cell banking system and stability of the cell banks is adequately described. Information of used plasmids with essential vector components and sequences of HC and LC have been provided, as well as a single cell image of the selected ABP 654 cell clone. Genetic stability of the cell banks was demonstrated for ABP 654 LC and HC. Engineering of the ABP 654 cell line has been adequately described. The expression plasmid map and the essential components of the plasmid were adequately presented. The N-glycan profile and levels were demonstrated to be comparable with that of the primary reference standard batch.

Qualification and acceptance criteria for future WCB were described in satisfactory detail and are considered acceptable.

Control of critical steps and intermediates

The manufacturing process is controlled by IPCs with action and/or rejection limits. Action limits were established for monitoring process consistency and rejection limits to ensure patient safety. Exceeding a rejection limit results in rejection of the batch and an excursion to an action limit triggers a deviation. All IPCs are included in the continued process verification programme to identify potential process trends or shifts.

A comprehensive overview of critical in-process controls and critical in-process tests performed throughout the ustekinumab active substance manufacturing process has been provided. Product quality critical IPCs include testing for product and process related impurities, product-related substances, and general quality attributes. Safety related critical IPCs include testing for bioburden, bacterial endotoxins, mycoplasma and adventitious agents, pH in viral inactivation step, and filter integrity tests. The applicant has explained the criteria for the choice of the criticality of a process parameter and control. In the process design studies, the applicant has explained the establishment of the acceptable ranges for process parameter. Relevant process parameters are set to control the manufacturing process. Process validation studies support the established process parameters. A justification for IPC limits is adequately provided.

Analytical methods used for in-process testing are adequately described and considered acceptable.

Process validation

The validation of the ABP 654 AS manufacturing process was performed at the commercial site using a minimum of three consecutive, successful batches originating from independent thaws of WCB followed by cell culture, harvest, and purification steps. Process validation protocols were written and approved prior to the start of validation to define the sampling, testing, and validation acceptance criteria for process parameters and performance indicators. Process validation was completed for cell culture, harvest, purification, and in-process pool holds.

Several deviations were reported in the validation of purification steps, which were appropriately addressed in the validation reports. Two deviations were reported during the manufacturing of one

batch, which did not impact product quality as demonstrated by performance indicators at subsequent steps. Results from this batch are presented in the dossier, but not used to support the qualification of specific steps which is considered appropriate.

In-process pool hold times were validated to demonstrate both the chemical stability and microbial control of ABP 654 AS over a defined period of time. The chemical stability studies were conducted by measuring product quality attributes. The microbial control was confirmed through testing for bioburden and endotoxins. Additional batches, produced to support FP validation representative of AS process validation batches were utilised to establish the in-process pool hold durations. The hold times are considered appropriately validated.

In conclusion, the active substance manufacturing process has been validated adequately. Consistency in production has been shown on 3 full scale commercial batches. All acceptance criteria for the critical operational parameters and likewise acceptance criteria for the in-process tests are fulfilled demonstrating that the purification process consistently produces ustekinumab active substance of reproducible quality that complies with the predetermined specification and in-process acceptance criteria.

Transportation qualification

ABP 654 AS is transported frozen. No product specific validation has been done, but controlled temperature shipping system (CTSS) has been qualified to maintain temperatures, which is considered acceptable.

Manufacturing process development

Manufacturing process development history

The development of the manufacturing process is adequately described. The ABP 654 AS has been manufactured at different sites.

The production scale remained unchanged across all sites except for an initial development batch. The manufacturing process flow was essentially similar in all manufacturing sites with some process adjustments and changes to improve process robustness, accommodate facility fit, and to address raw material shortage. To be mentioned, the target AS concentration was set to align with the reference product, Stelara. The manufacturing process development history was adequately described with sufficient details for each step.

Process characterisation and control strategy

ABP 654 AS process design is satisfactorily described including risk- and science-based assessment of reference product and ABP 654 quality attributes (QAs), prior knowledge, product specific process development studies and manufacturing experience. In addition to these, thorough process characterisation studies were conducted to provide deeper process understanding and impact on product quality.

To establish the ABP 654 control strategy, molecule specific and general product quality attributes (PQAs) were assessed and assigned a severity score based on each potential impact on safety and efficacy. Classification of critical quality attributes (CQAs) is considered relevant and acceptable. Severity scoring and selected CQAs are considered relevant and acceptable.

After identifying the CQAs, each manufacturing process step was evaluated for its potential impact on the product variants and process-related impurities (CQAs) with multivariate Design of Experiment (DOE) and/or univariate analysis using representative qualified small-scale models where appropriate. Acceptable ranges for process parameters (PPs) were established based on process characterisation studies.

Criticality assessment of PPs and IPCs and justification of acceptable ranges and action/rejection limits was satisfactorily described.

The appropriateness of the control strategy was assessed using a product quality risk assessment (PQRA) considering PQA severity scores combined with manufacturing process capability. Failure Modes and Effects Analysis (FMEA) approach was used for PQRA to assess quality risks of the process with all controls in place (procedural and testing). FMEA includes 3 components: severity (harm), likelihood (occurrence) and detection (ability to detect failure or hazard). Based on the FMEA assessment with appropriate controls in place the overall risk level of ABP 654 commercial process is considered acceptable.

The integrated control strategy of ABP 654 includes combination of process parameters, IPCs, release specifications, and periodic testing controls of the AS and FP to ensure safety and efficacy. Overall, ABP 654 AS process characterisation and control strategy are deemed appropriate and acceptable.

Characterisation

The ustekinumab active substance has been sufficiently characterised by physicochemical and biological state-of-the-art methods revealing that the active substance has the expected structure of a human IgG1-type antibody. Characterisation included determination of structure (primary, secondary, and tertiary), glycosylation (N- and O-linked glycans), disulfide structure, charge and size variants, thermal stability, biological characteristics, Fc receptor binding, and impurities. Details of the physicochemical and biological properties of ABP 654 are described in the biosimilarity section. Biological characterisation of ABP 654 was conducted to assess the structure-function properties related to the mechanism of action and the in vitro biological activity of stressed ABP 654 and product variants.

Forced degradation conditions indicated common antibody degradation patterns, such as aggregation, fragmentation, oxidation and isomerisation.

The commercial manufacturing process is able to clear process-related impurities to acceptable safety levels. Generally, product-related and process-related impurities have been identified and characterised at sufficient level, and the impact of impurities on safety and efficacy was appropriately evaluated.

Overall, the performed characterisation studies are considered relevant and cover a wide variety of physicochemical and biological characterisation studies. Justification of the identification and classification of the product-related impurities can be agreed. Process-related impurities, such as host cell proteins (HCP), host cell DNA, leached protein A, and process reagents were demonstrated to be consistently cleared by validated purification process. The analytical results are consistent with the proposed structure. Biological characterisation of Ustekinumab indicates that this antibody has the ability to bind IL-23 and IL-12, which are heterodimeric cytokines containing a common p40 subunit, with high affinity and to specifically bind to Fc Receptor as expected of an IgG1. In summary, the characterisation is considered appropriate for this type of molecule.

2.4.2.3. Specification

The following tests are included in the active substance specification: general tests (appearance, colour), identity, purity and impurities, adventitious agents (bacterial endotoxins, bioburden) and potency.

Overall, the test parameters included are considered adequate, however, the potency test has been changed and the acceptance criteria for potency has been tightened during the Marketing Authorisation procedure. All test parameters proposed to be included in the ABP 654 AS specification have been discussed separately and justification and historical data has been provided for each parameter. Overall, the set of release and in-process controls complies with ICH Q6B, Ph. Eur. 2031, and EMA/CHMP/BWP/532517/2008.

Analytical methods

Analytical procedures used for the routine control testing and for release and stability testing of the active substance are summarised in section S.4.2. The used analytical procedures have been sufficiently described, reference to compendial methods is made and considered acceptable. Compendial methods are performed in accordance with current pharmacopoeia.

Compendial methods are used for appearance (Ph.Eur. 2.9.20), colour (Ph. Eur. 2.2.2), and bacterial endotoxins (Ph. Eur. 2.6.14/method D). For the in-house methods, appropriate system suitability and sample acceptance criteria are provided, relevant reagents and equipment listed, and representative chromatograms provided. Analytical methods used during development, but later excluded from commercial specification or IPC controls were adequately described. In general, validation of non-compendial methods is sufficiently described and relevant parameters (e.g. specificity, precision (repeatability and reproducibility), linearity, range, accuracy, LOQ, robustness, and stability indicating property) were assessed in line with ICHQ2(R1).

Batch analysis

Batch analysis data (at commercial scale) of the active substance were provided. The results are within the specifications and confirm consistency of the manufacturing process.

Reference materials

The primary reference standard (PRS) was used for release and stability testing of all lots from development through completion of process validation. In 2021 a working reference standard (WRS) was manufactured, qualified against the PRS, and placed in the stability programme. The WRS is intended for lot release and stability testing of all lots after its implementation date.

The history of the two reference standards used throughout development of ABP 654 has been satisfactorily described. Qualification of both reference standards (RSs) was performed adequately. In comparability study, the parental AS batch of PRS was demonstrated to be representative of material used in the clinical studies. The parental AS batch of WRS was included in the comparability study between manufacturing sites and was shown to have some differences in charge profile compared to all other batches tested. These differences are not considered meaningful on the performance or use of the WRS. Both RSs can be considered representative of material used in the clinical trials.

Stability programme of RSs is satisfactorily described including a re-test at 12-month intervals for RSs stored at the recommended storage conditions (RSC). Based on the stability data provided both RSs are stable at RSC. Qualification and monitoring of future primary and working reference standards are adequately described including release tests and acceptance criteria. Potency of future RSs will be evaluated against the potency of the current PRS.

Container Closure System

The container closure system (CCS) used for the active substance is adequately described. The CCS specifications include Ph. Eur. tests for biological reactivity, physicochemical tests, bacterial endotoxins, particulates, and sterility performed by the supplier.

Additionally, the applicant has performed extractables and leachables studies. Based on the extractables studies, the levels are below the permitted daily exposure (PDE) for both extractables and leachables. Additionally, all leachables were below the concentration of toxicological concern.

Integrity of the CCS was confirmed by microbial aerosol challenge test using minimum and maximum fill volumes.

Sterility is according to ISO 11137. The specification and a representative certificate of analysis are available.

The CCS is considered suitable and appropriate for ABP 654 AS.

2.4.2.4. Stability

The stability results indicate that the active substance is sufficiently stable and justify the proposed shelf life in the proposed container with currently available data). The applicant has provided stability data at the long-term storage condition, at the accelerated storage condition and stressed storage condition according to the ICH guidelines. Stability studies at accelerated and stressed conditions have been completed and data is available for all stability batches for 6 months at accelerated storage condition and for 3 months at stressed storage conditions.

The comparability of the material produced at different sites has been confirmed and is discussed in section S.2.6. However, initial differences between the material from different sites are also reflected in the stability data.

The CCS used for the stability programme consists of bags which are smaller than, but otherwise identical to, the AS CCS used in manufacturing. The use of reduced size containers representative of the commercial scale containers in the stability studies is acceptable.

General attributes of ABP 654 including appearance, colour, protein concentration, and pH were assessed to confirm no unexpected changes over the course of stability. Aggregation, fragmentation, oxidation, isomerisation, non-CDR deamidation, and potency were monitored. The stability-indicating properties of the analytical procedures have been confirmed and the methods and their validation have been discussed.

In the long-term conditions, all study results presented were within the acceptance criteria in place during development and within the proposed commercial specifications. In stressed and accelerated conditions more pronounced trends could be seen for several attributes.

In addition, data has been provided to support AS shipping conditions. All data were within the acceptance criteria in place at the time of testing and no significant changes were observed. The data provided can be considered to support shipping of the AS

Overall, the applicant has designed and conducted the active substance stability programme following ICH Q1A and ICH Q5C guidelines.

2.4.2.5. Comparability exercise for active substance

The applicant has conducted three comparability studies in line with ICH Q5E, which were adequately performed and acceptable. Some differences were observed which were concluded not to impact on product efficacy or patient safety, which is agreed. Furthermore, some differences were observed in potency and those were appropriately explained by method variability. Despite the identified shortcoming, it is concluded that comparability has been mainly adequately demonstrated.

2.4.3. Finished Medicinal Product

2.4.3.1. Description of the product and pharmaceutical development

The finished product is a sterile, preservative-free, opalescent, colourless to light yellow solution in single-dose container, available in the following presentations:

- 45 mg (0.5 mL) PFS presentation for SC injection
- 90 mg (1.0 mL) PFS presentation for SC injection
- 45 mg (0.5 mL) vial presentation for SC injection
- 130 mg (26 mL) vial presentation intended for dilution prior intravenous (IV) infusion

The composition of the 45 mg and 90 mg PFS and 45 mg vial presentations is the same. All excipients are well known pharmaceutical ingredients and their quality is compliant with Ph. Eur standards. There are no novel excipients used in the finished product formulations. The composition of the final ABP 654 finished product presentations is the same as the reference medicinal product Stelara. No formula overages are included and the overfill ensures the administration of nominal volume of each ABP 654 finished product presentation.

For the PFS presentations, the primary packaging is a type I glass 1 mL pre-filled syringe with a fixed stainless-steel needle and a needle cap. The syringes are supplied washed, siliconised, and sterilised. The plunger-stoppers are supplied washed, siliconised and sterilised. The needle shield protects the needle cannula and is supplemented with an outer plastic rigid cover. The syringe also includes a plastic plunger rod and an automatic needle guard.

The Notified Body Opinion for the PFS has been provided. The technical documentation has been considered adequate to support compliance with the relevant safety and performance requirements.

For the 45 mg vial presentation, the primary packaging is a type I glass 2 mL vial closed with an elastomeric stopper. For the 130 mg vial presentation, the primary packaging is a type I glass 30 mL vial closed with an elastomeric stopper.

The materials comply with Ph. Eur. and EC requirements. The choice of the container closure systems has been validated by stability data and is adequate for the intended use of the product. The safety (compendial and non-compendial extractables and leachable testing), compatibility and performance/functionality of the primary container closure system was evaluated. Protection of the finished product from light is also provided by the secondary packaging. The primary container components met the relevant requirements of Ph.Eur. and ISO standards. Extractables studies performed in extreme solvent conditions revealed very low level of inorganic and organic extractables which are clearly below the acceptable exposure level. Although the extractable testing described above did not identify any extractables at sufficient level to be of toxicological concern, an assessment of organic and inorganic leachable levels was performed. These studies covering the proposed shelf-life of finished products (3 years for PFS presentations and 2 years for 45 mg and 130 mg vial presentations) indicated that the observed leachables were clearly below the permitted daily exposure.

ABP 654 finished product presentations were developed to have the same formulation, route of administration, dosage form and strength as the corresponding reference finished product presentations of EU-Stelara. The pharmaceutical development of ABP 654 finished product utilised principles described in the ICH Q8 Pharmaceutical Development guideline and was based on scientific knowledge and prior experience with similar protein products, as well as risk assessments and development studies.

Provided formulation development data demonstrated appropriate robustness of the formulations.

All four finished product presentation batches supporting for stability, development and clinical studies were manufactured at a development site and for commercial manufacturing the finished product manufacturing of all four presentations was transferred to Amgen Technology Ireland (ADL). Facility-fit adaptations were made, including changes in hold times, hold temperatures and the filling technology. The ABP 654 commercial process was characterised through process development studies both at laboratory and commercial scale. Process characterisation demonstrated that the finished product manufacturing process is robust and can deliver the required product quality and process consistency when operated within acceptable ranges. The applicant presented extensive ABP 654 finished product comparability studies between the finished products manufactured at different sites in line with ICH Q5E requirements.

The comparability was evaluated by comprehensive lot release, characterisation and stressed stability studies. Minor differences in purity were observed between the PFS and 130 mg vial presentations due to the lower protein concentration in the 130 mg vial which favoured less HMW formation. Additionally, minor differences were observed between the ranges for purity results among the finished product manufactured at different sites. These differences were attributed to the active substance source and manufacturing process variability. The applicant has provided adequate data to confirm the comparability of ABP 654 finished product presentations between manufacturing sites and therefore, the safety and efficacy of ABP 654 finished product are not expected to be impacted by the manufacturing site change.

Several additional development studies were conducted to support the development of the ABP 654 finished product manufacturing processes. The product contact material compatibility and light exposure studies were conducted with all ABP 654 presentations. The results of supportive studies demonstrated that neither light exposure nor material contact do have significant impact on product quality.

2.4.3.2. Manufacture of the product and process controls

Manufacture

ABP 654 finished product batch release testing is performed by Amgen Ireland (ADL), with the exception of Belgium and Luxembourg markets where the release testing is performed by Amgen Belgium (NV). Proof of GMP compliance has been demonstrated for all finished product manufacturers.

For the 45 mg and 90 mg PFS and 45 mg vial presentations, ABP 654 active substance is fully formulated, and no further formulation steps are conducted during finished product manufacture. The three presentations of the ABP 654 finished product are identical in all aspects except for the fill volume and primary container closure system. For the 130 mg vial presentation, during formulation the active substance is diluted to 5 mg/ml finished product.

The manufacturing process comprises of preparation and filtration of formulation buffer (only 130 mg vial), active substance thawing and pooling, dilution of the active substance (only 130 mg vial), mixing of bulk finished product, pre-filtration for bioburden reduction, sterile filtration, aseptic filling, plunger-stopper placement (PFS)/stoppering and capping (vials), visual inspection, labelling and packing and storage. There is no reprocessing for the finished product process. A process flow chart with process parameters, including hold times, and in-process testing has been provided. Overall, the process steps have been described with sufficient detail in the MAA. 45 mg vial manufacturing process is comparable to that of PFSs except aseptic filling, stoppering and capping steps which are same to the process of 130 mg vial.

Process validation

The finished product manufacturing process was validated by producing three consecutive finished product batches for each presentation at commercial scale. All ABP 654 finished product batches were successfully validated, the presented data met acceptance criteria, demonstrating consistency and reliability of the finished product manufacturing processes. All batches met the release results of the proposed commercial specification acceptance criteria. Validation was also successfully performed for the assembly process of the ABP 654 PFS with the automatic needle guard (ANG).

Hold-times during the manufacturing processes are appropriately validated.

The manufacturing process validation data of PFS supports relatively well the proposed filling time and can be accepted. Also, the proposed filling time for 130 mg vials is appropriately justified and considered acceptable.

Overall, the filter validation studies were performed in acceptable manner according to the principles of relevant guideline.

The aseptic process validation of each ABP 654 finished product presentation represented the commercial configuration. The media fill validation data have been provided. Appropriate validation reports for syringe and plunger-stopper sterilisation were provided.

The transport evaluation was conducted on the finished product presentations representative of commercial packaging. Overall, transport arrangements are relevant and have been justified and/or validated in acceptable manner.

The manufacturing process has been validated. It has been demonstrated that the manufacturing process is capable of producing the finished product of intended quality in a reproducible manner. The in-process controls are adequate.

2.4.3.3. Product specification

Comprehensive panel of specifications have been set in accordance with ICH Q6B principles and cover all relevant characteristics of ABP 654 finished products, including tests for appearance (appearance, clarity, coloration), identity, purity and impurities, adventitious agents including bacterial endotoxins, sterility and container closure integrity, potency, quantity (protein concentration) and general properties.

PFS presentations are integral drug-device combination products and break-loose and extraction (BLE) are tested as part of batch release and shelf-life specification to confirm device functionality.

The release and shelf-life specifications of 45 mg PFS, 90 mg PFS and 45 mg vial presentations are the same except for some of the 45 mg vial presentation (e.g., volume).

The approach to setting acceptance criteria for each quality attribute in the ABP 654 finished product specification included manufacturing experience and knowledge of process capability and consistency, experience with the analytical procedures and knowledge of the method capabilities and dataset consisting of analytical test results. The proposed acceptance limits are considered acceptable.

It has been appropriately demonstrated that the polysorbate 80 concentration remains stable during the shelf-life of the finished product.

Otherwise, sufficient panel of quality attributes was proposed for release and shelf-life specifications of ABP 654 finished product presentations and adequate justifications for specifications were provided.

The applicant has performed risk assessments of elemental and nitrosamine impurities. An elemental impurities risk assessment was performed in accordance with ICH Q3D and the results demonstrated that the elemental impurity levels in ABP 654 finished product presentations are well below 30% of the permitted daily exposure (PDE) limit. Conclusively, no additional controls are required. The risk assessment regarding nitrosamine impurities conducted in accordance with principles from ICH Q9 and M7 was designed to evaluate all potential sources of nitrosamine formation or contamination during manufacture of the finished products including the active substance, excipients, manufacturing process, equipment, utilities, and packaging. Overall, no significant risk of elemental or nitrosamine impurities were identified. It can be agreed that residual peroxide levels (less than 0.5 ppm) originated from the decontamination of isolator technology pose no toxicological concern. Other process- and product-related impurities are not introduced during the manufacturing process of ABP 654 finished product. Based on the information provided it is accepted that no risk was identified on the possible presence of nitrosamine impurities in the finished product. Therefore, no additional control measures are deemed necessary.

Analytical methods

The majority of methods are used to control both the active substance and finished product. Most of the methods, were based on respective Ph. Eur. monograph. Other in-house methods have been appropriately validated according to the principles of ICH Q2 (R1) guideline and are confirmed to be suitable for their intended use. Summary of validation of non-compendial methods have been provided.

The analytical methods used have been adequately described and non-compendial methods appropriately validated in accordance with ICH guidelines.

Batch analysis

Batch analysis data were provided for three consecutive batches of each presentation (commercial scale). All batches met the acceptance criteria of release in place at the time indicating adequate batch-to-batch consistency and controlled manufacturing process.

Reference materials

Refer to discussion in the active substance section.

Container closure

Specifications for primary and secondary container closure systems have been provided and the used methods of analysis are Ph.Eur. or ISO 9626 and ISO 7864 compliant. Compatibility of the primary container closure components with the ABP 654 finished product presentations and suitability of the container closure system was addressed during pharmaceutical development and confirmed by container closure integrity and stability tests.

2.4.3.4. Stability of the product

A shelf-life of 36 months is proposed for the 45 mg and 90 mg PFS presentations, and a shelf-life of 24 months is proposed for the 45 mg vial and 130 mg vial presentations stored at the recommended storage condition of 5°C. Additionally to enhance convenience, storage for up to 30 days at up to 30°C is proposed for PFS and 45 mg vial presentations. The provided stability data support the proposed shelf-lives at the recommended storage condition for ABP 654 finished product.

The applicant has designed the finished product stability programs following ICH Q1A and ICH Q5C guidelines. The provided stability data support the proposed shelf-lives at the recommended storage condition. To evaluate the shelf-life of the finished product, a statistical approach as mentioned in ICH Q1E guideline was followed.

The applicant has provided stability data at the long-term storage condition (2°C-8°C referred to as 5°C), at the accelerated storage condition [25°C (only for PFS) or 30°C] and at stressed storage condition (40°C). Samples stored at the recommended storage condition met the stability acceptance criteria.

The parameters tested are the same as for release. Samples stored at the recommended storage condition met the stability acceptance criteria for all presentations.

To support storage for 30 days at up to 30°C for 45mg and 90 mg PFS presentations, stability studies were performed. The currently available data remain within the stability specification. To enhance convenience and facilitate dosing, storage for up to 30 days at up to 30°C is also proposed for the 45 mg vial.

Photostability and transportation studies were performed to assess the finished product quality under conditions that may be experienced during transportation, storage, handling, and use. The secondary packaging (carton) employed in the photostability study is stated to be representative of the intended commercial packaging. Overall, it can be concluded that ABP 654 finished product remains stable under worst-case conditions that may be encountered during transport, storage, handling, and use, and the secondary packaging provides adequate protection from photodegradation.

Furthermore, temperature cycling studies were conducted to assess the potential impact on product quality if the finished product encounters temperatures outside the recommended storage condition.

The applicant concluded that temporary temperature fluctuations do not have an adverse impact on product quality, which is supported.

The proposed in-use storage times are based on compatibility studies performed only with ABP 654 vial presentations These studies showed compatibility for 24 hours when stored at room temperature.

Post-approval stability protocol

A post-approval stability protocol has been provided for all ABP 654 finished product presentations. The provided protocol is considered acceptable, but the stability acceptance criteria have been aligned during the procedure with the finally agreed commercial specification.

2.4.3.5. Comparability exercise for finished medicinal drug product

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. ABP 654, ustekinumab (EU) and ustekinumab (US) have been compared in the similarity tests. Comparability studies between ustekinumab (US) and (EU) have not been presented and the similarity is assessed between ABP 654 and ustekinumab (EU). ABP 654 has the same formulations, dosage forms, presentations, and product strengths as the reference product. The presentations for ABP 654 and ustekinumab reference product are: 45 mg (0.5 mL) in PFS (SC); 90 mg (1.0 mL) in PFS (SC); 45 mg (0.5 mL) in vial (SC); 130 mg (26 mL) in vial (IV).

All ABP 654 PFS FP and all reference product batches used in the clinical studies (20190230 and 20190232) are included in the similarity assessment. The batches reflected a range of expiration dates and product ages. Clinical studies 20190230 and 20190232 included the use of only the PFS presentations. Batches of vial presentations were not used in clinical studies. The 45 mg vial has the same formulation, dosage, and recommended administration as the 45 mg PFS presentation. The 130 mg vial has the same AS but different formulation and administration route compared to PFS presentations. Comparability at quality level between SC PFS presentations and 130 mg vial (IV) has been demonstrated. Hence, the FP material used in the analytical biosimilarity studies is considered representative of the material used in clinical trials.

Similarity data were generated using (1) side-by-side testing, (2) independent testing, and/or (3) age-dependent testing.

Batch data or age-adjusted batch data (for QAs where a change over time was observed when stored at the recommended storage condition) were presented, including calculation of mean and SD and analysis of the spread of the underlying distribution from quantitative analyses compared to quality range and min-max range. Differences have been highlighted and discussed. Tabular and graphical presentations allow a clear comparison of ABP 654 to reference product. In addition, sufficient raw data has been provided to allow assessment of biosimilarity independently of statistical approach chosen. The overall approaches used for establishment of the biosimilarity assessment criteria are considered acceptable.

The comparative testing included analysis of biological activity, primary structure, higher order structure, particles and aggregates, product-related substances and impurities, general properties and thermal stability and degradation studies. Appropriate analytical methods have been utilised to ensure an understanding of the ustekinumab (EU) product profile and the ABP 654 product developed.

Table 1 shows a summary of the critical evaluation of biosimilarity.

Table 1. Summary of biosimilarity assessment

Molecular parameter	Attribute	Methods	Key findings, conclusions
Biological activity	Inhibition of IL-23-mediated signalling	Cell-based reporter gene bioassay	Similar relative inhibition of IL-23-mediated signalling.
	IL-23 receptor-ligand binding	Bead-based luminescence proximity assay	Similar binding.
	Lack of binding to receptor-bound IL-23 on cell surface	Flow cytometry	Similar lack of binding to IL-23 captured by its receptor on the cell surface.
	IL-23 binding kinetics and affinity	Surface plasmon resonance (SPR)	Similar binding kinetics and affinity results.
	Inhibition of IL-12-mediated signalling	Cell-based reporter gene bioassay	Similar relative inhibition of IL-12-mediated signalling.
	IL-12 receptor-ligand binding	Bead-based luminescence proximity assay	Similar binding.
	Lack of binding to receptor-bound IL-12 on cell surface	Flow cytometry	Similar lack of binding to IL-23 captured by its receptor on the cell surface.
	IL-12 binding kinetics and affinity	SPR	Similar binding kinetics and affinity results.
	Binding specificity against IL-6, IL-35, and IL-39	SPR	The similar lack of binding.
	FcRn binding	Bead-based luminescent proximity assay	Minor differences (max 4%) both above and below ustekinumab (EU) quality range.
	FcγRIa, FcγRIIa (131R), FcγRIIb, FcγRIIIb and FcγRIIIa (158V) Binding	SPR	FcγRIa, FcγRIIa (131R), FcγRIIb binding results are similar for ABP 654 and ustekinumab (EU). ABP 654 has slightly lower FcγRIIIb binding compared to ustekinumab (EU). ABP 654 has lower FcγRIIIa (158V) binding compared to ustekinumab (EU).
	C1q binding	Direct binding ELISA method	Similar binding.

	Lack of ADCC /ADCP /CDC activity	ADCC/ADCP: Effector cell assay CDC: basal cell death assay	Similar lack of ADCC / ADCP / CDC activity.
Primary structure	Amino acid sequence/molecular mass	Intact molecular mass	The observed molecular masses for ABP 654 and ustekinumab (EU) were shown to be similar and all within 100 ppm of their theoretical masses. The deconvoluted mass profiles for both products are visually similar for the main peaks, with some differences attributed to glycosylation profile and C-terminal lysine level. LC-MS/MS fragmentation and similarity to theoretical sequence has been demonstrated in S.3.
	Amino acid sequence/molecular mass	Reduced and deglycosylated molecular mass	The major peaks correspond to the expected theoretical masses of HC and LC. HC with C-terminal lysine is observed in ustekinumab (EU) but not in ABP 654.
	Amino acid sequence/molecular mass	Reduced peptide map	The observed tryptic peptide masses were similar and within 100 ppm of their theoretical masses. The peptide map profiles were visually similar with minor differences primarily attributed to glycosylation profile (e.g. type of sialic acid) and C-terminal lysine differences. Some minor differences were observed in post-translational modification levels, that are not considered clinically significant due to low levels.
	Disulfide structure	Non-reduced peptide map	ABP 654 has the same disulfide structure compared to ustekinumab (EU).
	Free sulfhydryl	Ellman’s reagent	ABP 654 and ustekinumab (EU) can be considered similar for total free sulfhydryl content.
	Glycan map analysis	HILIC HPLC	High mannose: ~2.5% higher level in ABP 654 Sialylation: ~3% higher level in ABP 654 Afucosylation: <3% lower level in ABP 654

			β-Galactosylation: ~5% higher level in ABP 654 α-Galactosylation: Ustekinumab contains <5% α-galactoses (1.7-4.9%). ABP 654 does not contain α-galactosylated glycans. The glycan map profiles of ABP 654 and ustekinumab (EU) were observed to be visually similar, with some new and missing species detected for ABP 654 due to the differences in NANA-containing glycans for ABP 654 and NGNA-containing glycans for ustekinumab (EU) resulting from the difference in the production cell line.
	Extinction coefficient	amino acid analysis	The extinction coefficients were determined experimentally to be similar (ABP 654 1.46 vs. ustekinumab 1.40).
	Isoelectric point	Capillary isoelectric focusing (cIEF)	The cIEF profiles were found similar, except for the significantly reduced basic peaks levels in ABP 654 due to extensive C-terminal lysine processing in ABP 654. Differences in C-terminal lysine are not expected to impact biological function.
Higher order structure	Secondary structure for finished product (PFS) and active substance	Fourier-transform infrared spectroscopy (FTIR)	The secondary and tertiary structures were similar and similar thermal stability was demonstrated.
	Secondary structure for finished product (130 mg vial)	Far UV circular dichroism (CD)	
	Tertiary structure	Near UV CD	
	Thermal stability	Differential scanning calorimetry (DSC)	
Particles and Aggregates	Subvisible particles	HIAC, micro-flow imaging (MFI)	ABP 654 generally has lower levels of particles in PFS presentations and higher level of particles in 130 mg vial. The subvisible particle levels in both products comply with the compendial limits, thus the differences are not expected to be clinically significant.

	Submicron particles	Dynamic light scattering (DLS)	Similar main peaks.
	Aggregates	Sedimentation velocity analytical centrifugation (SV-AUC)	Profiles and monomer and HMW content were similar
		SE-HPLC-LS	Molar masses for the monomer and HMW were similar. Light scattering profiles were similar with no new or missing peaks.
Product-related Substances and Impurities	Size variants	SE-UHPLC	The level of HMW was higher (<0.5% difference; 0.5-0.8% for ABP 654, 0.3-0.4% for ustekinumab (EU)) and main peak lower (<1% difference; 98.5-98.8% for ABP 654, ≥99.0% for ustekinumab (EU)) in ABP 654 compared to ustekinumab (EU).
		rCE-SDS	HC + LC in ABP 654 was below the quality range of reference product. The difference was <1%. LMW + MMW fragment levels were similar. The levels of both HMW and NGHC were both slightly (<1%) higher in ABP 654.
		nrCE-SDS	Slightly higher level of pre-peaks and lower level of main peak in ABP 654. The differences are <2%.
			Differences in size variants are all minor differences and have not shown to impact biological function related to the mechanism of action and are likely not to be clinically meaningful.
	Charge variants	CEX-HPLC	ABP 654 has 38% lower level of basic peaks (due to a lower level of unprocessed HC C-terminal lysine variants) and 27% higher level of acidic peaks (due to slightly higher level of sialic acid-containing species). The CEX-HPLC charge variants were characterised by carboxypeptidase B treatment, with and without deglycosylation as well as by reduced peptide map, glycan map, inhibition of IL-

			23 signalling, and IL-23 binding. Enriched CEX-HPLC acidic peaks, main peak, and basic peaks fractions from ustekinumab (EU) and ABP 654 contained the same post-translational modifications and showed similar biological activities, except for a lower level of inhibition of IL-23 signalling for the ABP 654 basic fraction (77% ABP 654 vs. 97% ustekinumab (EU), only one batch each was tested). The differences between ABP 654 and ustekinumab (EU) in the levels of acidic and basic peaks are not considered clinically meaningful.
Thermal Stability and Degradation	Forced Degradation at 50°C		Testing was carried out for size variants using SE-UHPLC, rCE-SDS and nrCE-SDS, charge variants using CEX-HPLC, post-translational modifications by reduced peptide map and biological activity by IL-23 receptor-ligand binding and inhibition of IL-23-mediated signalling assay methods. The observed differences in the degradation profiles are considered minor and not clinically meaningful. The presented degradation profiles support the claim for biosimilarity.
	Stressed Stability at 40°C and Accelerated Stability at 30°C		
	Photostability		
General properties	Protein concentration	Spectrophotometric	Similar protein concentration. The target protein concentration was changed from 90 mg/ml to 92 mg/ml (for the 0.5 mL PFS, 1 mL PFS, and 45 mg vial) during development to match with the measured protein concentration of the reference product
	Volume	Gravimetric	Similar volume.

Similarity between ABP 654 and ustekinumab (EU) has been demonstrated for the following physicochemical and biological properties:

- Primary structure (including glycosylation)
- Higher order structure
- Particles and aggregates
- Product-related substances and impurities
- Thermal stability and degradation studies

- General properties including protein concentration and volume
- Biological activity:
  - Inhibition of IL-12 and IL-23 -mediated signalling
  - IL-23 and IL-12 Receptor-ligand Binding
  - Lack of Binding to Receptor-bound IL-23 and IL-12 on Cell Surface
  - IL-23 and IL-12 Binding Kinetics and Affinity
  - Binding Specificity Against IL-6, IL-35, and IL-39 (lack of binding)
  - FcRn Binding
  - FcγRIa, FcγRIIa (131R), FcγRIIb, FcγRIIIb and FcγRIIIa (158V) Binding
  - C1q Binding
  - Lack of ADCC / ADCP / CDC Activity.

The totality of the presented biological and physiochemical data supports the claim of biosimilarity for ABP 654 and ustekinumab (EU). Most biological activities relevant to the primary mechanism of action, including IL-23 receptor ligand binding, IL-12 receptor ligand binding and inhibition of IL-12 and IL-23 mediated signalling are similar. A lower binding activity of ABP 654 to FcγRIIIa (158V) and FcγRIIIb compared to ustekinumab (EU) was observed and attributed to lower levels for afucosylated glycans in ABP 654. The difference is considered to result from the cell line change and not considered to be clinically meaningful based on the similar lack of ADCC activity for both ABP 654 and ustekinumab.

Differences were also observed in charge variant levels (38% lower level of basic peaks and 27% higher level of acidic peaks). Lower level of basic peaks in ABP 654 is primarily due to a lower level of unprocessed HC C-terminal lysine variants. Higher acidic peak level is due to lower level of basic peaks and slightly higher level of sialic acid-containing species in ABP 654. C-terminal lysine variants and sialylation are both non-critical quality attributes. The differences between ABP 654 and ustekinumab (EU) 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 glycan map analysis, post-translational modifications, basic peaks in cIEF profiles and size variants in ABP 654 compared to reference product. All observed differences are well discussed and justified, are not considered to be clinically meaningful, and are unlikely to have an impact on PK, efficacy, or safety.

In conclusion, the presented quality data support the biosimilarity of ABP 654 to EU-approved ustekinumab (Stelara EU).

2.4.3.6. Medical device issues

N.A.

2.4.3.7. Adventitious agents

The risk of microbial and mycoplasma contamination is adequately addressed. MCB, WCB, and LIVCA are sterile and free of mycoplasma and detectable viruses except for A-type retrovirus-like particles expected for CHO cells. Overall, the safety evaluation of cell banks is performed adequately and in line with ICH Q5A. All unprocessed bulk batches tested met the acceptance criteria and showed no mycoplasma or viruses and very low level of bioburden (0 CFU/10 mL).

Viral clearance studies were conducted in accordance with ICH Q5A.

Overall, the risk of microbial, mycoplasma and viral contamination is adequately addressed, and appropriate safety programme is in place to prevent contaminations and maintain microbial control during manufacturing process of ABP 654.

The assessment of TSE risk has been performed on all raw materials used from transfection of the cell line through fill and finish of the finished product. No material of animal or human origin is used in the manufacturing of ABP 654, except the CHO-derived ABP 654 production cell line. One material, obtained from a fermentation process including materials of animal origin, was used as a media additive in MCB and WCB generation. The origin and use of this material were clearly described and appropriate Certificates of Suitability were provided. This material is not used in the routine manufacturing. The risk of TSE associated with ABP 654 is considered negligible.

2.4.3.8. GMO

N.A.

2.4.4. Discussion on chemical, pharmaceutical and biological aspects

Overall, the provided Module 3 for ABP 654 is of good quality, and relevant aspects of ABP 654 manufacturing are appropriately addressed. The presented quality data support the biosimilarity of ABP 654 to EU-approved ustekinumab (Stelara EU). No major objections related to Module 3 were identified. All other concerns identified during assessment have been appropriately addressed. Therefore, a positive opinion on the quality part can be recommended to the CHMP. However, data provided for the filter used in the 130 mg vial formulation step are requested to be included in the consolidated eCTD at the end of the procedure.

2.4.5. Conclusions on chemical, pharmaceutical and biological aspects

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

2.5. Non-clinical aspects

2.5.1. Introduction

The active substance of Wezenla and Stelara is ustekinumab, humanised immunoglobulin isotype class G subclass 1 kappa (IgG1κ) monoclonal antibody. It binds to the common p40 subunit of the heterodimeric cytokines IL-23 (composed of p19 and p40 subunits) and IL-12 (composed of p35 and p40 subunits). The binding disrupts the interaction of these cytokines with a shared cell surface receptor, IL-12 receptor subunit beta 1 (IL-12Rβ1), thereby preventing IL-23- and IL-12-mediated signalling.

ABP 654 is manufactured in a glyco-engineered Chinese hamster ovary (CHO) cell line whereas Stelara is manufactured in a murine myeloma (Sp2/0) cell line.

The demonstration of biosimilarity of ABP 654 to Stelara (EU) is based on the totality of evidence data of analytical, nonclinical, and clinical comparative studies to demonstrate structural and functional similarity.

The non-clinical package consists of *in vitro* biological activity studies, discussed under quality aspects, and briefly summarised under nonclinical aspects. Four *in vitro* pharmacology studies were also conducted to evaluate similar functional activity of ABP 654 and Stelara relevant to the mechanism of action (MOA) as part of the totality of evidence to support the functional similarity. These *in vitro* pharmacology studies assessed inhibition of IL-23-induced signal transducer and activator of transcription (STAT)3 signalling, IL-12-induced STAT4 signalling, IL-23-induced interferon gamma (IFN-γ) release, and IL-12-induced IFN-γ release in peripheral blood mononuclear cells (PBMCs) from healthy human donors.

No comparative *in vivo* -pharmacology, secondary pharmacodynamic (PD), safety pharmacology or PD drug interaction studies nor *in vivo* pharmacokinetic (PK), toxicokinetic (TK) or toxicology studies were conducted.

2.5.2. Pharmacology

2.5.2.1. Primary pharmacodynamic studies

ABP 654 has the same amino acid sequence, formulations, dosage forms, and product strengths with Stelara. The most relevant difference between ABP 654 and Stelara is that APB 654 is manufactured in CHO cell line whereas Stelara is manufactured in murine myeloma (Sp2/0) cell line, and this change has led to some differences in glycans between ABP 654 and ustekinumab (EU). ABP 654 does not contain detectable levels of non-human glycans, such as N-glycolylneuraminic acid (NGNA) and alpha-galactosylation.

Further differences were observed in the levels of high mannose. Compared to the reference medicinal product, ABP 654 shows an increase in high mannose. No difference in the PK profile was observed in clinical study 20190230.

Assays address inhibition of IL-23 and IL-12 mediated signalling, IL-23 and IL-12 receptor-ligand binding, lack of binding to receptor-bound IL-23 and IL-12 on a cell surface, binding kinetics and affinity for IL-23 and IL-12, binding specificity to cytokines related to IL-23 and IL-12, lack of antibody dependent cell mediated cytotoxicity (ADCC), complement dependent cytotoxicity (CDC), and antibody dependent cell mediated cytotoxicity (ADCP) activity, binding to neonatal Fc receptor (FcRn) and first sub-component of complement (C1q), and binding to Fc gamma receptors (FcγRIa, IIa, IIb, IIIa, and IIIb).

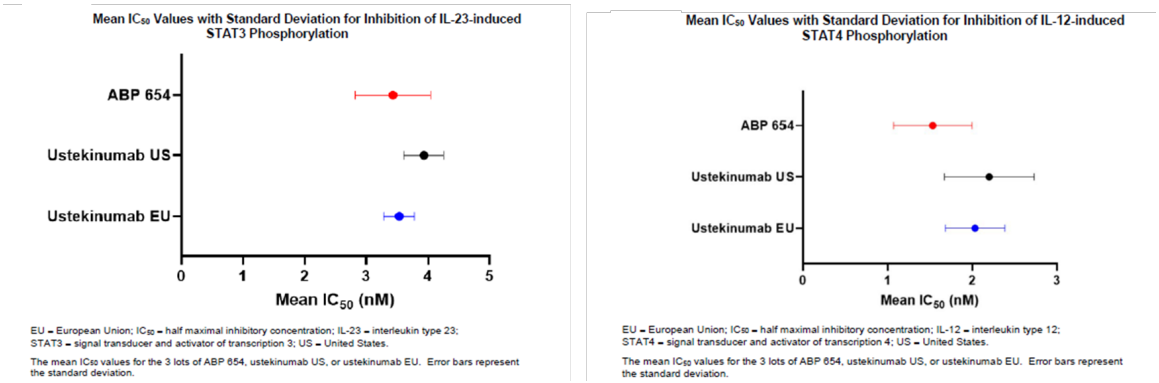
The *in vitro* pharmacology studies to investigate the functional activity of ABP 654 compared to Stelara EU/US assessed inhibition of IL-23-induced STAT-3 signalling, IL-12-induced STAT-4 signalling, IL-23 induced IFN-γ release and IL-12-induced IFN-γ release in activated T-cells from healthy human donors Human peripheral blood mononuclear cells isolated from one donor were used in the experiments.

The formulation of the ABP 654 that was used during the pharmacology programme is representative to ABP 654 clinical SC formulation and identical with RMP Stelara SC formulation. The IV formulation of ABP 654 has a slightly different formulation and is also identical with RMP Stelara IV formulation however has not been included to the pharmacology studies.

The inhibition of the STAT-3 and STAT-4 phosphorylation in activated T cells were investigated by using flow cytometry in three different batches of ABP 654, Stelara EU and Stelara US. The concentration range for tested materials was 100nM to 5pM in 3-fold dilutions. ABP 654 showed slightly lower IC_{50}-values of IL-23 inhibited STAT-3 (2.9 - 4.1) in comparison to Stelara EU/US (3.3 - 3.8) with higher standard deviation (0.6 vs 0.3) and lower IC_{50}-values of IL-12 inhibited STAT-4 phosphorylation (1.0 - 1.8) in comparison to Stelara EU/US (1.7 - 2.4) with slightly higher standard deviation (0.5 vs 0.4) (Figure 5). The supportive data from an IL-12-induced IFN-γ production assay

demonstrated that ABP 654 is similar to ustekinumab (EU) for inhibition of IL-12-induced IFN-γ production. ABP 654 is within the ustekinumab (EU) quality range, and also in the min-max range – except for one lot.

Figure 1. Mean IC_{50} values with standard deviation for inhibition of IL-23 induced STAT-3 and IL-12 induced STAT-4 phosphorylation.



The inhibition of IL-23 and IL-12 induced release of IFN-γ was assessed for ABP 654, Stelara EU and Stelara US in 3 pairwise comparison experiments using one batch of each product. The standard deviation presented is associated with the 3 replicate experiments and does not represent the batch variability but the test conditions. The concentration range for tested materials was 30 - 0.00384 µg/ml (155322) and 90 - 0.0012 µg/ml (155353) in 5-fold dilutions. The homogenous time resolved fluorescence (HTRF) kit was used to measure IFN-γ levels (human IFN-γ kit).

The % relative potency was similar for ABP 654, Stelara (EU) and Stelara (US). The summaries of pairwise comparisons are represented in the Table 8 and Table 9.

Table 2. Summary of pairwise comparison on ABP 654, Stelara (EU) and Stelara (US) in inhibition of IL-23 induced IFN-γ release assay.

		Relative Potency (%)					
Test Article		Similarity Assay 1	Similarity Assay 2	Similarity Assay 3	Average	SD	%CV
ABP versus EU	ABP 0010485699	98.7	91.9	115.4	102.0	12	12
	EU JES0TML	95.4	110.1	94.6	100.0	9	9
ABP versus US	ABP 0010485699	84.9	101.5	82.2	89.5	10	12
	US JCS0WMD	94.9	86.2	90.4	90.5	4	5
EU versus US	EU JES0TML	87.3	89.2	91.0	89.2	2	2
	US JCS0WMD	81.1	110.4	104.8	98.8	16	16

CV = coefficient of variation; EU = European/Europe; IFN-γ = interferon gamma; IL-23 = interleukin-23; PBMC = peripheral blood mononuclear cell; US = United States.
Source: ELN ID 20211207-00065

Table 3. Summary of pairwise comparison on ABP 654, Stelara (EU) and Stelara (US) in inhibition of IL-12 induced IFN-γ release assay.

		Relative Potency to Plate Control									
Test Article		Similarity Assay 1	Similarity Assay 2	Similarity Assay 3	Similarity Assay 4	Similarity Assay 5	Similarity Assay 6	Average	SD	%CV	Total Valid Runs of Pairwise Comparison
ABP versus EU	ABP 0010485699	99.1%	116.4%	—	87.0%	98.9%	—	100.4%	12%	12%	4
	EU JES0TML	86.4%	92.9%	—	87.7%	91.8%	—	89.7%	3%	3%	
ABP versus US	ABP 0010485699	84.4%	88.2%	111.2%	87.1%	—	—	92.7%	12%	13%	4
	US JCS0WMD	81.3%	83.5%	101.5%	91.2%	—	—	89.4%	9%	10%	
EU versus US	EU JES0TML	110.7%	—	—	—	105.5%	111.5%	109.2%	3%	3%	3
	US JCS0WMD	107.4%	—	—	—	97.5%	118.5%	107.8%	11%	10%	

— = not applicable; CV = coefficient of variation; EU = European/Europe; IFN-γ = interferon gamma; IL-12 = interleukin-12; PBMC = peripheral blood mononuclear cell; US = United States.
Source: ELN ID 20220118-00020

No *in vivo* non-clinical pharmacology studies were conducted.

2.5.2.2. Secondary pharmacodynamic studies

No secondary PD studies were conducted.

2.5.2.3. Safety pharmacology programme

Safety pharmacology studies were not conducted.

2.5.2.4. Pharmacodynamic drug interactions

No PD drug interaction studies were conducted.

2.5.3. Pharmacokinetics

No comparative *in vivo* nonclinical PK/TK studies with ABP 654 and Stelara were conducted.

No ADME-studies, pharmacokinetic drug interaction studies or other pharmacokinetics studies were conducted.

2.5.4. Toxicology

2.5.4.1. Single dose toxicity

Comparative single-dose toxicity studies with ABP 654 and Stelara were not conducted.

2.5.4.2. Repeat dose toxicity

Comparative repeat-dose toxicity studies with ABP 654 and Stelara were not conducted.

2.5.4.3. Genotoxicity

Genotoxicity studies comparing ABP 654 and Stelara were not conducted.

2.5.4.4. Carcinogenicity

Carcinogenicity studies comparing ABP 654 and Stelara were not conducted.

2.5.4.5. Reproductive and developmental toxicity

Reproductive and developmental toxicity studies comparing ABP 654 and Stelara were not conducted.

2.5.4.6. Toxicokinetic data

Toxicokinetic studies comparing ABP 654 and Stelara were not conducted.

2.5.4.7. Local tolerance

Local tolerance studies comparing ABP 654 and Stelara were not conducted.

2.5.4.8. Other toxicity studies

No other toxicity studies were conducted.

2.5.5. Ecotoxicity/environmental risk assessment

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, ABP 654 is not expected to pose a risk to the environment.

2.5.6. Discussion on non-clinical aspects

Pharmacology

The non-clinical data package consisted of four *in vitro* pharmacology studies to evaluate similar functional activity of ABP 654 and Stelara relevant to the mechanism of action (MOA) as part of the totality of evidence to support the functional similarity. These *in vitro* pharmacology studies assess inhibition of IL-23- STAT3 signalling, IL-12-induced STAT4 signalling, IL-23-induced IFN-γ release, and IL-12-induced IFN-γ release in PBMCs from healthy human donors as agreed during CHMP scientific advice process (EMEA/H/SA/4328/1/2019/III). The CHMP noticed that the cells from only one donor were used in each assay. Hence, the CHMP agreed that the comparability results of functional activity could not biased by interindividual variability. The studies' design was endorsed by the CHMP.

No comparative *in vivo* pharmacology, secondary PD, safety pharmacology or PD drug interaction studies nor *in vivo* PK, TK or toxicology studies were conducted and are not required for biosimilars.

The amino acid sequence, formulations, dosage forms, presentations and product strengths of ABP 654 are identical to that of Stelara. However, ABP 654 is manufactured in glyco-engineered CHO cell line whereas reference product Stelara is manufactured in a murine myeloma (Sp2/0) cell line leading to some differences in glycans between ABP 654 and ustekinumab (EU). However, these differences are not expected to impact the clinical PK, safety or efficacy.

The formulation of the ABP 654 that was used during the pharmacology programme is fully representative to ABP 654 clinical SC formulation and identical with RMP Stelara SC formulation. The IV formulation of ABP 654 has a slightly different formulation and is also identical with RMP Stelara IV formulation. The IV formulation was not included in functional activity studies but was investigated in the biological activity studies. This is acceptable.

The demonstration of similar functional activity of ABP 654 and Stelara is overall adequate reflecting the main mechanism of action of Stelara supporting the claimed indication. The methods used were scientifically valid and suitable for the purpose.

Some similarity of ABP 654 to Stelara in their ability to inhibit IL-23 and IL-12 -mediated signalling was shown, however, the higher standard deviation suggests more variability in the potency of different batches in comparison to Stelara (EU). Similar phenomena were observed in biological similarity evaluation studies but not considered clinically significant (please see the Quality Section). For the inhibition of IL-12- induced STAT4 phosphorylation, it is noted that the mean IC_{50} values are lower for ABP 654 compared to the reference medicinal product: 1.5 ± 0.5 nM for ABP 654 and 2.0 ± 0.4 nM for Stelara (EU). The supportive data from an IL-12-induced IFN-γ production assay demonstrated that ABP 654 is similar to ustekinumab (EU) for inhibition of IL-12-induced IFN-γ production. ABP 654 is within the ustekinumab (EU) quality range, and also in the min-max range – except for one lot. Considering the supportive data provided, the CHMP agreed that ABP 654 is similar with regard to inhibition of IL-12-mediated signalling.

The number of representative batches was considered adequate for the assessment of IL-23 induced STAT3 signalling, and IL-12 induced STAT4 signalling but not for the IL- 23/12 induced IFN-γ release where only one representative batch of the DP was studied and inter-assay variability (SD) was high. Therefore, no solid conclusions can be made for these endpoints and the results presented for IFN-γ

release assays can be considered only as supportive data. Even if there are identified deficiencies in the PD data, the totality of the data together with the analytical similarity assessment and clinical PK studies suggest the biosimilarity of the ABP 654 and Stelara (EU). The NC PD data suggest some variability between batches of ABP 654 in their potency to inhibit especially IL-23 induced STAT-3 phosphorylation. This is not considered clinically significant as the clinical PK data show similarity for ABP 654 and Stelara (EU).

The concentration ranges used in the pharmacology studies were sufficient in demonstrating similar dose-dependent inhibition of IL-23 and IL-12 mediated signalling of ABP 654 and Stelara EU/US.

Pharmacokinetics

No non-clinical pharmacokinetic (PK) studies comparing ABP 654 and Stelara (ustekinumab) were conducted. This is acceptable for a biosimilar application.

Toxicology

No comparative toxicology studies have been conducted with ABP 654 and Stelara (ustekinumab). From the provided similarity exercise, no uncertainties arise which could be addressed in non-clinical *in vivo* toxicology studies. Observed differences in the analytical similarity exercise are small and do not preclude biosimilarity.

The approach is in line with the relevant guidelines for biosimilars (EMA "Guideline on similar biological medicinal products CHMP/437/04 Rev 1" and EMA "Guideline on similar biological medicinal products containing biotechnology-derived proteins as active substance: non-clinical and clinical issues EMEA/CHMP/BMWP/42832/2005 Rev1"), on basis that the *in vivo* studies animals for demonstrating biosimilarity are generally more insensitive than in *vitro* studies, and no differences were observed in comparative *in vitro* analysis on IL-23 and IL-12 receptor-ligand binding of ABP 654 and Stelara.

Labelling of ABP 654 is based on the product labelling for Stelara (ustekinumab) and addresses the following PK aspects based on human data:

- Concomitant use of immunosuppressants or corticosteroids did not appear to influence the safety or efficacy of ustekinumab,
- Ustekinumab crosses the placenta and has been detected in the serum of infants born to female patients treated with ustekinumab during pregnancy,
- Data from published literature suggests that ustekinumab is excreted in human breast milk in very small amounts,
- Distribution, elimination etc. was addressed in human subjects,
- CYP450 enzyme activities are not altered by ustekinumab.

Ecotoxicity/environmental risk assessment

The active substance is a natural substance, the use of which will not alter the concentration or distribution of the substance in the environment. Furthermore, ustekinumab is already used in existing marketed products and no significant increase in environmental exposure is anticipated.

Therefore, ABP 654 is not expected to pose a risk to the environment.

2.5.7. Conclusion on non-clinical aspects

The non-clinical *in vitro* functional activity data support the biosimilarity of ABP 654 in comparison to Stelara (EU).

Four *in vitro* pharmacology studies were conducted to evaluate similar functional activity of ABP 654 and Stelara relevant to the mode of action. inhibition of IL-23-induced signal transducer and activator of transcription (STAT)3 signalling, inhibition of IL-12-induced STAT4 signalling, inhibition of IL-23-induced interferon gamma (IFN-γ) release, and inhibition of IL-12-induced IFN-γ release. For the inhibition of IL-12- induced STAT4 phosphorylation, slight differences were observed. However, the CHMP agreed that ABP 654 is similar with regard to inhibition of IL-12-mediated signalling.

Overall, from a non-clinical perspective, Wezenla is biosimilar to Stelara.

2.6. Clinical aspects

2.6.1. Introduction

GCP aspects

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

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

- **Tabular overview of clinical studies**

Type of Study	Study Identifier	Objective(s) of the Study	Study Design and Type of Control	Test Product (s); Dosage Regimen; Route of Administration	Number Subjects Randomized / Analyzed for Safety	Healthy Subjects or Diagnosis of Subjects	Duration of Treatment	Study status; Type of Report/ Location
Study Reports of Patient PK and Initial Tolerability Study Reports (Module 5.3.3.2)								
PK similarity	20190230	Primary: PK similarity of ABP 654 relative to ustekinumab (US) and to ustekinumab (EU) Secondary: PK similarity of ustekinumab (US) relative to ustekinumab (EU); Safety, tolerability, and immunogenicity	Randomized, double-blind, single-dose, 3-arm, parallel group, stratified by gender and ethnicity (Japanese vs non-Japanese)	ABP 654, ustekinumab (US) , ustekinumab (EU); 90 mg SC injection, single dose	238/237[a]	Healthy subjects, 18 to 45 years of age; body weight ≥ 50 kg and ≤ 90 kg at screening; BMI 18.0 to 30.0 kg/m^2 for non-Japanese subjects; BMI 18.0 to 25.0 kg/m^2 for Japanese subjects	112 days	Complete, CSR/Module 5.3.3.1 (20190230)

Type of Study	Study Identifier	Objective(s) of the Study	Study Design and Type of Control	Test Product (s); Dosage Regimen; Route of Administration	Number Subjects Randomized / Analyzed for Safety	Healthy Subjects or Diagnosis of Subjects	Duration of Treatment	Study status; Type of Report/ Location
Study Reports of Controlled Clinical Studies Pertinent to the Claimed Indication (Module 5.3.5.1)								
Clinical similarity	20190232	Primary: Efficacy of ABP 654 compared with ustekinumab (EU) Secondary: safety and immunogenicity of ABP 654 compared with ustekinumab (EU)	Randomized, multicenter, double-blind, active-controlled study	ABP 654, ustekinumab (EU); 45 mg (baseline BW ≤ 100 kg) or 90 mg (baseline BW > 100 kg) SC injction on day 1, wk 4, wk 16, wk 28 and wk 40[b] At wk 28, subjects receiving ustekinumab re-randomized to continue ustekinumab or switch to ABP 654 At wk 28, subjects with PASI 50 response or better but less than PASI 75 response who did not dose intensify were re-randomized.	563/562	• Adult men and women, ≥ 18 years and ≤ 75 years of age, with stable moderate to severe Plaque psoriasis • BSA ≥ 10%, PASI ≥ 12, and sPGA ≥3 at screening and at baseline	52 weeks	Complete, CSR /Module 5.3.5.1 (20190232)

2.6.2. Clinical pharmacology

2.6.2.1. Pharmacokinetics

ABP 654 has been developed by the applicant as a biosimilar candidate Ustekinumab to the Stelara (ustekinumab, the proposed invented name is Wezenla).

Comparative PK data of ABP 654 has been generated in one PK similarity study in healthy adult subjects (study 20190230) 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 20190232).

Analytical methods

An MSD ECL method with mouse anti-ABP 654 monoclonal antibody for capture and ruthenium labelled mouse anti-ABP 654 monoclonal antibody was used for the quantitation of ustekinumab in patient serum samples. The method was fully validated by PPD according to validation plan and current guidance. The quantitation range was 20.0-32000 ng/ml.

Anti-drug antibodies were determined by an MSD-ECL method with acid dissociation of the complexes and incubation with Biotin-ABP 654 and Sulfo-Tag-ABP 654. A bridge forms between the Biotin-ABP 654 and Sulfo-Tag-ABP 654 molecules and this complex is bound to a blocked MSD-Streptavidin plate and detected by an electrochemiluminescent signal that is generated when voltage is applied. An anti-ABP 654 rabbit polyclonal antibody is used as positive control. In a 3-tiered approach the samples are first screened. Positive samples are confirmed by incubating with excess drug. Titre was determined for confirmed positive samples. The method was validated for cut points, intra- and inter-assay precision, sensitivity, Hook effect and selectivity. Haemolysis, lipaemia and bilirubinaemia had no effect on the detection of anti-ABP 654 antibodies. Equivalency between ABP 654, Stelara US, and Stelara EU, was demonstrated with 15 serum lots from normal healthy individuals and 14 serum lots from individuals with plaque psoriasis, spiked at the LPC and analysed in the confirmatory assay. Drug tolerance was demonstrated.

Neuralising antibodies were detected by an ECL immunoassay using an anti-ABP 654 rabbit polyclonal antibody as positive control. The assay was validated for assay cut point, intra- and inter assay precision, sensitivity, Hook effect, selectivity, and stability. Lipaemia and haemolysis did not interfere with detection of the neutralising antibodies. The drug tolerance for all tested PCs was demonstrated. Similar performance of the assay for ABP 654, Stelara EU and Stelara US was demonstrated.

PK similarity study in healthy adult subjects (20190230)

The study was a phase 1, randomised, double-blind, single-dose, 3-arm, parallel-group study in healthy subjects. The study was conducted at 3 centres in the US between 17 Nov 2020 and 16 June 2021.

The primary objective was to determine the PK similarity of ABP 654 (90 mg SC injection) compared with ustekinumab (US) and ustekinumab (EU). Secondary objectives were to determine PK similarity of ustekinumab (US) compared with ustekinumab (EU), and the safety, tolerability, and immunogenicity of ABP 654 in healthy adult subjects compared with ustekinumab (US) and ustekinumab (EU).

The eligibility criteria were acceptable and demographic and baseline characteristics were well-balanced between the 3 treatment-groups. The eligibility subjects were randomised in a ratio of 1:1:1 stratified by gender and ethnicity (Japanese vs non-Japanese) prior to dosing on Day 1.

Each subject received either a single 90 mg SC injection of ABP 654, ustekinumab (EU), or ustekinumab (US) on Day 1.

PK blood samples were collected at pre-dose, at 8, 24, 48, 144, 192, 240, 268, 480, 648, 816, 1152, 1320, 1656, 2328, and 2664 hours after end-of-injection. The ADA samples were collected at pre-dose, and at 240, 816, 2664 hours after drug administration.

- The primary PK parameters: AUC_{inf} and C_{max}
- The secondary PK parameters: AUC_{last}, t_{max}, $t_{½}$, CL/F and MRT

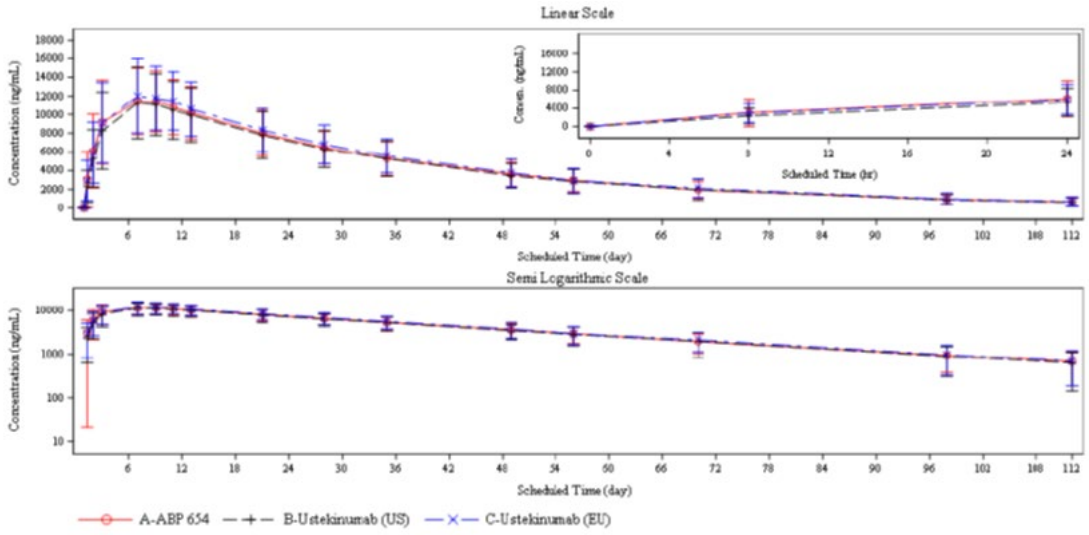
Overall, 37 (46.8%), 35 (44.3%), and 49 (61.3%) subjects in the ABP 654, ustekinumab (US), and ustekinumab (EU) treatment groups, respectively, experienced at least 1 important protocol deviation. The most common important protocol deviations were in the categories of "visit window/other" and "study procedures/safety assessment". One subject in the ustekinumab (US) treatment group had an important protocol deviation that resulted in subject exclusion from the PP PK parameter analysis set due to the presence of a disease which met a protocol exclusion criterion.

PK results

PK analysis sets included n = 78 in the ABP 654 group, n = 80 in the ustekinumab (EU) group and n = 79 in the ustekinumab (US) group. One subject (male) in the ustekinumab (EU) treatment group had an incorrect stratification for gender at randomisation.

In general, the geometric means (GM) of individual PK parameters were similar following a single SC injection of ABP 654, ustekinumab (US), and ustekinumab (EU). Exposure was similar across the 3 treatment groups. Peak concentrations were observed on average about 6 to 8 days following a single SC injection. After achieving peak concentrations, concentrations declined in a monophasic manner with a $t_{1/2}$ of about 21.9 to 23.9 days (see Figure 6 and Table 10). The estimated $t_{1/2}$ were consistent with the reported $t_{1/2}$ for ustekinumab. The mean AUC%Extrap was < 6% for each treatment group, confirming the adequacy of the duration of PK sampling for the evaluation of AUC_{inf}.

Figure 2. Mean ± SD PK concentrations over time by treatment (PK concentration analysis set)



EU = European Union; PK = pharmacokinetic; US = United States

Table 4. Summary of ABP654, ustekinumab (EU) and ustekinumab (US) key PK parameters (PK parameter analysis set)

Treatment	C_{max} (ng/mL) GM (Geo CV [%])	C_{last} (ng/mL) GM (Geo CV [%])	T_{max} (h) Median (range)	AUC_{last} (h*ng/mL) GM (Geo CV [%])	AUC_{inf} (h*ng/mL) GM (Geo CV [%])	$t_{1/2}$ (h) Mean (SD)	AUC%Extrap (%) Mean (SD)
ABP 654	11500 (36.1)	561 (107.3)	145.592 (24.05, 313.15)	10200000 (39.2)	10900000 (40.8)	588.110 (133.6061)	5.95 (6.252)
Ustekinumab (US)	11300 (33.8)	516 (155.8)	190.567 (48.00, 647.38)	9870000 (37.6)	10500000 (37.6)	556.998 (168.9308)	5.66 (6.304)
Ustekinumab (EU)	12100 (32.8)	541 (121.4)	188.550 (48.00, 649.12)	10800000 (33.5)	11500000 (34.8)	579.246 (148.8189)	5.41 (4.174)

AUC = area under the concentration-time curve; AUC%Extrap = percentage of AUC_{inf} due to extrapolation from the last quantifiable concentration observed to infinity; AUC_{inf} = AUC from time 0 extrapolated to infinity; AUC_{last} = AUC from time 0 to the last quantifiable concentration; C_{last} = last measurable serum concentration, C_{max} = maximum observed serum concentration; EU = European Union; Geo CV = geometric coefficient of variation; GM = geometric mean; $t_{1/2}$ = terminal elimination half-life; T_{max} = time at which C_{max} is observed; US = United States

Note: Geometric mean and Geo CV are only calculated for values > 0.

For the comparisons of ABP 654 to ustekinumab (US), ABP 654 to ustekinumab (EU), and ustekinumab (US) to ustekinumab (EU), the point estimates and 90% CIs of the GMRs were fully contained within the prespecified margin of 0.8 to 1.25 for both the primary PK endpoints (AUC_{inf} and C_{max}) and the secondary PK endpoint of AUC_{last} for the PK parameter analysis set. Therefore, PK similarity was demonstrated between ABP 654 and ustekinumab (US), ABP 654 and ustekinumab (EU), and ustekinumab (US) and ustekinumab (EU).

Table 5. Summary of statistical assessment of PK parameters (ANCOVA with baseline weight) (PK parameter analysis set)

Treatment and Comparison	AUC_{inf} (hr*ng/mL) LS Geometric Mean [n]	C_{max} (ng/mL) LS Geometric Mean [n]	AUC_{last} (hr*ng/mL) LS Geometric Mean [n]
ABP 654	10783692.1 [76]	11419.0 [78]	10137829.7 [78]
Ustekinumab (US)	10651782.5 [76]	11384.9 [79]	9975870.4 [79]
Ustekinumab (EU)	11482547.0 [77]	12081.5 [80]	10752507.0 [80]
Ratio of LS Geometric Means (90% CI)			
ABP 654 vs ustekinumab (US)	1.0124 (0.9289, 1.1034)	1.0030 (0.9314, 1.0801)	1.0162 (0.9358, 1.1035)
ABP 654 vs ustekinumab (EU)	0.9391 (0.8620, 1.0232)	0.9452 (0.8779, 1.0175)	0.9428 (0.8685, 1.0235)
Ustekinumab (US) vs ustekinumab (EU)	0.9276 (0.8514, 1.0107)	0.9423 (0.8755, 1.0143)	0.9278 (0.8549, 1.0069)

ANCOVA = analysis of covariance; AUC_{inf} = area under the concentration-time curve from time 0 extrapolated to infinity; AUC_{last} = area under the concentration-time curve from time 0 to the last quantifiable concentration; C_{max} = maximum observed drug concentration; EU = European Union; LS = least squares; PK = pharmacokinetic; US = United States

Note: Geometric LS mean, ratio of geometric LS means and 90% CI were estimated based on the ANCOVA model with a fixed effect for treatment and adjusting for baseline weight.

The partial AUCs were within the prespecified range of 0.80-1.25 (see Table 6).

Table 6. Summary of statistical assessment of PK parameters of partial AUC (ANCOVA with baseline weight) (PK parameter analysis set)

Treatment and Comparison	AUC_{Tmax_inf} (h*ng/mL) LS Geometric Mean [n]	AUC_{Tmax_last} (h*ng/mL) LS Geometric Mean [n]
ABP 654	9589122.1 [76]	8937943.4 [78]
Ustekinumab (US)	8992759.1 [76]	8271681.4 [79]
Ustekinumab (EU)	9728791.8 [75]	9032682.2 [78]
Ratio of LS Geometric Means (90% CI)		
ABP 654 vs ustekinumab (US)	1.0663 (0.9731,1.1684)	1.0805 (0.9878,1.1820)
ABP 654 vs ustekinumab (EU)	0.9856 (0.8993,1.0802)	0.9895 (0.9044,1.0826)
Ustekinumab (US) vs ustekinumab (EU)	0.9243 (0.8434,1.0131)	0.9158 (0.8372,1.0016)

AUC = area under the concentration-time curve; AUC_{Tmax_inf} = AUC from the median T_{max} to the concentration extrapolated to infinity; AUC_{Tmax_last} = AUC from the median T_{max} to the C_{last}; C_{last} = last reported concentration; EU = European Union; LS = least squares; PK = pharmacokinetic; T_{max} = time of maximum concentration; US = United States

Note: Geometric LS mean, ratio of geometric LS means, and 90% CI were estimated based on the ANCOVA model with a fixed effect for treatment and adjusting for baseline weight. AUC_{Tmax_last} was calculated from median T_{max} to C_{last} and $AUC_{Tmax\ inf}$ was calculated from median T_{max} to concentration extrapolated to infinity.

Clinical study in adult patients with moderate to severe plaque psoriasis (20190232)

Study 20190232 was a phase 3, multicentre, randomised, active-controlled, double-blind study evaluating the efficacy and safety of ABP 654 compared with ustekinumab (EU).

PK endpoint: Trough serum ABP 654 and ustekinumab concentrations at baseline on Day 1/week 0, pre-dose at weeks 4, 12, 28, 32, 40 and 52 (EoS).

PK results

From baseline to week 28, the geometric LS means of trough serum concentrations were similar between ABP 654 and ustekinumab treatment groups (see Table 5).

Table 7. Summary of PK trough concentrations (ng/ml)-through week 28 (safety analysis set)

Visit Statistic	ABP 654 (N = 280)	Ustekinumab (N = 282)
Week 4		
m	273	271
Geometric LS mean	2942.53	2727.13
Ratio of geometric LS mean (ABP 654/Ustekinumab)	1.0790	
90% CI for ratio of geometric LS mean	(0.9900, 1.1760)	
Week 12		
m	267	266
Geometric LS mean	1870.72	1628.28
Ratio of geometric LS mean (ABP 654/Ustekinumab)	1.1489	
90% CI for ratio of geometric LS mean	(1.0351, 1.2752)	
Week 28		
m	267	254
Geometric LS mean	608.38	539.67
Ratio of geometric LS mean (ABP 654/Ustekinumab)	1.1273	
90% CI for ratio of geometric LS mean	(1.0022, 1.2680)	

ANCOVA = analysis of covariance; LS = least squares; m = number of subjects with a non-zero concentration

Note: Lower limit of quantification was < 20.0 ng/mL. Pharmacokinetic concentrations below the lower limit of quantification were assigned a value of 0 and were excluded from the calculations of geometric LS mean, geometric mean ratio, and 90% CI (calculated only if m ≥ 5).

The geometric LS mean, ratio of geometric LS means, and 90% CI were estimated based on ANCOVA model adjusted for the actual stratification factors of prior biologic use for psoriasis, baseline body weight group, and geographic region.

The geometric LS means of trough serum concentrations were similar across treatment groups at the week 32, week 40, and week 52 time points (see Table 7).

Table 8. Summary of PK concentrations (ng/ml)- post week 28 (re-randomised safety analysis set)

Visit Statistic	ABP 654/ ABP 654 (N = 247)	Ustekinumab/ ABP 654 (N = 117)	Ustekinumab/ Ustekinumab (N = 116)
Week 32			
m	239	111	114
Geometric LS mean	3187.09	3063.98	3464.74
Ratio of geometric LS means[a]	0.9199	0.8843	
90% CI for ratio of geometric LS means[a]	(0.8398, 1.0075)	(0.7949, 0.9838)	
Week 40			
m	236	112	110
Geometric LS mean	635.14	529.65	635.77
Ratio of geometric LS means[a]	0.9990	0.8331	
90% CI for ratio of geometric LS means[a]	(0.8650, 1.1537)	(0.7048, 0.9848)	
Week 52			
m	239	112	109
Geometric LS mean	649.80	562.08	664.12
Ratio of geometric LS means[a]	0.9784	0.8463	
90% CI for ratio of geometric LS means[a]	(0.8481, 1.1288)	(0.7168, 0.9993)	

- = Not Available
ANCOVA = analysis of covariance; LS = least squares; m = number of subjects with a non-zero concentration
Note: Lower limit of quantification was < 20.0 ng/mL. Pharmacokinetic concentrations below the lower limit of quantification were assigned a value of 0 and were excluded from the calculations of geometric LS mean, geometric mean ratio, and 90% CI (calculated only if m ≥ 5).
The geometric LS mean, ratio of geometric LS means, and 90% CI were estimated based on ANCOVA model adjusted for the actual stratification factors of prior biologic use for psoriasis, baseline body weight group, and geographic region.
[a] For treatment group ABP 654/ABP 654 and Ustekinumab/ABP 654, ratio of geometric LS means was calculated by comparing ABP 654/ABP 654 vs Ustekinumab/Ustekinumab and Ustekinumab/ABP 654 vs Ustekinumab/Ustekinumab, respectively.

The geometric LS means of serum concentrations were similar between ABP 654 and ustekinumab treatment groups at the week 32 and week 52 time points (see Table 8).

Table 9. Summary of PK concentrations (ng/ml)- post week 28 (dose intensification subjects)

Visit Statistic	ABP 654 (N = 25)	Ustekinumab (N = 34)
Week 32		
m	24	33
Geometric LS mean	2436.45	2464.68
Ratio of geometric LS mean (ABP 654/Ustekinumab)	0.9885	
90% CI for ratio of geometric LS mean	(0.7598, 1.2862)	
Week 52		
m	25	33
Geometric LS mean	1047.23	1196.39
Ratio of geometric LS mean (ABP 654/Ustekinumab)	0.8753	
90% CI for ratio of geometric LS mean	(0.6061, 1.2642)	

- = Not Available
ANCOVA = analysis of covariance; LS = least squares; m = number of subjects with a non-zero concentration
Note: Lower limit of quantification was < 20.0 ng/mL. Pharmacokinetic concentrations below the lower limit of quantification were assigned a value of 0 and were excluded from the calculations of geometric LS mean, geometric mean ratio, and 90% CI (calculated only if m ≥ 5).
The geometric LS mean, ratio of geometric LS means, and 90% CI were estimated based on ANCOVA model adjusted for the actual stratification factors of prior biologic use for psoriasis, baseline body weight group, and geographic region.

2.6.2.2. Pharmacodynamics

Mechanism of action

Primary and secondary pharmacology

No data on PD has been provided. Validated PD markers do not exist for the efficacy of interleukin-23 (IL-23) and interleukin-12 (IL-12) antagonists.

2.6.3. Discussion on clinical pharmacology

Analytical methods

The MSD ECL methods for quantitation of ustekinumab was fully validated and found suitable for the purposes. The validated assay range was between 20.0 (LLOQ) to 32 000 (ULOQ) ng/mL. Therefore, taking into account the Cmax-s and trough concentrations the assay was sufficiently sensitive. Sample stability has been demonstrated up to 373 days at -20 °C and -80 °C.

In accordance with the Guideline on Immunogenicity assessment of biotechnology-derived therapeutic proteins (EMEA/CHMP/BMWP/14327/2006 Rev.1), the presence of ADA was evaluated using the recommended three-tiered approach: an initial screening assay to identify potentially ADA positive samples, a confirmation (specificity) assay based on competition with exogenously added ustekinumab, and a determination of the titre of ADA for confirmed positive samples. The assay was fully validated and 100 ng/ml ADAs could be detected in the presence of 50 µg/ml ustekinumab. The ustekinumab concentrations were consistently below this in both studies.

Neutralising anti-drug antibodies (NAb) against ABP 654 in human serum were detected using an electrochemiluminescent (ECL) immunoassay. This assay is not the standard cell-based assay, but an ECL assay using plates coated with biotinylated p40 monomer protein. This later assay format is considered to be more sensitive and more reliable. The neutralising antibody assay was also fully validated. This is acceptable.

PK similarity study in healthy adult subjects (20190230)

To detect potential PK differences between ABP 654, ustekinumab US, and ustekinumab EU, a single 90 mg SC injection was administered to healthy volunteers. The dose in the study was set as advised by the CHMP and consistent with the recommended dose for the treatment of adults with psoriasis. The applicant had requested also the scientific advice (EMEA/H/SA/43281/1/2019/III) in relation to the analyses (including endpoints and margins) and PK/ADA sampling timepoints. The proposed primary (i.e., AUC_{inf} and C_{max}) and secondary endpoints (i.e., AUC_{last}, t_{max}, $t_{1/2}$, CL/F and MRT) were acceptable by the CHMP (the PK parameters %AUCextrap and V_Z were also determined). The number and timing of PK sampling timepoints was thought to be sufficiently dense to adequately characterise the whole PK profile but should include daily sampling around t_{max} to provide reliable estimate of peak exposure. This advice was not followed. Nonetheless, this issue was not pursued, as the range of t_{max} is very large (i.e., from day 2 to day 28). In relation to the ADA sampling, the CHMP strongly recommended an increased frequency for measuring ADA to capture any possible immune mediated effects. Consequently, the applicant added one timepoint (i.e., day 35) in the ADA sampling timepoints (in addition to the initially proposed timepoints (days 1, 11 and 112). This is agreed by the CHMP.

None of the subjects had pre-dose ustekinumab concentrations. The study design was acceptable and there were no changes in the conduct of the study.

Almost all subjects' AUC_{last} was > 80% of the AUC_{inf} confirming that the duration of the PK sampling was adequate (i.e., long enough). In the ABP 654 group, one study subject's AUC_{last} was < 80% of the AUC_{inf}, in the ustekinumab (EU) n = 1 and in the ustekinumab (US) n = 2.

The 90% CIs of the GMRs for the primary PK endpoints AUC_{inf} and C_{max} (also for the AUC_{last}) were within the BE criteria of 0.80 to 1.25 in all comparisons of ABP 654 vs ustekinumab (EU), ABP 654 vs ustekinumab (US) and ustekinumab (US) vs ustekinumab (EU). Also, the secondary PK endpoints (i.e., t_{max}, $t_{½}$, CL/F and MRT) were similar between ABP654, ustekinumab (EU) and ustekinumab (US).

Regarding the application for the iv presentation of ABP 654 vial, the CHMP agreed that additional comparative PK study with the iv presentation of the reference product is not needed, and results obtained with the sc formulations can be extrapolated. Nevertheless, the concentration profiles after sc and iv formulation are rather different. The declining concentration phase after the peak concentration was considered to be independent of absorption and resembled what would be expected to see following iv administration. That is why CHMP recommended in its scientific advice to compare the late (after C_{max}) partial AUCs between ABP 654 and the reference product. The MAH was asked to compute the partial AUC ratio and corresponding 90% CIs.

In the response, the applicant provided the partial AUC GMRs with 90% CIs and the 90% CIs of the AUC GMRs were fully contained within the margin of 0.80 to 1.25 supporting the equivalence of these partial AUCs across treatment groups following peak concentrations and providing justification for extrapolation of the PK results obtained with the sc presentations to the iv presentations. This is agreed by the CHMP.

Subgroup analyses:

In the Japanese subgroup, the point estimate of geometric mean ratios was within 0.8-1.25. While the 90% CI was outside the 0.8-1.25 limit in all comparisons of ABP 654 vs ustekinumab (EU), the consistency of PK similarity in the Japanese subgroup is not a concern for the approval of ABP 654 as a biosimilar in EU.

Within the subgroup analyses in binding ADA negative subgroup, all comparisons between ABP 654 vs ustekinumab (US) and ustekinumab (US) vs (ustekinumab (EU) all 90% CIs of the GMRs were within BE range 0.80 to 1.25. In the ABP 654 vs ustekinumab (EU), the 90% CIs of GMRs in AUCs were below 1.00 indicating that the exposure to ustekinumab was higher with ustekinumab (EU) treatment than with ABP 654. The applicant was asked to provide an explanation for the differences in the exposure in ADA negative subjects between ABP 654 and ustekinumab (EU) group, and to specifically discuss whether this result could arise from different protein content in the batches. In the response, the applicant argued that the slightly higher protein content in the ustekinumab (EU) batch could have influenced the observed exposure results in ADA negative subjects, although the difference in protein content between used batches was less than 5%. The CHMP acknowledged the presented justification and was of the opinion that similarity in PK exposure between ABP 654 and ustekinumab (US and EU) as well as between ustekinumab (US) and ustekinumab (EU) was demonstrated in healthy subjects and comparative analytical similarity data demonstrated similarity between ABP 654 and Stelara supporting the totality of evidence biosimilarity.

Sensitivity analyses:

The sensitivity analyses explored whether the comparison of primary PK parameters between the products would change with or without adjustments to site, race, gender, and baseline weight which turned out not to be the case: in all comparisons, the 90% CIs of GMRs were within the BE range 0.80-1.25.

Clinical study in adult patients with moderate to severe plaque psoriasis (20190232)

The Phase 3 clinical study compared sc injections of ABP 654 and ustekinumab at doses of 45 mg or 90 mg administered on day 1, week 4, and week 16 followed by administration every 8 or 12 weeks through week 52. The results of Study 20190232 further supported the demonstration of PK similarity between ABP 654 and reference ustekinumab product. The ustekinumab source was EU. No additional PK parameters (i.e., C_{max}, T_{max}, $t_{1/2}$ or partial AUCs) were presented although the CHMP recommended in a scientific advice (EMEA/H/SA/4328/1/2019/III). The applicant only presented the C_{trough} values at different weeks. However, the CHMP considered the data provided sufficient.

The trough concentrations were comparable at different timepoints between ABP 654 and ustekinumab. From baseline to week 28, the geometric LS means of trough serum concentrations generally were within a narrow 0.8 – 1.25 range.

Other issues

No clinical studies in special populations and no *in vitro* or *in vivo* drug-drug interaction studies were conducted with the ABP 654 and this is acceptable.

The SmPC for ABP 654 Section 5.2 "Pharmacokinetic properties" is similar to that of Stelara.

No data on PD have been provided. Validated PD markers do not exist for the efficacy of interleukin-23 (IL-23) and interleukin-12 (IL-12) antagonists. Since this is a biosimilar application, the secondary pharmacology does not have to be characterised anew.

2.6.4. Conclusions on clinical pharmacology

Pharmacokinetics and immunogenicity of ABP 654 and the reference product(s) were investigated with state-of-art analytical methods in a single dose study. The primary PK endpoints were within predefined limits. Additional PK data from a Phase 3 study supported biosimilarity. Therefore, from a clinical pharmacology perspective, ABP 654 is considered biosimilar to EU-sourced reference product.

2.6.5. Clinical efficacy

In order to demonstrate similarity in efficacy between ABP 654 and the reference product, Stelara (EU) (also referred to as Ustekinumab (EU)), a randomised, double-blind, active-controlled clinical Phase III study (Study 20190232) was conducted in adult patient with moderate to severe chronic plaque-type psoriasis (table 10).

Table 10. Description of the comparative clinical study

Study ID	No. of Study Centres Locations	Study Start Completion Date Total Enrolment/ Enrolment Goal	Study Design Control Type	Study and Control Drugs, Dose, Route, and Regimen[a]	Study Objectives	No. Subjects by Group Entered/ Completed	Study Duration	No. M/F Median Age (Range)	Key Inclusion Criteria	Efficacy Endpoints
Study Reports of Controlled Clinical Studies Pertinent to the Claimed Indications										
Study 20190232	84 Poland, Germany, Estonia, Latvia, Lithuania, Hungary, Canada, and the United States	11 November 2020 (start) 03 June 2022 (completion) 563/542	Randomised, multicentre, double-blind, active-controlled, multiple-dose study	ABP 654 or ustekinumab (EU); 45 mg (baseline BW ≤ 100 kg) or 90 mg (baseline BW > 100 kg) SC on day 1, wk 4, wk 16, wk 28 and wk 40[a] At wk 28, subjects receiving ustekinumab re-randomised to continue ustekinumab or switch to ABP 654[b]	Primary: Efficacy of ABP 654 compared with Stelara (ustekinumab) Secondary: safety and immunogenicity of ABP 654 compared with Stelara (ustekinumab)	ABP 654: 281/16 Ustekinumab: 282/10	Up to 52 wks[c]	368/195 44.4 yrs (18 to 75 yrs)	• Men and women ≥ 18 years and ≤ 75 years of age • Stable moderate to severe Ps for at least 6 months • Baseline score of PASI ≥ 12, involvement of ≥ 10% BSA, and sPGA ≥ 3 at screening and at baseline	Primary: PASI percent improvement from baseline to wk 12 Secondary: • PASI percent improvement at other timepoints • PASI 75 response throughout the study • PASI 100 response throughout the study • sPGA responses (0/1) at wk 12 and wk 52 • BSA change from baseline at wk 12 and wk 52

BSA = body surface area; BW = body weight; EU = European Union; M/F = male/female; PASI = Psoriasis Area and Severity Index; PASI 50/75 = ≥ 50%/75% improvement in PASI; Ps = plaque psoriasis; SC = subcutaneous; sPGA = Static Physician's Global Assessment; wk(s) = week(s); yrs = years

[a] For subjects with PASI 50 response or better but less than PASI 75 response at week 28, dosing frequency may have been increased to every 8 weeks based on investigator discretion (ie, dosing at wks 28, 36, and 44).

[b] For subjects with a PASI 75 response or better and for subjects with PASI 50 response or better but less than PASI 75 response at week 28 who did not dose intensify [c] Does not include screening period.

2.6.5.1. Dose-response studies

No dose response studies were performed.

2.6.5.2. Main study

Study 20190232

A Phase 3, Multicenter, Randomized, Double-blind Study Evaluating the Efficacy and Safety of ABP 654 Compared with Ustekinumab in Subjects With Moderate to Severe Plaque Psoriasis.

Methods

Study Participants

Main inclusion/exclusion criteria

The study was conducted at 84 centres in Canada, Estonia, Germany, Hungary, Latvia, Lithuania, Poland, and the US.

Eligible subjects met the following key criteria:

- Subject was ≥ 18 years and ≤ 75 years of age at time of randomisation.
- Subject had stable moderate to severe Ps for at least 6 months.
- Subject had involved BSA ≥ 10%, PASI ≥ 12, and sPGA ≥ 3 at screening and at baseline.
- Subject was a candidate for systemic therapy or phototherapy.
- Subject had previously failed, had an inadequate response, intolerance to, or contraindication to at least 1 conventional anti-psoriatic systemic therapy (e.g., methotrexate, cyclosporine, psoralen plus ultraviolet light A).

Subjects were excluded from participation if they

- were diagnosed with erythrodermic psoriasis, pustular psoriasis, guttate psoriasis, medication-induced psoriasis, or other skin conditions at the time of the screening visit that would interfere with evaluations of the effect of the investigational product on psoriasis;
- had previous treatment with any agent specifically targeting IL-23 or IL-12;
- had received biologic treatment for psoriasis within the previous month or 5 drug half-lives (whichever was longer) prior to randomisation;
- had received non-biologic systemic psoriasis therapy within 4 weeks prior to randomisation;
- received ultra-violet A phototherapy or excimer laser within 4 weeks prior to randomisation or ultra-violet B phototherapy within 2 weeks prior to randomisation; or
- received topical psoriasis treatment within 2 weeks prior to randomisation.
- Subjects were excluded from participation if they were pregnant, breastfeeding, or planning to become pregnant. Sexually active subjects and their partners who are of childbearing potential were excluded if they were unwilling to use adequate contraception while on study and for 5 months after the last dose of investigational product.

Treatments

During the approximately 56 weeks of total study participation, each subject was to receive a total of either 5 or 6 doses, based on the group to which they were assigned, as described below.

Subjects were initially randomised to 1 of 2 treatment groups to receive a dose of either ABP 654 or Stelara (below named ustekinumab), as follows:

- ABP 654 treatment group: ABP 654, SC injection, 45 mg (baseline BW $\leq$ 100 kg) or 90 mg (baseline BW $>$ 100 kg) at weeks 0, 4, and 16
- Ustekinumab treatment group: Ustekinumab, SC injection, 45 mg (baseline BW $\leq$ 100 kg) or 90 mg (baseline BW $>$ 100 kg) at weeks 0, 4, and 16

At week 28, subjects with a PASI 75 response or better may have been subsequently re-randomised to receive either ustekinumab (SC, every 12 weeks [Q12W]) or ABP 654 (SC, Q12W), as follows:

- ABP 654 treatment group: Continued to receive ABP 654 Q12W at weeks 28 and 40 (ABP 654/ABP 654 treatment group)
- Ustekinumab treatment group: Re-randomised 1:1 to either continue on ustekinumab Q12W at weeks 28 and 40 (ustekinumab/ustekinumab treatment group) or switch to ABP 654 Q12W at weeks 28 and 40 (ustekinumab/ABP 654 treatment group)

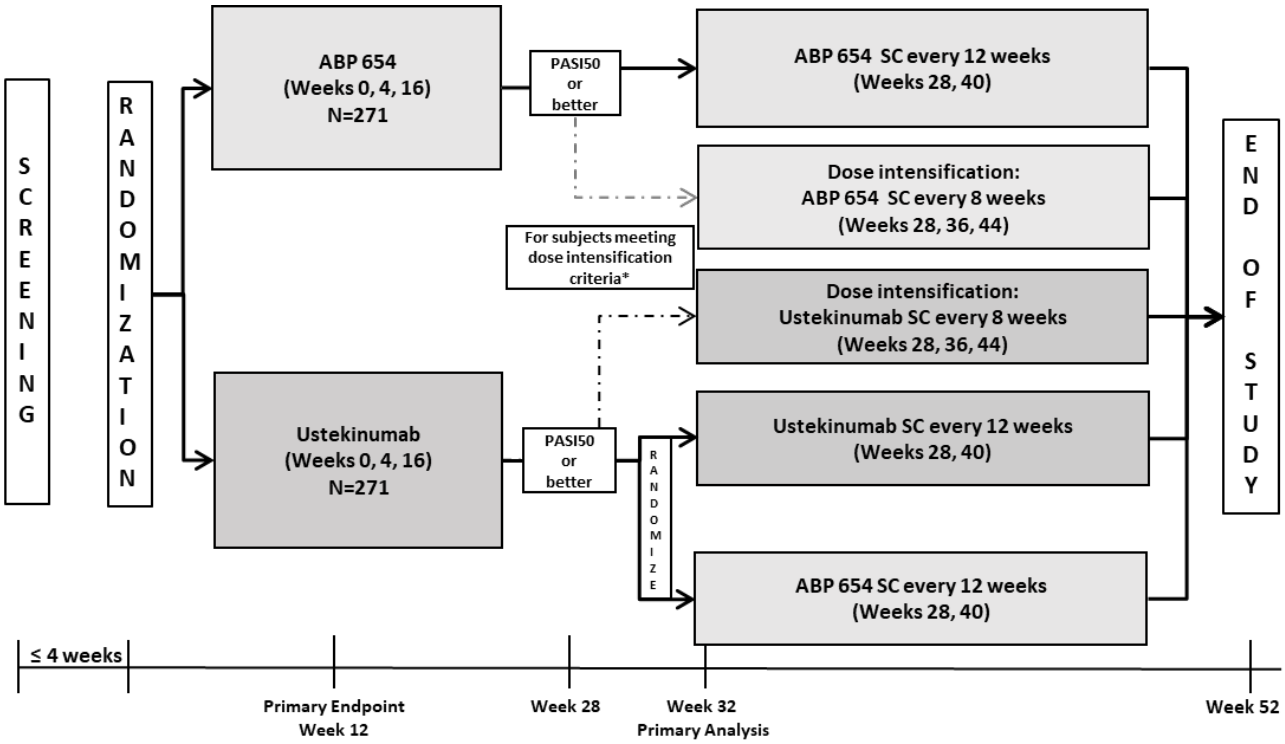
Subjects with PASI 50 response or better but less than PASI 75 response at week 28 were also re-randomised as described above if they were not recommended a dose intensification. At the investigator's discretion, subjects from the ABP 654 and ustekinumab treatment groups who achieved PASI 50 response or better, however did not achieve PASI 75 response or better may have received dose intensification (i.e., dosing frequency may have been increased to Q8W at weeks 28, 36, and 44). These subjects remained on their original treatment and were not re-randomised.

ABP 654 was supplied as a sterile, single dose, preservative-free solution for SC injection in a prefilled syringe (PFS) containing 45 mg/0.5 mL ABP 654 or 90 mg/mL ABP 654.

Ustekinumab was supplied in 45 mg/0.5 mL and 90 mg/mL single use PFS of Stelara (EU).

A study schema is provided in Figure 3.

Figure 3. Study diagram for study 20190232



- Subjects with body weight at baseline ≤100kg receive 45mg SC; >100kg receive 90 mg SC
- At week 28, non-responders (ie, subjects not achieving PASI 50 response of better) will be considered to have completed the study and will complete the end of study procedures (ie, week 52 procedures) at week 28. Subjects missing the week 28 visit or missing the PASI assessment at week 28, will be discontinued from the study.
- *For subjects with PASI 50 response or better but less than PASI 75 response at week 28, based on investigator's discretion, subjects may increase dose frequency to every 8 weeks (Q8W). Subjects with body weight at baseline ≤ 100kg will receive 45mg Q8W and subjects > 100kg at baseline will receive 90mg Q8W at weeks 28, 36, and 44. These subjects will continue on original treatment and will NOT be re-randomized.

PASI = Psoriasis Area and Severity Index; Q8W = every 8 weeks; Q12W = every 12 weeks; SC = subcutaneous

Objectives

The primary objective of the study was to compare the efficacy of ABP 654 with ustekinumab in subjects with moderate to severe Ps.

The secondary objective was to assess the safety and immunogenicity of ABP 654 compared with ustekinumab.

Null Hypothesis (H_0): Mean difference in PASI percent improvement from baseline at week 12 between ABP 654 and ustekinumab is outside an equivalence margin of (-15, 15),

versus

Alternative Hypothesis (H_A): Mean difference in PASI percent improvement from baseline at week 12 between ABP 654 and ustekinumab is within an equivalence margin of (-15, 15).

Outcomes/endpoints

The primary efficacy endpoint is the Psoriasis Area and Severity Index (PASI) percent improvement from baseline to week 12.

Secondary Endpoints

- PASI percent improvement at other timepoints
- ≥75% improvement in PASI (PASI 75) response throughout the study
- 100% improvement in PASI (PASI 100) response throughout the study
- Static Physician's Global Assessment (sPGA) response (0/1) at week 12 and week 52
- Body surface area (BSA) change from baseline at week 12 and week 52

Safety Endpoints

- treatment-emergent adverse events and serious adverse events
- events of interest (EOIs)
- incidence of antidrug antibodies (ADAs)

Sample size and randomisation

Approximately 542 adult subjects were to be randomised in a 1:1 ratio to ABP 654 or ustekinumab. The sample size was expected to provide greater than 95% power to demonstrate equivalence at a significance level of 0.025 (1-sided) on the primary efficacy endpoint of PASI percent improvement from baseline to week 12 with similarity margin of (-15, +15), assuming a common standard deviation of 30.0, a true mean difference of 0 in the primary efficacy endpoint between the 2 groups, and a 10% dropout rate. Randomisation was stratified based on prior biologic use for psoriasis (yes vs no), baseline BW group (≤ 100 kg vs > 100 kg), and geographic region (North America vs Europe).

Statistical methods

Clinical similarity of the primary efficacy endpoint was performed in the full analysis set (FAS) consisting of all randomised subjects, with missing postbaseline PASI scores at weeks 4 and 12 imputed by multiple imputation. Missing data were multiple imputed using the Markov Chain Monte Carlo (MCMC) method for sporadic missing data followed by regression-based imputation. A total of 400 complete data sets were generated. Observed PASI data at Week 12 were to be used regardless of whether study medication dose was missed on Day 1 or Week 4.

For each complete dataset, the mean difference in PASI percent improvement from baseline to week 12 was estimated from an analysis of covariance (ANCOVA) model with baseline PASI value and the stratification factors of baseline body weight group, prior biologic use, and region as covariates. Results from these analyses were pooled to produce the combined point estimate for the mean difference and the associated standard error. The 90% and 95% CIs of the mean difference in PASI percent improvement from baseline to week 12 were derived from this mean and standard error.

Clinical similarity of the primary endpoint was evaluated by comparing the 2-sided 95% CI of the mean difference of PASI percent improvement from baseline to week 12 between ABP 654 versus ustekinumab with a similarity margin of (-15, +15). If the 2-sided 95% CI was within the prespecified similarity margin (-15, +15), then it was declared that ABP 654 and ustekinumab were clinically similar.

Results

Participant flow

Variable	ABP 654 (N = 281) n (%)	Ustekinumab (N = 282) n (%)	Total (N = 563) n (%)
Subjects randomised	281 (100)	282 (100)	563 (100)
Subjects treated with IP	280 (99.6)	282 (100)	562 (99.8)
Completed IP prior to week 28[a]	277 (98.6)	275 (97.5)	552 (98.0)
Discontinued IP prior to week 28	3 (1.1)	6 (2.1)	9 (1.6)
Adverse event	1 (0.4)	3 (1.1)	4 (0.7)
Lost to follow-up	1 (0.4)	1 (0.4)	2 (0.4)
Death	0 (0.0)	1 (0.4)	1 (0.2)
Subject dissatisfaction with treatment efficacy	0 (0.0)	1 (0.4)	1 (0.2)
Other	1 (0.4)	0 (0.0)	1 (0.2)
Discontinued IP prior to week 28 due to COVID-19 related reasons	0 (0.0)	1 (0.4)	1 (0.2)
Subjects re-randomised at week 28	247 (87.9)	233 (82.6)	480 (85.3)
Subjects not re-randomised at week 28[b]	34 (12.1)	49 (17.4)	83 (14.7)
Required intensified dose	25 (8.9)	34 (12.1)	59 (10.5)
PASI percent improvement < 50	2 (0.7)	3 (1.1)	5 (0.9)
Subject did not have week 28 visit	0 (0.0)	1 (0.4)	1 (0.2)
Discontinued study prior to week 28	7 (2.5)	11 (3.9)	18 (3.2)
Adverse event	2 (0.7)	3 (1.1)	5 (0.9)
Death	0 (0.0)	1 (0.4)	1 (0.2)
Consent withdrawn	0 (0.0)	2 (0.7)	2 (0.4)
Lost to follow-up	2 (0.7)	2 (0.7)	4 (0.7)
Protocol violation	0 (0.0)	3 (1.1)	3 (0.5)
Other	3 (1.1)	0 (0.0)	3 (0.5)
Completed IP[c,d]	270 (96.1)	264 (93.6)	534 (94.8)
Discontinued IP[d,e]	10 (3.6)	17 (6.0)	27 (4.8)
Adverse event	3 (1.1)	4 (1.4)	7 (1.2)
Lost to follow-up	3 (1.1)	5 (1.8)	8 (1.4)
Death	0 (0.0)	1 (0.4)	1 (0.2)
Subject dissatisfaction with treatment efficacy	0 (0.0)	1 (0.4)	1 (0.2)
Protocol violation	0 (0.0)	3 (1.1)	3 (0.5)
Other	4 (1.4)	3 (1.1)	7 (1.2)
Discontinued IP due to COVID-19 related reasons	0 (0.0)	4 (1.4)	4 (0.7)
Death	0 (0.0)	1 (0.4)	1 (0.2)
Protocol violation	0 (0.0)	3 (1.1)	3 (0.5)

Variable	ABP 654 (N = 281) n (%)	Ustekinumab (N = 282) n (%)	Total (N = 563) n (%)

Completed study[f]	269 (95.7)	261 (92.6)	530 (94.1)
At week 28	2 (0.7)	3 (1.1)	5 (0.9)
At week 52	267 (95.0)	258 (91.5)	525 (93.3)
Discontinued study[e]	12 (4.3)	21 (7.4)	33 (5.9)
Adverse event	3 (1.1)	4 (1.4)	7 (1.2)
Death	0 (0.0)	1 (0.4)	1 (0.2)
Consent withdrawn	2 (0.7)	5 (1.8)	7 (1.2)
Lost to follow-up	4 (1.4)	8 (2.8)	12 (2.1)
Protocol violation	0 (0.0)	3 (1.1)	3 (0.5)
Other	3 (1.1)	0 (0.0)	3 (0.5)
Discontinued study due to COVID-19 related reasons	0 (0.0)	4 (1.4)	4 (0.7)
Death	0 (0.0)	1 (0.4)	1 (0.2)
Protocol violation	0 (0.0)	3 (1.1)	3 (0.5)

COVID-19 = coronavirus disease 2019; CSR = clinical study report; eCRF = electronic case report form; IP = investigational product; PASI 50 = ≥ 50% improvement in Psoriasis Area and Severity Index

[a] Completed IP prior to week 28 included subjects who completed dosing at week 16.

[b] Subjects not re-randomised at week 28 included subjects who reached week 28 but could not be re-randomised in addition to subjects who discontinued the study prior to week 28, and subjects who did not have a week 28 visit.

[c] Completed IP included PASI 50 non-responders who completed dosing at week 16 and dose intensification subjects who completed dosing at week 44 and re-randomised subjects who completed dosing at week 40.

[d] One subject had missing end of IP data and was not included in either the completed IP or discontinued IP category.

[e] Included subjects who discontinued IP/study due to COVID-19 related reasons and non-COVID-19 related reasons.

[f] Completed study included PASI 50 non-responders who completed study at week 28 and PASI 50 responders at week 28 who completed study at week 52.

A total of 563 subjects were randomised at 84 centres across 8 countries. Overall, 562 randomised subjects were treated with investigational product (280 subjects in the ABP 654 treatment group and 282 subjects in the ustekinumab treatment group). Most subjects (480 [85.3%]) underwent re-randomisation at week 28. Of the 480 subjects who were re-randomised at week 28, 247 (51.5%) were initially randomised to ABP 654 and, thus, continued to receive ABP 654 (ABP 654/ABP 654 treatment group); 117 (24.4%) subjects were initially randomised to ustekinumab and were re-randomised to receive ABP 654 (ustekinumab/ABP 654 treatment group); and 116 (24.2%) subjects were initially randomised to ustekinumab and were re-randomised to continue receiving ustekinumab (ustekinumab/ustekinumab treatment group).

Overall, 25 (8.9%) subjects in the ABP 654 treatment group and 34 (12.1%) subjects in the ustekinumab treatment group required dose intensification (i.e. shorter dosing intervals) from week 28 onward and were, therefore, not re-randomised. Two (0.7%) subjects in the ABP 654 treatment group and 3 (1.1%) subjects in the ustekinumab treatment group were PASI 50 non-responders at week 28 and were not eligible for re-randomisation.

Recruitment

Description of Key Dates	Date
First subject enrolment	11NOV2020
Last subject enrolment	07JUN2021
Last subject end of IP	31MAR2022
Last subject end of study	03JUN2022

IP = Investigational Product.

Note: Enrolment was defined as when the subject was randomised.

Conduct of the study

Protocol amendments

There were no changes in the conduct of the study.

The initial SAP (version 1.0, dated 11 December 2020) was amended once (version 2.0, dated 25 March 2022). The most important changes pertain to handling of missing data and the addition of COVID-19 related analyses. The amendments were finalised prior to unblinding and did not seem to be data driven.

Protocol deviations

Through week 28, a total of 152 (27.0%) subjects had 1 or more important protocol deviations. The most common important protocol deviations were within the category of IP administration/study treatment (52 [18.5%] subjects in the ABP 654 treatment group and 58 [20.6%] subjects in the ustekinumab treatment group) and within the category of informed consent (12 [4.3%] subjects in the ABP 654 treatment group and 10 [3.5%] subjects in the ustekinumab treatment group). Most of the deviations in the category IP administration/study treatment were due to "IP not prepared, handled, or stored per Investigator Manual Clinical Trial Supply and IP was administered to subject." Six subjects in the ABP 654 group and 5 subjects in the Stelara group were administered disallowed medication (e.g., non-biologic systemic psoriasis therapy) while on study.

Through week 28, 7 (2.5%) subjects in the ABP 654 treatment group and 9 (3.2%) subjects in the ustekinumab treatment group experienced at least 1 COVID-19-related protocol deviation, most commonly in the category of visit schedule.

Post week 28, a total of 21 (4.4%) re-randomised subjects had 1 or more important protocol deviations. The most common important protocol deviations for re-randomised subjects were within the categories of investigational product administration/study treatment and procedures/tests.

The reported protocol deviations were balanced between the groups and do not raise concerns regarding validity of the results or compliance with GCP.

Baseline data

Overall, 368 (65.4%) were male, 497 (88.3%) were white, and 500 (88.8%) were not Hispanic or Latino. The mean (SD) age was 44.4 (13.39) years with a range of 18 to 75 years; 518 (92.0%) subjects were younger than 65 years of age.

Table 11. Demographic and baseline physical characteristics by initial randomisation (Study 20190232 Full Analysis Set)

Characteristic	ABP 654 (N = 281)	Ustekinumab (N = 282)	Total (N = 563)
Sex, n (%)			
Female	104 (37.0)	91 (32.3)	195 (34.6)
Male	177 (63.0)	191 (67.7)	368 (65.4)
Race, n (%)			
American Indian or Alaska Native	1 (0.4)	2 (0.7)	3 (0.5)
Asian	20 (7.1)	25 (8.9)	45 (8.0)
Black or African American	4 (1.4)	2 (0.7)	6 (1.1)
Native Hawaiian or other Pacific Islander	0 (0.0)	1 (0.4)	1 (0.2)
White	250 (89.0)	247 (87.6)	497 (88.3)
Multiple	1 (0.4)	0 (0.0)	1 (0.2)
White, Black or African American	1 (0.4)	0 (0.0)	1 (0.2)
Not allowed to collect	1 (0.4)	0 (0.0)	1 (0.2)
Other	4 (1.4)	5 (1.8)	9 (1.6)
Ethnicity, n (%)			
Hispanic or Latino	32 (11.4)	28 (9.9)	60 (10.7)
Not Hispanic or Latino	248 (88.3)	252 (89.4)	500 (88.8)
Not allowed to collect	1 (0.4)	0 (0.0)	1 (0.2)
Unknown	0 (0.0)	2 (0.7)	2 (0.4)
Age (years)			
n	281	282	563
Mean (SD)	43.7 (14.15)	45.0 (12.58)	44.4 (13.39)
Median	42.0	44.0	44.0
Min, Max	18, 75	18, 74	18, 75
Age group, n (%)			
< 65 years	257 (91.5)	261 (92.6)	518 (92.0)
≥ 65 years	24 (8.5)	21 (7.4)	45 (8.0)
Weight (kg)			
n	281	282	563
Mean (SD)	90.81 (23.916)	93.64 (23.234)	92.23 (23.598)
Median	87.10	90.00	89.00
Min, Max	50.0, 213.0	52.0, 181.7	50.0, 213.0

Overall, 166 (29.5%) subjects had prior biologic use for psoriasis and most subjects 556 (98.8%) had a duration of psoriasis of more than 1 year. The overall mean (SD) PASI score at study baseline was 20.92 (8.379) and the overall mean (SD) BSA at study baseline was 25.7% (15.16%). Overall, 284 (50.4%) subjects had baseline sPGA categorised as moderate (sPGA score 3) and 279 (49.6%) subjects had baseline sPGA categorised as severe or very severe (sPGA score 4 and 5).

Table 12. Baseline disease characteristics (Study 20190232 Full Analysis Set)

Characteristic	ABP 654 (N = 281)	Ustekinumab (N = 282)	Total (N = 563)
Prior biologic use for psoriasis, n (%)			
Yes	84 (29.9)	82 (29.1)	166 (29.5)
No	197 (70.1)	200 (70.9)	397 (70.5)
Prior topical steroid use for psoriasis in the last 6 months prior to randomisation, n (%)			
Yes	193 (68.7)	202 (71.6)	395 (70.2)
No	88 (31.3)	80 (28.4)	168 (29.8)
Disease duration, n (%)			
< 1 year	4 (1.4)	3 (1.1)	7 (1.2)
≥ 1 year	277 (98.6)	279 (98.9)	556 (98.8)
Baseline PASI			
n	281	282	563
Mean (SD)	21.50 (8.855)	20.35 (7.850)	20.92 (8.379)
Median	18.60	18.25	18.40
Min, Max	12.0, 60.9	12.0, 66.0	12.0, 66.0
Baseline sPGA, n (%)			
0 (clear)	0 (0.0)	0 (0.0)	0 (0.0)
1 (almost clear)	0 (0.0)	0 (0.0)	0 (0.0)
2 (mild)	0 (0.0)	0 (0.0)	0 (0.0)
3 (moderate)	130 (46.3)	154 (54.6)	284 (50.4)
4 and 5 (severe and very severe)	151 (53.7)	128 (45.4)	279 (49.6)
4 (severe)	132 (47.0)	114 (40.4)	246 (43.7)
5 (very severe)	19 (6.8)	14 (5.0)	33 (5.9)
Baseline BSA (%)			
n	281	282	563
Mean (SD)	26.5 (15.25)	24.9 (15.05)	25.7 (15.16)
Median	20.0	20.0	20.0
Min, Max	10, 81	10, 90	10, 90

BSA = body surface area; CSR = clinical study report; max = maximum; min = minimum; PASI = Psoriasis Area and Severity Index; sPGA = Static Physician's Global Assessment

Overall, 530 (94.3%) subjects had any prior medication. The most common (≥ 10% of subjects) prior medications included methotrexate, clobetasol propionate, corticosteroids, calcipotriol, folic acid and adalimumab (32 (11.4%) 28 (9.9%) in the ABP 654 group and the Stelara group, respectively).

Overall, 304 (54.1%) subjects received concomitant medications through week 12 of the study. The most common (≥ 5% of subjects) concomitant medications included tozinameran, elasomeran and COVID-19 vaccine.

Numbers analysed

The number of analysed subjects is shown in table 13.

Table 13. Number of subjects in different analysis sets (Study 20190232)

Population	ABP 654 n (%)	Ustekinumab n (%)	Total n (%)
Subjects screened			648
Subjects randomised	281	282	563
Subjects re-randomised at week 28	247	233	480
FAS inclusion	281 (100)	282 (100)	563 (100)
FAS exclusion	0 (0.0)	0 (0.0)	0 (0.0)
Re-randomised FAS inclusion	247 (87.9)	233 (82.6)	480 (85.3)
Re-randomised FAS exclusion	34 (12.1)	49 (17.4)	83 (14.7)
Required intensified dose	25 (8.9)	34 (12.1)	59 (10.5)
Discontinued prior to week 28	7 (2.5)	11 (3.9)	18 (3.2)
PASI percent improvement < 50	2 (0.7)	3 (1.1)	5 (0.9)
Subject did not have week 28 visit	0 (0.0)	1 (0.4)	1 (0.2)
Safety analysis set inclusion	280 (99.6)	282 (100)	562 (99.8)
Safety analysis set exclusion	1 (0.4)	0 (0.0)	1 (0.2)
Not treated	1 (0.4)	0 (0.0)	1 (0.2)
Re-randomised safety analysis set inclusion	247 (87.9)	233 (82.6)	480 (85.3)
Re-randomised safety analysis set exclusion	34 (12.1)	49 (17.4)	83 (14.7)
Required intensified dose	25 (8.9)	34 (12.1)	59 (10.5)
Discontinued prior to week 28	7 (2.5)	11 (3.9)	18 (3.2)
PASI percent improvement < 50	2 (0.7)	3 (1.1)	5 (0.9)
Subject did not have week 28 visit	0 (0.0)	1 (0.4)	1 (0.2)
Per-protocol analysis set inclusion	275 (97.9)	275 (97.5)	550 (97.7)
Per-protocol analysis set exclusion	6 (2.1)	7 (2.5)	13 (2.3)
Did not complete dosing at study day 1 or week 4	2 (0.7)	3 (1.1)	5 (0.9)
Did not complete PASI assessment at week 12	6 (2.1)	7 (2.5)	13 (2.3)
Experienced an IPD that affects evaluation of primary endpoint	6 (2.1)	2 (0.7)	8 (1.4)

FAS = full analysis set; IPD = important protocol deviation; PASI = Psoriasis Area and Severity Index
Note: Percentages were calculated based on the number of randomised subjects.

Outcomes and estimation

Primary endpoint

Percent Improvement from Baseline to Week 12 in Psoriasis Area and Severity Index

Results of the primary analysis of PASI Percent Improvement from Baseline to Week 12 Using Multiple Imputation are provided in Table 14. The 95% CI was within the prespecified similarity margin of (-15, +15).

Table 14. Primary analysis of PASI percent improvement from baseline to week 12 using multiple imputation (Study 20190232 Full Analysis Set)

	ABP 654 (N = 281)		Ustekinumab (N = 282)	
Visit Statistic	PASI Score	PASI Percent Improvement from Baseline	PASI Score	PASI Percent Improvement from Baseline
Week 12				
n	281	281	282	282
Mean (SD), MI[a]	3.94 (4.855)	81.46 (20.058)	3.76 (4.511)	81.45 (20.004)
n	272	272	276	276
Mean (SD), observed[b]	3.89 (4.875)	81.92 (19.872)	3.70 (4.493)	81.91 (19.611)
95% CI of mean[b]	(3.31, 4.47)	(79.54, 84.29)	(3.17, 4.23)	(79.58, 84.23)
Difference between means[c]		0.14		
90% CI[c]		(-2.63, 2.90)		
95% CI[c]		**(-3.16, 3.43)**		

ANCOVA = analysis of covariance; CSR = clinical study report; MI = multiple imputation; PASI = Psoriasis Area and Severity Index

[a] The summary statistics by each visit were derived based on MI data.

[b] The summary statistics by each visit were derived based on observed data. Multiple imputation was only applied for the point estimate and CI of the mean difference between the 2 groups.

[c] Estimated using ANCOVA model adjusted for baseline PASI value, and the stratification factors of prior biologic use for psoriasis, baseline body weight group, and geographic region. Multiple imputation was performed using PROC MI in 2 steps: the Markov Chain Monte Carlo was used for data with sporadic missing values to create imputed datasets with monotone missing pattern, and then for the resulting datasets the regression method was used to generate complete datasets for final analysis.

Sensitivity analyses

Sensitivity analyses were performed to assess the robustness of results from analysis of the primary efficacy endpoint. The ANCOVA analysis described above was repeated using the FAS based on last observation carried forward (LOCF) data, and was also repeated using the per-protocol analysis set based on observed data. In addition, a mixed model repeated-measures analysis based on the FAS using observed data was performed.

Sensitivity analyses showed that results were consistent over different analysis sets (FAS and PP) and regardless of choice of imputation method for missing values (LOCF or MMRM).

Subgroup analyses were performed for the following subgroups: prior biologic use for psoriasis (yes, no), baseline BW group (≤ 100 kg vs > 100 kg), geographic region (North America vs Europe), age (< 65 years vs ≥ 65 years), race (white vs non-white), sex (female vs male), and disease duration (< 1 year vs ≥ 1 year). Clinical comparability was concluded in all subgroups, including patients with BW >100kg and patients aged ≥ 65 years.

Secondary endpoints

PASI percent improvement at other timepoints

Results of PASI percent improvement from baseline at weeks 4, 12, 16, and 28 for the FAS based on LOCF and over the entire study for the re-randomised FAS based on LOCF are summarised in the tables below.

Table 15. PASI percent improvement from baseline – through week 28 (LOCF) (Study 20190232 Full Analysis Set)

	ABP 654 (N = 281)		Ustekinumab (N = 282)	
Visit Statistic	PASI Score	PASI Percent Improvement from Baseline	PASI Score	PASI Percent Improvement from Baseline
Baseline				
n	281		282	
Mean (SD)	21.50 (8.855)		20.35 (7.850)	
Week 4				
n	280	280	281	281
Mean (SD)	12.04 (7.358)	44.15 (23.587)	11.83 (6.903)	42.40 (24.536)
Difference between means[a]		1.95		
90% CI[a]		(-1.41, 5.30)		
95% CI[a]		(-2.05, 5.94)		
Week 12				
n	280	280	281	281
Mean (SD)	4.12 (5.139)	80.66 (21.226)	3.91 (4.882)	80.69 (22.314)
Difference between means[a]		0.12		
90% CI[a]		(-2.85, 3.10)		
95% CI[a]		(-3.42, 3.67)		
Week 16				
n	280	280	281	281
Mean (SD)	3.01 (4.260)	85.88 (18.704)	2.87 (4.474)	85.86 (19.953)
Difference between means[a]		0.17		
90% CI[a]		(-2.47, 2.80)		
95% CI[a]		(-2.97, 3.31)		
Week 28				
n	280	280	281	281
Mean (SD)	2.25 (3.322)	89.41 (14.228)	2.40 (3.903)	88.18 (18.771)
Difference between means[a]		1.34		
90% CI[a]		(-0.95, 3.63)		
95% CI[a]		(-1.39, 4.07)		

ANCOVA = analysis of covariance; CSR = clinical study report; LOCF = last observation carried forward; PASI = Psoriasis Area and Severity Index

[a] Estimated using ANCOVA model adjusted for baseline PASI value, and the stratification factors of prior biologic use for psoriasis, baseline body weight group, and geographic region.

Results of PASI percent improvement from baseline at other timepoints are summarised over the entire study for the re-randomised FAS based on LOCF in the table below.

Of note, summaries of data over the entire study period do not include subjects who dose intensified.

Table 16. PASI percent improvement from baseline – entire study (LOCF) (Study 20190232 Re-randomised Full Analysis Set)

	ABP 654/ABP 654 (N = 247)		Ustekinumab/ABP 654 (N = 117)		Ustekinumab/Ustekinumab (N = 116)	
Visit Statistic	PASI Score	PASI Percent Improvement from Baseline	PASI Score	PASI Percent Improvement from Baseline	PASI Score	PASI Percent Improvement from Baseline
Baseline						
n	247		117		116	
Mean (SD)	21.67 (8.917)		20.56 (7.722)		19.89 (7.973)	
Week 4						
n	247	247	117	117	116	116
Mean (SD)	11.73 (7.289)	46.01 (23.364)	10.99 (6.856)	47.64 (24.323)	11.37 (6.745)	43.32 (22.226)
Difference between means[a]		3.07		4.45		
90% CI[a]		(-1.28, 7.43)		(-0.60, 9.50)		
95% CI[a]		(-2.12, 8.27)		(-1.57, 10.47)		
Week 12						
n	247	247	117	117	116	116
Mean (SD)	3.64 (4.719)	82.94 (19.708)	2.99 (3.568)	85.49 (15.762)	2.94 (4.276)	85.48 (17.711)
Difference between means[a]		-2.20		0.11		
90% CI[a]		(-5.58, 1.17)		(-3.80, 4.02)		
95% CI[a]		(-6.22, 1.82)		(-4.55, 4.77)		
Week 16						
n	247	247	117	117	116	116
Mean (SD)	2.41 (3.589)	88.86 (15.717)	1.94 (2.994)	90.60 (13.274)	2.01 (3.914)	90.19 (15.269)
Difference between means[a]		-1.00		0.52		
90% CI[a]		(-3.76, 1.76)		(-2.68, 3.72)		
95% CI[a]		(-4.29, 2.29)		(-3.29, 4.33)		

Table 16. Continued. PASI percent improvement from baseline – entire study (LOCF) (Study 20190232 Re-randomised Full Analysis Set)

	ABP 654/ABP 654 (N = 247)		Ustekinumab/ABP 654 (N = 117)		Ustekinumab/Ustekinumab (N = 116)	
Visit Statistic	PASI Score	PASI Percent Improvement from Baseline	PASI Score	PASI Percent Improvement from Baseline	PASI Score	PASI Percent Improvement from Baseline
Week 28						
n	247	247	117	117	116	116
Mean (SD)	1.54 (2.024)	92.82 (8.408)	1.24 (1.673)	94.12 (7.000)	1.16 (1.623)	94.07 (7.516)
Difference between means[a]		-1.08		0.09		
90% CI[a]		(-2.53, 0.36)		(-1.58, 1.76)		
95% CI[a]		(-2.80, 0.64)		(-1.90, 2.09)		
Week 40						
n	247	247	117	117	116	116
Mean (SD)	1.34 (1.977)	93.60 (9.738)	1.18 (1.831)	94.22 (8.296)	0.97 (1.829)	95.10 (8.529)
Difference between means[a]		-1.41		-0.85		
90% CI[a]		(-3.09, 0.27)		(-2.79, 1.10)		
95% CI[a]		(-3.42, 0.59)		(-3.17, 1.48)		
Week 52						
n	247	247	117	117	116	116
Mean (SD)	1.52 (2.472)	92.54 (11.808)	1.33 (2.348)	93.90 (8.987)	1.33 (3.099)	93.23 (16.029)
Difference between means[a]		-0.56		0.70		
90% CI[a]		(-2.85, 1.73)		(-1.95, 3.35)		
95% CI[a]		(-3.29, 2.17)		(-2.46, 3.86)		

ANCOVA = analysis of covariance; CSR = clinical study report; LOCF = last observation carried forward; PASI = Psoriasis Area and Severity Index

Note: The differences for the mean percent improvement from baseline and the corresponding CIs in the ABP 654/ABP 654 and ustekinumab/ABP 654 columns were for ABP 654/ABP 654 minus ustekinumab/ustekinumab and ustekinumab/ABP 654 minus ustekinumab/ustekinumab, respectively.

[a] Estimated using ANCOVA model adjusted for baseline PASI value, and the stratification factors of prior biologic use for psoriasis, baseline body weight group, and geographic region.

PASI 75 response

Results of PASI 75 response at weeks 4, 12, 16, and 28 for the FAS analysis set with non-responder imputation (NRI) are summarised in the table below.

Table 17. PASI 75 response by visit – through week 28 (NRI) (Study 20190232 Full Analysis Set)

Visit Statistic	ABP 654 (N = 281)	Ustekinumab (N = 282)
Week 4		
PASI 75 responder (n/N1 [%])	32/281 (11.4)	29/282 (10.3)
95% CI for responder	(7.67, 15.10)	(6.74, 13.83)
Response difference (ABP 654 – ustekinumab) (%)[a]	1.20	
90% CI[a]	(-3.16, 5.56)	
95% CI[a]	(-4.02, 6.42)	
Week 12		
PASI 75 responder (n/N1 [%])	196/281 (69.8)	198/282 (70.2)
95% CI for responder	(64.38, 75.12)	(64.88, 75.55)
Response difference (ABP 654 – ustekinumab) (%)[a]	-0.32	
90% CI[a]	(-6.67, 6.02)	
95% CI[a]	(-7.87, 7.23)	
Week 16		
PASI 75 responder (n/N1 [%])	227/281 (80.8)	226/282 (80.1)
95% CI for responder	(76.18, 85.39)	(75.49, 84.80)
Response difference (ABP 654 – ustekinumab) (%)[a]	0.82	
90% CI[a]	(-4.69, 6.32)	
95% CI[a]	(-5.75, 7.37)	
Week 28		
PASI 75 responder (n/N1 [%])	241/281 (85.8)	232/282 (82.3)
95% CI for responder	(81.68, 89.85)	(77.81, 86.73)
Response difference (ABP 654 – ustekinumab) (%)[a]	3.75	
90% CI[a]	(-1.37, 8.85)	
95% CI[a]	(-2.37, 9.84)	

CSR = clinical study report; N1 = the number of subjects having available (included imputation) PASI data at each visit; NRI = non-responder imputation; PASI = Psoriasis Area and Severity Index

Note: PASI response was defined as a subject meeting or surpassing a prespecified threshold for percent improvement in PASI score compared to the baseline PASI score. An improvement of at least 75% qualified a subject as being a PASI 75 responder.

[a] Response difference was estimated by the Mantel-Haenszel estimate, and the 90% and 95% confidence intervals were estimated by the stratified Newcombe confidence limits, adjusting for actual stratification factors of prior biologic use for psoriasis, baseline body weight group, and geographic region.

Results for analyses of PASI 75 response over the entire study are summarised for the re-randomised FAS with NRI in the table below.

Table 18. PASI 75 response by visit – entire study (NRI)
(Study 20190232 Re-randomised Full Analysis Set)

Visit Statistic	ABP 654/ ABP 654 (N = 247)	Ustekinumab/ ABP 654 (N = 117)	Ustekinumab/ Ustekinumab (N = 116)
Week 4			
PASI 75 responder (n/N1 [%])	31/247 (12.6)	20/117 (17.1)	8/116 (6.9)
95% CI for responder	(8.42, 16.68)	(10.27, 23.92)	(2.29, 11.51)
Response difference (%)[a]	5.73	10.03	
90% CI[a]	(-0.27, 10.63)	(2.87, 17.14)	
95% CI[a]	(-1.65, 11.55)	(1.38, 18.58)	
Week 12			
PASI 75 responder (n/N1 [%])	185/247 (74.9)	90/117 (76.9)	94/116 (81.0)
95% CI for responder	(69.49, 80.31)	(69.29, 84.56)	(73.90, 88.17)
Response difference (%)[a]	-6.14	-3.95	
90% CI[a]	(-13.27, 1.78)	(-12.66, 4.87)	
95% CI[a]	(-14.55, 3.38)	(-14.32, 6.57)	
Week 16			
PASI 75 responder (n/N1 [%])	217/247 (87.9)	106/117 (90.6)	106/116 (91.4)
95% CI for responder	(83.78, 91.93)	(85.31, 95.89)	(86.27, 96.49)
Response difference (%)[a]	-3.40	-0.61	
90% CI[a]	(-8.55, 2.70)	(-7.04, 5.80)	
95% CI[a]	(-9.49, 4.03)	(-8.38, 7.13)	
Week 28			
PASI 75 responder (n/N1 [%])	239/247 (96.8)	116/117 (99.1)	112/116 (96.6)
95% CI for responder	(94.55, 98.97)	(97.48, 100.00)	(93.23, 99.87)
Response difference (%)[a]	0.54	2.74	
90% CI[a]	(-2.77, 5.88)	(-3.17, 7.94)	
95% CI[a]	(-3.49, 7.41)	(-4.91, 9.46)	
Week 40			
PASI 75 responder (n/N1 [%])	234/247 (94.7)	112/117 (95.7)	109/116 (94.0)
95% CI for responder	(91.95, 97.52)	(92.06, 99.39)	(89.63, 98.30)
Response difference (%)[a]	1.10	1.85	
90% CI[a]	(-2.95, 6.30)	(-3.58, 7.18)	
95% CI[a]	(-3.74, 7.54)	(-4.89, 8.39)	
Week 52			
PASI 75 responder (n/N1 [%])	221/247 (89.5)	108/117 (92.3)	107/116 (92.2)
95% CI for responder	(85.65, 93.30)	(87.48, 97.14)	(87.37, 97.11)
Response difference (%)[a]	-2.75	0.14	
90% CI[a]	(-7.69, 3.12)	(-5.99, 6.16)	
95% CI[a]	(-8.61, 4.41)	(-7.32, 7.43)	

CSR = clinical study report; N1 = the number of subjects having available PASI data at each visit; NRI = non-responder imputation; PASI = Psoriasis Area and Severity Index

Note: PASI response was defined as a subject meeting or surpassing a prespecified threshold for percent improvement in PASI score compared to the baseline PASI score. An improvement of at least 75% qualified a subject as being a PASI 75 responder. The response differences for PASI responders and the corresponding CIs

in the ABP 654/ABP 654 and ustekinumab/ABP 654 columns were for ABP 654/ABP 654 minus ustekinumab/ustekinumab and ustekinumab/ABP 654 minus ustekinumab/ustekinumab, respectively.

[a] Response difference was estimated by the Mantel-Haenszel estimate, and the 90% and 95% CIs were estimated by the stratified Newcombe confidence limits, adjusting for actual stratification factors of prior biologic use for psoriasis, baseline body weight group, and geographic region.

PASI 100 response

PASI 100 response was similar between the 2 treatment groups through week 28 and over the entire study for each population/dataset analysed (data not shown for brevity). At week 28, 38.9% in the ABP 654 group and 35.9% in the ustekinumab group were PASI 100 responders. Any observed differences across the treatment groups before or after re-randomisation and switching were not clinically relevant and there was no trend of divergence between groups.

sPGA responses (0/1) at week 12 and week 52

The sPGA was a 6-point scale (0-5) used to measure the severity of disease (induration, scaling, and erythema). An sPGA score of 0 or 1 (clear or almost clear) qualified a subject as being an sPGA responder. At baseline, all subjects had an sPGA score of 3 or higher by pre-specified inclusion criteria.

Results of sPGA response at week 12 for the FAS analysis set with NRI are summarised in the table below. At week 12, the difference between treatment groups of ABP 654 and ustekinumab in the sPGA response was 2.55% with a 95% CI of (-5.65, 10.71).

Table 19. sPGA response at week 12 (NRI) (Study 20190232 Full Analysis Set)

Visit Statistic	ABP 654 (N = 281)	Ustekinumab (N = 282)
Week 12		
sPGA responder (n/N1 [%])	155/281 (55.2)	149/282 (52.8)
95% CI for responder	(49.35, 60.98)	(47.01, 58.66)
Response difference (ABP 654 – ustekinumab) (%)[a]	2.55	
90% CI[a]	(-4.34, 9.42)	
95% CI[a]	(-5.65, 10.71)	

CSR = clinical study report; N1 = the number of subjects having available (included imputation) sPGA data; NRI = non-responder imputation; sPGA = Static Physician's Global Assessment

The sPGA was a 6-point scale (0-5) used to measure the severity of disease (induration, scaling, and erythema). An sPGA score of 0 or 1 qualified a subject as being an sPGA responder.

[a] Response difference was estimated by the Mantel-Haenszel estimate, and the 90% and 95% confidence intervals were estimated by the stratified Newcombe confidence limits, adjusting for actual stratification factors of prior biologic use for psoriasis, baseline body weight, and geographic region

Table 20. sPGA response at week 12 and week 52 (NRI) (Study 20190232 Re-randomised Full Analysis Set)

Visit Statistic	ABP 654/ABP 654 (N = 247)	Ustekinumab/ABP 654 (N = 117)	Ustekinumab/Ustekinumab (N = 116)
Week 12			
sPGA responder (n/N1 [%])	150/247 (60.7)	69/117 (59.0)	70/116 (60.3)
95% CI for responder	(54.64, 66.82)	(50.06, 67.89)	(51.44, 69.25)
Response difference (%)[a]	0.59	-1.12	
90% CI[a]	(-8.28, 9.70)	(-11.57, 9.37)	
95% CI[a]	(-9.92, 11.43)	(-13.52, 11.33)	
Week 52			
sPGA responder (n/N1 [%])	176/247 (71.3)	83/117 (70.9)	91/116 (78.4)
95% CI for responder	(65.61, 76.90)	(62.71, 79.17)	(70.97, 85.93)
Response difference (%)[a]	-6.57	-7.46	
90% CI[a]	(-14.06, 1.65)	(-16.68, 1.94)	
95% CI[a]	(-15.41, 3.29)	(-18.41, 3.74)	

BSA change from baseline at week 12 and week 52

BSA change represents the change in percent of the affected body's surface area. Results of BSA change from baseline at week 12 for the FAS based on LOCF are summarised in the table below.

Table 21. BSA change from baseline at week 12 (LOCF) (Study 20190232 Full Analysis Set)

	ABP 654 (N = 281)		Ustekinumab (N = 282)	
Visit Statistic	BSA (%)	Change from Baseline	BSA (%)	Change from Baseline
Baseline				
n	281		282	
Mean (SD)	26.5 (15.25)		24.9 (15.05)	
Week 12				
n	280	280	281	281
Mean (SD)	8.7 (11.47)	-17.8 (14.32)	7.7 (10.21)	-17.2 (14.51)
Difference between means[a]		0.47		
90% CI[a]		(-0.89, 1.84)		
95% CI[a]		(-1.15, 2.10)		

ANCOVA = analysis of covariance; BSA = Body Surface Area; CSR = clinical study report; LOCF = last observation carried forward

Note: The percent of BSA affected (BSA %) was estimated by assuming that the subject's palm, excluding the fingers and thumb, represented roughly 1% of the body's surface area.

[a] Estimated using ANCOVA model adjusted for baseline BSA value, and the stratification factors of prior biologic use for psoriasis, baseline body weight group, and geographic region.

Table 22. BSA change from baseline at week 12 and week 52 – entire study (LOCF) (Study 20190232 Re-randomised Full Analysis Set)

Visit	ABP 654/ABP 654 (N = 247)		Ustekinumab/ABP 654 (N = 117)		Ustekinumab/Ustekinumab (N = 116)	
Statistic	BSA (%)	Change from Baseline	BSA (%)	Change from Baseline	BSA (%)	Change from Baseline
Baseline						
n	247		117		116	
Mean (SD)	26.7 (15.28)		24.9 (14.92)		24.4 (14.14)	
Week 12						
n	247	247	117	117	116	116
Mean (SD)	8.0 (11.20)	-18.7 (14.25)	6.1 (7.71)	-18.8 (13.29)	6.4 (9.98)	-18.0 (12.77)
Difference between means[a]		0.81		-0.46		
90% CI[a]		(-0.86, 2.49)		(-2.40, 1.49)		
95% CI[a]		(-1.19, 2.81)		(-2.78, 1.86)		
Week 52						
n	247	247	117	117	116	116
Mean (SD)	2.0 (3.63)	-24.7 (14.81)	2.1 (4.17)	-22.8 (13.86)	1.9 (4.79)	-22.5 (14.11)
Difference between means[a]		-0.13		0.10		
90% CI[a]		(-0.85, 0.60)		(-0.74, 0.94)		
95% CI[a]		(-0.99, 0.74)		(-0.90, 1.10)		

2.6.5.3. Summary of main efficacy results

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

Table 23. Summary of efficacy for trial 20190232

Title: A Phase 3, Multicenter, Randomized, Double-blind Study Evaluating the Efficacy and Safety of ABP 654 Compared with Ustekinumab in Subjects With Moderate to Severe Plaque Psoriasis	
Study identifier	Protocol No.: 20190232 EudraCT No.: 2020-003184-25 NCT No.: NCT04607980
Design	This was a randomised, double-blind, active-controlled study to evaluate the efficacy, safety, and immunogenicity of ABP 654 compared with ustekinumab in subjects with moderate to severe plaque psoriasis. Subjects were randomised in a 1:1 ratio to receive either ABP 654 or ustekinumab at a dose of 45 mg (baseline body weight [BW] ≤ 100 kg) or 90 mg (BW > 100 kg) administered subcutaneously on day 1, week 4, and week 16. At week 28, subjects with a ≥ 75% improvement in Psoriasis Area and Severity Index (PASI) or better were re-randomised in a blinded fashion such that subjects initially randomised to ABP 654 continued to receive ABP 654 and those initially randomised to ustekinumab were re-randomised to either continue on ustekinumab or switch to ABP 654. Subjects received investigational product at week 28 and the last dose of investigational product at week 40.

	Duration of main phase: Duration of Run-in phase: Duration of Extension phase:		52 weeks Not applicable Not applicable
Hypothesis	Mean difference in PASI percent improvement from baseline at week 12 between ABP 654 and ustekinumab is within an equivalence margin of (-15, 15)		
Treatments groups	ABP 654 (initial randomisation)		ABP 654 on day 1, week 4 and week 16; 281 subjects randomised
	Ustekinumab (initial randomisation)		Ustekinumab on day 1, week 4 and week 16; 282 subjects randomised
	ABP 654/ABP 654 (initial/re-randomisation)		ABP 654 on day 1, week 4, week 16, week 28, and week 40; 247 subjects re-randomised
	Ustekinumab/ABP 654 (initial/re-randomisation)		Ustekinumab on day 1, week 4, and week 16, then ABP 654 on week 28, and week 40; 117 subjects re-randomised
	Ustekinumab/Ustekinumab (initial/re-randomisation)		Ustekinumab on day 1, week 4, week 16, week 28, and week 40; 116 subjects re-randomised
Endpoints and definitions	Primary endpoint	PASI percent improvement from baseline to week 12	The PASI is a measure of the average redness (erythema), thickness (induration), and scaliness of the lesions, with each graded on a 0 to 4 scale and weighted by the area of involvement. PASI combines the assessment of the severity of lesions and the area affected into a single score in the range of 0 (no disease) to 72 (maximal disease).
	Secondary endpoint	PASI percent improvement at other timepoints	See above
	Secondary endpoint	PASI 75 response	PASI response was defined as a subject meeting or surpassing a prespecified threshold for percent improvement in PASI score compared to the baseline PASI score. An improvement of at least 75% qualified a subject as being a PASI 75 responder.
	Other secondary endpoints (not included in the table)		Percentage of PASI 100 response throughout the study. Static Physician's Global Assessment (sPGA) response (0/1) at week 12 and week 52. Body surface area (BSA) change from baseline at week 12 and week 52
Database lock	03 June 2022 (last subject last visit)		
Results and Analysis			

Analysis description	**Primary Analysis**		
Analysis population and time point description	Full analysis set (all randomised subjects) **Week 12**		
Descriptive statistics and estimate variability	Treatment group	ABP 654 (initial randomisation)	Ustekinumab (initial randomisation)
	Number of subjects	281	282
	PASI percent improvement from baseline to week 12 (Mean)	81.92	81.91
	Standard deviation	19.872	19.611
Effect estimate per comparison	PASI percent improvement from baseline to week 12	Comparison groups	ABP 654 (initial randomisation); Ustekinumab (initial randomisation)
		Difference between means	0.14
		95% CI	(-3.16, 3.43)
Notes	The 2-sided 95% CI of the mean difference in PASI percent improvement from baseline to week 12 between treatment groups was within the prespecified similarity margin of (-15, +15), thus supporting a demonstration of no clinically meaningful differences between ABP 654 and ustekinumab. Results from prespecified sensitivity analyses were consistent with results from the primary analysis.		
Analysis population and time point description	Full analysis set (all randomised subjects) **Week 28**		
Descriptive statistics and estimate variability	Treatment group	ABP 654 (initial randomisation)	Ustekinumab (initial randomisation)
	Number of subjects	281	282
	PASI percent improvement from baseline to week 28 (Mean)	89.41	88.18
	Standard deviation	14.228	18.771
Effect estimate per comparison	PASI percent improvement from baseline to week 28	Comparison groups	ABP 654 (initial randomisation); Ustekinumab (initial randomisation)
		Difference between means	1.34
		95% CI	(-1.39, 4.07)

Analysis population and time point description	Re-randomised full analysis set (a subset of the full analysis set consisting of subjects who were re randomised) **Week 52**			
Descriptive statistics and estimate variability	Treatment group	ABP 654/ABP 654	Ustekinumab/ ABP 654	Ustekinumab/ Ustekinumab
	Number of subjects	247	117	116

	PASI percent improvement from baseline to week 52 (Mean)	92.54	93.90	93.23
	Standard deviation	11.808	8.987	16.029
Effect estimate per comparison	PASI percent improvement from baseline to week 52	Comparison groups	ABP 654/ABP 654; Ustekinumab/ Ustekinumab	Ustekinumab/ABP 654; Ustekinumab/ Ustekinumab
		Difference between means	-0.56	0.70
		95% CI	(-3.29, 2.17)	(-2.46, 3.86)

Analysis population and time point description	Full analysis set (all randomised subjects) **Week 12**		
Descriptive statistics and estimate variability	Treatment group	ABP 654 (initial randomisation)	Ustekinumab (initial randomisation)
	Number of subjects	281	282
	PASI 75 response (%)	69.8	70.2
	95% CI	(64.38, 75.12)	(64.88, 75.55)
Effect estimate per comparison	PASI 75 response	Comparison groups	ABP 654 (initial randomisation); Ustekinumab (initial randomisation)
		Response difference	-0.32
		95% CI	(-7.87, 7.23)
Notes	Results of the secondary endpoints of PASI percent improvement from baseline at other timepoints, PASI 75 response throughout the study, PASI 100 response throughout the study, sPGA response at week 12 and week 52, and BSA change from baseline at week 12 and week 52 support the conclusion of clinical similarity.		

2.6.5.4. Clinical studies in special populations

N/A

2.6.5.5. In vitro biomarker test for patient selection for efficacy

N/A

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

N/A

2.6.5.7. Supportive study(ies)

Usability of the pre-filled syringe – Human factor studies

The human factors engineering programme for the pre-filled syringe of ABP 654 included use-related risk analysis (URRA), formative testing and a final human factors summative validation study including simulated use and knowledge assessment.

A total of 66 study participants in the final human factor validation study represented adult patients, adolescents, caregivers, and healthcare professionals/providers (HCPs). Additional 18 pharmacist participants were also included to evaluate the ABP 654 Commercial PFS with ANG+ labelling to support dispensing medication for patient use, but they did not perform the simulated injection task. Overall, only forty-nine (49) of sixty-six (66) participants completed a successful injection (delivered a full and correct dose of medication). However, it must be noted that device training was not provided during the study and the participants were not prompted to use the instructions for use during the simulated use. Also 10 of the 17 participants who did not successfully administer the full dose were adolescents. In the product information of ABP 654 it is however prompted that patients or their caregivers may inject the product only if a physician determines that it is appropriate and after they have received proper training in subcutaneous injection technique.

2.6.6. Discussion on clinical efficacy

No dose response studies were performed and such studies are not required in the biosimilarity setting.

Design and conduct of clinical studies

The clinical development programme to compare clinical efficacy, safety and immunogenicity between ABP 654 and Stelara comprised a single randomised, double-blind, active-controlled, multicentre phase III study (Study 20190232). The study was designed to assess equivalence of ABP 654 to Stelara in patients with moderate to severe plaque psoriasis.

The currently approved indications for Stelara (EU) (ustekinumab) are adult and paediatric plaque psoriasis (Ps), adult psoriatic arthritis (PsA), Crohn's disease (CD) and ulcerative colitis (UC). The same indications and posology are claimed for Wezenla except for ulcerative colitis (UC).

Participants and treatment

The study was conducted in men and women ≥ 18 years and ≤ 75 years of age with stable moderate to severe Ps for at least 6 months. 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.

Overall, the study population is considered representative of the target population in plaque-type psoriasis and baseline characteristics were generally balanced between study arms. Contrary to the scientific advice, there were no restrictions regarding upper and lower body weight (BW) in the eligibility criteria. Patients with BW ≤100 kg received a dose of 45mg ustekinumab, while patients with BW >100 kg received a dose of 90 mg. This is suboptimal as two different dosing regimens create heterogeneity and could reduce sensitivity to detect differences. However, based on the results and the subgroup analyses, the heterogeneity did not seem problematic. This was accepted by the CHMP.

Subjects received ABP 654 or Stelara subcutaneously at a dose of 45 mg (baseline body weight [BW] ≤ 100 kg) or 90 mg (baseline BW > 100 kg). Initial loading doses were administered at Weeks 1 and 4, followed by the same dose once every 12 weeks (Weeks 16, 28 and 40). The dosing regimen is in line with the approved dosing for Stelara.

The study was conducted at 84 centres in Europe and North America. The comparator used was at all centres was EU approved Stelara. This was agreed by the CHMP.

Conduct and methods of analysis

The study was divided into two phases. Initially, subjects were randomised to 1 of 2 treatment groups to receive either ABP 654 or Stelara. After week 28, only responders (PASI 50 or better) continued. At week 28, all subjects with a PASI 75 response or better who initially received Stelara were re-randomised to receive either Stelara (SC, every 12 weeks [Q12W]) or ABP 654. Subjects with a PASI 50 response or better who initially received Stelara were also re-randomised if not deemed to benefit from a dose-intensification. Responders who initially received ABP 654 continued to receive ABP 654 Q12W at weeks 28 and 40, if not deemed to benefit from a dose-intensification.

At the investigator's discretion, a subgroup of subjects who achieved PASI 50 response or better, but did not achieve PASI 75 response or better at week 28 received dose intensification. These subjects remained on their original treatment and were not re-randomised but the dosing frequency was increased to Q8W at weeks 28, 36, and 44. These subjects were included in a separate treatment arm, the results of which are not relevant for the bioequivalence setting as the dose intensification scheme is not in line with the EU approved label for Stelara in the treatment of Ps.

The primary efficacy endpoint was the Psoriasis Area and Severity Index (PASI) percent improvement from baseline to week 12, which is considered sufficiently sensitive to detect potential clinically meaningful differences in efficacy of ABP 654 and Stelara, if such differences exist. The 15% noninferiority margin is acceptable to the CHMP.

With respect to the timing of the primary analysis, during the scientific advice (EMA/CHMP/SAWP/647848/2019), the CHMP criticised the choice of Week 12, since at this time point the plateau is almost reached. As the sensitivity to detect differences between treatments is potentially higher at the steeper part of the time/response curve, an earlier time point (e.g. week 8) was recommended to be used instead. Although this advice was not followed, additional comparisons have been provided for Weeks 4, 12, 16, 28, 40 (EoT), and 52 (EoS). According to the PI, the dosing is done at weeks 0, 4 and 16 and subsequently Q12W. Discontinuing treatment should be considered in patients who have shown no response up to 28 weeks of treatment. Based on the approved instructions on dosing and evaluation of response for Stelara, response evaluation at week 8 is not clinically meaningful. Therefore, this deviation from the given scientific advice is acceptable to the CHMP.

The end of study evaluations were done at week 52. The one-year follow up is appropriate for evaluation of efficacy, safety and immunogenicity of the continuous treatment.

Sample size and statistical analysis

Approximately 542 adult subjects were planned to be randomised. The sample size of the study was adequately justified based on the data from the placebo-controlled trials PHOENIX 1 or PHOENIX 2 of the originator and was sufficient to meet the primary study objective. The estimand and methodology for statistical analysis of the primary endpoint were overall appropriate. Given the low number of intercurrent events or missing data, the pre-planned sensitivity analyses to address these aspects appeared redundant.

The clinical development followed the applicable guidelines Guideline on similar biological medicinal products (EMEA/CHMP/42832/2005 Rev. 1) and Guideline on Similar Biological Medicinal Products Containing Monoclonal Antibodies - Non-Clinical and Clinical Issues (EMA/CHMP/BMWP/403543/2010).

Scientific advice on the design of the clinical comparability study was given by EMA in December 2019 EMA/CHMP/SAWP/647848/2019. The advice was sufficiently followed.

Overall, the study design agreed by the CHMP.

Efficacy data and additional analyses

Primary endpoint

The primary efficacy endpoint was PASI percent improvement from baseline to week 12. The 95% CI of the mean difference between the treatment groups was within the prespecified similarity margin of (-15, +15). The observed mean difference was 0.14 percentage points (95% CI 3.16, 3.43), i.e., neither clinically nor statistically significant.

Sensitivity analyses showed that results were consistent over different analysis sets (FAS and PP) and regardless of choice of imputation method for missing values (LOCF or MMRM), which could be expected given the low number of intercurrent events or missing evaluations at Week 12.

Subgroup analyses were performed for the following subgroups: prior biologic use for psoriasis (yes, no), baseline BW group (≤ 100 kg vs > 100 kg), geographic region (North America vs Europe), age (< 65 years vs ≥ 65 years), race (white vs non-white), sex (female vs male), and disease duration (< 1 year vs ≥ 1 year). In general, PASI percent improvement was comparable to the overall study population across all subgroups and similar between treatment groups.

Clinical comparability is concluded in all subgroups, including patients with BW >100kg and patients aged ≥ 65 years. Hence, results from the primary endpoint are robust and support similarity of Wezenla with the reference product.

Secondary endpoints

PASI percent improvement from baseline was evaluated at weeks 4, 12, 16, and 28. In line with the MA studies for the reference product, a clear improvement in PASI scores was seen in both treatment arms already at 4 weeks and most of the response was achieved by week 12. PASI percent improvement from baseline was similar between the 2 treatment groups through week 28.

Only responders (PASI 50 or higher) continued in the study beyond week 28. Among subjects who did not undergo dose intensification, no relevant difference was seen between treatment arms in PASI improvement up to week 52, regardless of whether the treatment was switched at week 28 or continued as initially randomised.

The overall PASI improvement seemed similar between treatment groups also among subjects who had a dose intensification from week 28 onward but no apparent benefit associated with the dose intensification was seen.

With regard to percentage of patients achieving PASI75, PASI100, sPGA response and BSA change from baseline, no clinically or statistically meaningful differences were seen between the groups through week 28 and over the entire study for each population/dataset analysed. Any observed differences across the treatment groups after re-randomisation and switching were not clinically relevant and there was no trend of divergence between groups.

Usability

The human factors engineering programme for the pre-filled syringe of ABP 654 included use-related risk analysis (URRA), formative testing and a final human factors summative validation study including simulated use and knowledge assessment. In general, the human factors validation test participants should be representative of the range of characteristics within their user group and i.e., if the device is intended to treat patients who have a medical condition that can cause them to have functional limitations, such patients should be included in the human factor validation testing. The adult patients in summative validation study seemed to include only a few users with psoriatic arthritis, a condition which may affect the use of the device due to dexterity impairments. During the procedure, the

applicant provided further information on the disease characteristics of the users and justified how the usability of the device has been ensured among PsA patients with potential dexterity limitations. This was accepted by the CHMP.

The IFU contains step by step instructions on how to use the ABP 654 pre-filled syringe along with graphic representations of what each step looks like. One minor amendment was made to the final IFU concerning the product administration in children and adolescents 12 years of age and older which was accepted by the CHMP.

Therefore, it is considered that study results adequately supported the safe and effective use of the PFS.

2.6.7. Conclusions on clinical efficacy

The clinical development programme of Wezenla is adequate to support biosimilarity with the reference product.

The efficacy of ABP 654 is similar to that of Stelara (EU) in subjects with moderate to severe Ps. Comparability has also been shown in subgroups, including patients with BW >100kg and patients aged ≥ 65 years.

Switch from Stelara to ABP 654 has also been studied. Most efficacy parameters support the switch and there is no or only slight difference between switched and non-switched groups.

The Human factor study results adequately supported the safe and effective use of the PFS.

2.6.8. Clinical safety

The safety information is based on two clinical studies: a single dose PK study in healthy volunteers (Study 20190230) and a clinical efficacy and safety study in patients with moderate to severe plaque psoriasis (Ps, Study 20190232). Both studies have been completed, with full data included in the MAA.

For both clinical studies, the safety analyses were performed on the safety analysis set which included all randomised subjects who received any investigational product; all safety analyses were conducted according to the actual treatment received. The safety data are presented individually for each study given the different patient populations (healthy adult subjects and subjects with moderate to severe Ps) using different dosing regimens.

The safety endpoints analysed in both clinical studies include treatment-emergent adverse events (TEAEs), serious adverse events (SAEs), and events of interest (EOIs). Immunogenicity (i.e., incidence of antidrug antibodies [ADA]) and changes in laboratory values and vital signs were also reviewed to assess clinical significance in the overall safety profile. All safety analyses, including immunogenicity, are presented descriptively.

EOIs (defined as clinically noteworthy events for a particular product or class of products that a sponsor may wish to monitor carefully) identified for the PK similarity study and the comparative clinical study were serious systemic hypersensitivity reactions, facial palsy, pustular psoriasis, erythrodermic psoriasis, serious infections (including mycobacterial and salmonella infections), malignancy, cardiovascular events, reversible posterior leukoencephalopathy syndrome (RPLS), serious depression including suicidality, and venous thromboembolism.

All safety data for the clinical studies are summarised by treatment group; for Study 20190232, when discussing safety data through week 28, treatment groups are identified by actual treatment received (i.e., ABP 654 treatment group and ustekinumab* treatment group); when discussing safety data post week 28 and when discussing safety data over the entire study, treatment groups are identified by the

actual treatment sequence received (i.e., ABP 654/ABP 654 treatment group, ustekinumab/ustekinumab treatment group, and ustekinumab/ABP 654 treatment group). Safety data are summarised over the entire study for both studies.

* ***N.B.*** *In the MAA documents, the applicant refers to Stelara as Ustekinumab. Therefore, in many of the tables and data copied from the submitted materials the name ustekinumab is used for Stelara. For the biosimilar under assessment only the name ABP 654 is used.*

2.6.8.1. Patient exposure

Within the development programme, a total of 799 subjects, either healthy subjects or subjects with moderate to severe Ps, received any amount of ABP 654 or Stelara (referred to as "ustekinumab" below). Of the 799 subjects who received investigational product, 475 received ABP 654. Overall extent of exposure is summarised in Table 24.

Table 24. Overall extent of exposure to investigational product (all clinical studies)

Study Type / Study Number	Number of Subjects Receiving any Amount of Investigational Product			
	ABP 654	Ustekinumab (US)	Ustekinumab (EU)[a]	Total
PK similarity study in healthy adult subjects				
Study 20190230	78	79	80	237
Comparative clinical study in subjects with moderate to severe plaque psoriasis				
Study 20190232	397[b]		282	562
All clinical studies				
Total	475	79	362	799

CSR = clinical study report; EU = European Union; PK = pharmacokinetic; US = United States
[a] Only ustekinumab (EU) is being used in Study 20190232.
[b] Includes 280 subjects that were initially randomized to and treated with ABP 654 in the ABP 654 treatment group and 117 subjects that were initially randomized to and treated with ustekinumab in the ustekinumab treatment group and were re-randomized and treated with ABP 654 at week 28 (ie, the ustekinumab/ABP 654 treatment group).
Sources: Table 14-1.2.1 in the Study 20190230 CSR and Table 14-1.3 and Table 14-1.2.2 in the Study 20190232 CSR

In the PK study 20190230, all 237 subjects in the safety analysis set received a single 90 mg SC injection of either ABP 654, ustekinumab (US), or ustekinumab (EU).

Of the 563 subjects randomised into the clinical Ps study, 562 (99.8%) were treated with investigational product and were included in the safety analysis set. Of these, 280 subjects were exposed to ABP 654 throughout their participation, 165 subjects were exposed to ustekinumab (EU) throughout their participation, and 117 subjects were treated with ustekinumab (EU) until week 28 and then switched to ABP 654.

Extent of exposure through week 28, post week 28 for re-randomised subjects who were treated post re-randomisation (re-randomised safety analysis set), and post week 28 for subjects who received dose intensification (these subjects remained on their original treatment and were not re-randomised) are summarised in Tables 23, 24 and 25 below.

Table 25. Exposure summary through week 28 (Study 20190232 Safety Analysis Set)

Variable	ABP 654 (N = 280)	Ustekinumab (N = 282)
Subjects receiving at least 1 dose	280	282
Total number of doses administered[a]		
n	280	282
Mean (SD)	3.0 (0.19)	3.0 (0.23)
Total dose received (mg)		
n	280	282
Mean (SD)	179.5 (64.26)	176.6 (63.49)
Total investigational product exposure duration (weeks)		
n	280	282
Mean (SD)	27.92 (1.771)	27.83 (3.259)
Subjects who missed at least 1 dose of investigational product due to COVID-19-related reasons – n (%)	0 (0.0)	2 (0.7)
One dose not administered	0 (0.0)	2 (0.7)
Subjects with at least 1 dose delay/not administered – n (%)	65 (23.2)	61 (21.6)
Related to COVID-19	2 (0.7)	6 (2.1)
Not related to COVID-19	64 (22.9)	56 (19.9)
Reasons for dose delay/not administered – n (%)[b]		
Adverse event – related to COVID-19	0 (0.0)	0 (0.0)
Adverse event – not related to COVID-19	0 (0.0)	1 (0.4)
Other – related to COVID-19 control measures	2 (0.7)	6 (2.1)
Other – not related to COVID-19 control measures	64 (22.9)	55 (19.5)

COVID-19 = coronavirus disease 2019; eCRF = electronic case report form

Note: A dose was considered delayed/not administered when the investigational product administration eCRF indicated that no dose was given and a reason for dose delay/not administered was present.

[a] Subject with baseline weight ≥ 100 kg was incorrectly stratified to the < 100 kg group, which resulted in 2 partial doses of study drug (45 mg) on study days 1 and 7, 2 partial doses of study drug (45 mg) on study day 33 (week 4), and a full dose of study drug (90 mg) on study day 113 (week 16). Therefore, the subject received 4 partial doses and 1 full dose of study drug for a total of 3 full doses of study drug.

[b] Subjects could have more than one incidence of event. Their corresponding events are displayed for each reason but are only counted once for each reason.

Source: Modified from Table 14-5.1.2 in the Study 20190232 CSR

Subject dispositions for the initial 28-week period and for the re-randomised population are displayed in Table 26 and Table 27, respectively.

Table 26. Exposure summary post week 28 (Study 20190232 Re-randomised Safety Analysis Set)

Variable	ABP 654/ ABP 654 (N = 247)	Ustekinumab/ ABP 654 (N = 117)	Ustekinumab/ Ustekinumab (N = 116)
Subjects receiving at least 1 dose	247	117	116
Total number of doses administered			
n	247	117	116
Mean (SD)	2.0 (0.09)	2.0 (0.13)	2.0 (0.18)
Total dose received (mg)			
n	247	117	116
Mean (SD)	119.0 (42.42)	118.8 (42.80)	117.2 (42.74)
Total investigational product exposure duration (weeks)			
n	247	117	116
Mean (SD)	24.24 (1.466)	23.99 (2.174)	23.70 (3.069)
Subjects who missed at least 1 dose of investigational product due to COVID-19-related reasons – n (%)	0 (0.0)	0 (0.0)	0 (0.0)
Subjects with at least 1 dose delay/not administered – n (%)	38 (15.4)	19 (16.2)	13 (11.2)
Related to COVID-19	2 (0.8)	1 (0.9)	2 (1.7)
Not related to COVID-19	36 (14.6)	18 (15.4)	11 (9.5)
Reasons for dose delay/not administered – n (%)[a]			
Adverse event – related to COVID-19	0 (0.0)	1 (0.9)	1 (0.9)
Adverse event – not related to COVID-19	3 (1.2)	2 (1.7)	1 (0.9)
Other – related to COVID-19 control measures	2 (0.8)	0 (0.0)	1 (0.9)
Other – not related to COVID-19 control measures	33 (13.4)	16 (13.7)	10 (8.6)

COVID-19 = coronavirus disease 2019; CSR = clinical study report; eCRF = electronic case report form
Note: A dose was considered delayed/not administered when the investigational product administration eCRF indicated that no dose was given and a reason for dose delay/not administered was present.
[a] Subjects could have more than one incidence of event. Their corresponding events are displayed for each reason but are only counted once for each reason.
Source: Modified from Table 14-5.1.3 in the Study 20190232 CSR

Table 27. Exposure summary post week 28 (Study 20190232 Dose Intensification Subjects)

Variable	ABP 654 (N = 25)	Ustekinumab (N = 34)
Subjects receiving at least 1 dose	25	34
Total number of doses administered		
n	25	34
Mean (SD)	3.0 (0.00)	3.0 (0.00)
Total dose received (mg)		
n	25	34
Mean (SD)	180.0 (63.64)	162.8 (55.41)
Total investigational product exposure duration (weeks)		
n	25	34
Mean (SD)	24.37 (0.431)	24.22 (0.680)
Subjects who missed at least 1 dose of investigational product due to COVID-19-related reasons – n (%)	0 (0.0)	0 (0.0)
Subjects with at least 1 dose delay/not administered – n (%)	3 (12.0)	5 (14.7)
Related to COVID-19	0 (0.0)	0 (0.0)
Not related to COVID-19	3 (12.0)	5 (14.7)
Reasons for dose delay/not administered – n (%)[a]		
Adverse event – related to COVID-19	0 (0.0)	0 (0.0)
Adverse event – not related to COVID-19	0 (0.0)	0 (0.0)
Other – related to COVID-19 control measures	0 (0.0)	0 (0.0)
Other – not related to COVID-19 control measures	3 (12.0)	5 (14.7)

COVID-19 = coronavirus disease 2019; CSR = clinical study report; eCRF = electronic case report form
Note: A dose was considered delayed/not administered when the investigational product administration eCRF indicated that no dose was given and a reason for dose delay/not administered was present.
[a] Subjects could have more than one incidence of event. Their corresponding events are displayed for each reason but are only counted once for each reason.
Source: Modified from Table 14-5.1.4 in the Study 20190232 CSR

Table 28. Study and investigational product disposition by initial randomisation (Study 20190232 Full Analysis Set)

Variable	ABP 654 (N = 281) n (%)	Ustekinumab (N = 282) n (%)	Total (N = 563) n (%)
Subjects randomized	281 (100)	282 (100)	563 (100)
Subjects treated with IP	280 (99.6)	282 (100)	562 (99.8)
Completed IP prior to week 28[a]	277 (98.6)	275 (97.5)	552 (98.0)
Discontinued IP prior to week 28	3 (1.1)	6 (2.1)	9 (1.6)
Adverse event	1 (0.4)	3 (1.1)	4 (0.7)
Lost to follow-up	1 (0.4)	1 (0.4)	2 (0.4)
Death	0 (0.0)	1 (0.4)	1 (0.2)
Subject dissatisfaction with treatment efficacy	0 (0.0)	1 (0.4)	1 (0.2)
Other	1 (0.4)	0 (0.0)	1 (0.2)
Discontinued IP prior to week 28 due to COVID-19 related reasons	0 (0.0)	1 (0.4)	1 (0.2)
Subjects re-randomized at week 28	247 (87.9)	233 (82.6)	480 (85.3)
Subject not re-randomized at week 28[b]	34 (12.1)	49 (17.4)	83 (14.7)
Required intensified dose	25 (8.9)	34 (12.1)	59 (10.5)
PASI percent improvement < 50	2 (0.7)	3 (1.1)	5 (0.9)
Subject did not have week 28 visit	0 (0.0)	1 (0.4)	1 (0.2)
Discontinued study prior to week 28	7 (2.5)	11 (3.9)	18 (3.2)
Adverse event	2 (0.7)	3 (1.1)	5 (0.9)
Death	0 (0.0)	1 (0.4)	1 (0.2)
Consent withdrawn	0 (0.0)	2 (0.7)	2 (0.4)
Lost to follow-up	2 (0.7)	2 (0.7)	4 (0.7)
Protocol violation	0 (0.0)	3 (1.1)	3 (0.5)
Other	3 (1.1)	0 (0.0)	3 (0.5)
Completed IP[c,d]	270 (96.1)	264 (93.6)	534 (94.8)
Discontinued IP[d,e]	10 (3.6)	17 (6.0)	27 (4.8)
Adverse event	3 (1.1)	4 (1.4)	7 (1.2)
Lost to follow-up	3 (1.1)	5 (1.8)	8 (1.4)
Death	0 (0.0)	1 (0.4)	1 (0.2)
Subject dissatisfaction with treatment efficacy	0 (0.0)	1 (0.4)	1 (0.2)
Protocol violation	0 (0.0)	3 (1.1)	3 (0.5)
Other	4 (1.4)	3 (1.1)	7 (1.2)

Table 28. (Continued) Study and investigational product disposition by initial randomisation (Study 20190232 Full Analysis Set)

Variable	ABP 654 (N = 281) n (%)	Ustekinumab (N = 282) n (%)	Total (N = 563) n (%)
Completed study[f]	269 (95.7)	261 (92.6)	530 (94.1)
At week 28	2 (0.7)	3 (1.1)	5 (0.9)
At week 52	267 (95.0)	258 (91.5)	525 (93.3)
Discontinued study[e]	12 (4.3)	21 (7.4)	33 (5.9)
Adverse event	3 (1.1)	4 (1.4)	7 (1.2)
Death	0 (0.0)	1 (0.4)	1 (0.2)
Consent withdrawn	2 (0.7)	5 (1.8)	7 (1.2)
Lost to follow-up	4 (1.4)	8 (2.8)	12 (2.1)
Protocol violation	0 (0.0)	3 (1.1)	3 (0.5)
Other	3 (1.1)	0 (0.0)	3 (0.5)
Discontinued study due to COVID-19 related reasons	0 (0.0)	4 (1.4)	4 (0.7)
Death	0 (0.0)	1 (0.4)	1 (0.2)
Protocol violation	0 (0.0)	3 (1.1)	3 (0.5)

COVID-19 = coronavirus disease 2019; eCRF = electronic case report form; IP = investigational product; PASI 50 = ≥ 50% improvement in Psoriasis Area and Severity Index

[a] Completed IP prior to week 28 included subjects who completed dosing at week 16.

[b] Subjects not re-randomised at week 28 included subjects who reached week 28 but could not be re-randomised in addition to subjects who discontinued the study prior to week 28, and subjects who did not have a week 28 visit.

[c] Completed IP included PASI 50 non-responders who completed dosing at week 16 and dose intensification subjects who completed dosing at week 44 and re-randomised subjects who completed dosing at week 40.

[d] One subject had missing end of IP data and was not included in either the completed IP or discontinued IP category.

[e] Included subjects who discontinued IP/study due to COVID-19 related reasons and non-COVID-19 related reasons.

[f] Completed study included PASI 50 non-responders who completed study at week 28 and PASI 50 responders at week 28 who completed study at week 52.

Source: Modified from Table 14-1.2.1 in the Study 20190232 CSR

Table 29. Study and investigational product disposition by initial/re-randomisation (Study 20190232 Re-randomised Full Analysis Set)

Variable	ABP 654/ ABP 654 (N = 247) n (%)	Ustekinumab/ ABP 654 (N = 117) n (%)	Ustekinumab/ Ustekinumab (N = 116) n (%)	Total (N = 480) n (%)
Subjects re-randomised at week 28	247 (100)	117 (100)	116 (100)	480 (100)
Subjects treated post week 28 re-randomisation	247 (100)	117 (100)	116 (100)	480 (100)
Completed IP[a,b]	245 (99.2)	115 (98.3)	112 (96.6)	472 (98.3)
Discontinued IP[b,c]	2 (0.8)	1 (0.9)	4 (3.4)	7 (1.5)
Adverse event	1 (0.4)	0 (0.0)	1 (0.9)	2 (0.4)
Lost to follow-up	1 (0.4)	1 (0.9)	2 (1.7)	4 (0.8)
Other	0 (0.0)	0 (0.0)	1 (0.9)	1 (0.2)

Discontinued IP due to COVID-19 related reasons	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
Completed study	242 (98.0)	113 (96.6)	110 (94.8)	465 (96.9)
Discontinued study[c]	5 (2.0)	4 (3.4)	6 (5.2)	15 (3.1)
Adverse event	1 (0.4)	0 (0.0)	1 (0.9)	2 (0.4)
Consent withdrawn	2 (0.8)	1 (0.9)	2 (1.7)	5 (1.0)
Lost to follow-up	2 (0.8)	3 (2.6)	3 (2.6)	8 (1.7)
Discontinued study due to COVID-19 related reasons	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)

COVID-19 = coronavirus disease 2019; IP = investigational product

[a] Completed IP included subjects who completed dosing at week 40.

[b] One subject had missing end of IP data and was not included in either the completed IP or discontinued IP category.

[c] Included subjects who discontinued IP/study due to COVID-19 related reasons and non-COVID-19 related reasons.

Source: Modified from Table 14-1.2.2 in the Study 20190232 CSR

2.6.8.2. Adverse events

Single dose PK study 20190230

In Study 20190230, AEs were reported by 22 (28.2%) subjects in the ABP 654 treatment group, 18 (22.8%) subjects in the ustekinumab (US) treatment group, and 29 (36.3%) subjects in the ustekinumab (EU) treatment group. A summary of AEs is displayed in Table 30.

Table 30. Overall summary of adverse events (Study 20190230 Safety Analysis Set)

	ABP 654 (N = 78) n (%)	Ustekinumab (US) (N = 79) n (%)	Ustekinumab (EU) (N = 80) n (%)
Any adverse event	22 (28.2)	18 (22.8)	29 (36.3)
Any grade ≥ 3 adverse event	0	1 (1.3)	1 (1.3)
Any fatal adverse event	0	0	0
Any serious adverse event	0	1 (1.3)	1 (1.3)
Any adverse event leading to discontinuation of study	0	0	0
Any adverse event of interest	0	1 (1.3)	1 (1.3)
Any COVID-19 adverse event	0	2 (2.5)	0

COVID-19 = coronavirus disease 2019; CSR = clinical study report; EU = European Union; US = United States

Note: Only treatment-emergent adverse events were summarized by actual treatment received. For each category, subjects were included only once, even if they experienced multiple adverse events in that category.

Sources: Modified from Table 14-6.1 and Table 14-6.2.1.1.2 in the Study 20190230 CSR

The most common AEs are shown in Table 29. Most AEs were CTCAE grade 1 or 2 in severity. Grade ≥ 3 AEs were reported in 1 (1.3%) subject each in the ustekinumab (US) (grade 3 events of Crohn's disease and small intestinal obstruction) and ustekinumab (EU) (grade 3 event of appendicitis perforated) treatment groups. Each of the grade ≥ 3 AEs were also identified as SAEs and considered not related to study drug.

Table 31. Treatment-emergent adverse events experienced by ≥ 2 subjects in any treatment group by preferred term (Study 20190230 Safety Analysis Set)

Preferred Term	ABP 654 (N = 78) n (%)	Ustekinumab (US) (N = 79) n (%)	Ustekinumab (EU) (N = 80) n (%)
Any adverse event	22 (28.2)	18 (22.8)	29 (36.3)
Headache	9 (11.5)	3 (3.8)	9 (11.3)
Oropharyngeal pain	2 (2.6)	1 (1.3)	1 (1.3)
Vomiting	2 (2.6)	0	0
Pruritus	1 (1.3)	2 (2.5)	1 (1.3)
Abdominal pain	0	1 (1.3)	4 (5.0)
Acne	0	0	3 (3.8)
Back pain	0	2 (2.5)	2 (2.5)
COVID-19	0	2 (2.5)	0
Diarrhea	0	0	3 (3.8)
Epistaxis	0	0	2 (2.5)
Myalgia	0	2 (2.5)	2 (2.5)
Nausea	0	2 (2.5)	1 (1.3)
Rhinorrhea	0	2 (2.5)	0

COVID-19 = coronavirus disease 2019; CSR = clinical study report; EU = European Union; US = United States
Note: Only treatment-emergent adverse events were summarized. For each preferred term, subjects were included only once, even if they experienced multiple events in that preferred term.
Source: Modified from Table 14-6.2.1.1.1 from the Study 20190230 CSR

Clinical Ps study 20190232

An overall summary of AEs through week 28 is presented in Table 32.

Table 32. Overall summary of adverse events through week 28 (Study 20190232 Safety Analysis Set)

Adverse Event Category	ABP 654 (N = 280) n (%)	Ustekinumab (N = 282) n (%)
Any adverse event	106 (37.9)	99 (35.1)
Any grade ≥ 3 adverse event	8 (2.9)	5 (1.8)
Any fatal adverse event	0 (0.0)	1 (0.4)
Any serious adverse event	7 (2.5)	5 (1.8)
Any adverse event leading to discontinuation of IP/study	2 (0.7)	4 (1.4)
Any EOI	5 (1.8)	7 (2.5)
Any adverse event leading to dose delayed[a]	0 (0.0)	1 (0.4)
Any COVID-19 adverse event	6 (2.1)	5 (1.8)

COVID-19 = coronavirus disease 2019; CSR = clinical study report; EOI = event of interest; IP = investigational product
Note: Only treatment-emergent adverse events were summarized by actual treatment received. For each category, subjects were included only once, even if they experienced multiple events in that category.
[a] An adverse event was only summarized as leading to dose delay of IP if that was the last action taken with IP for the given event.
Sources: Modified from Table 14-6.1.2 and Table 14-6.2.44 in the Study 20190232 CSR

The AEs reported by 2% or more of subjects in any treatment group through week 28 are presented by SOC in Table 33.

Table 33. Adverse events experienced by ≥ 2% of subjects in any treatment group by system organ class through week 28 (Study 20190232 Safety Analysis Set)

System Organ Class	ABP 654 (N = 280) n (%)	Ustekinumab (N = 282) n (%)
Infections and infestations	40 (14.3)	31 (11.0)
Musculoskeletal and connective tissue disorders	20 (7.1)	16 (5.7)
Injury, poisoning, and procedural complications	12 (4.3)	12 (4.3)
Skin and subcutaneous tissue disorders	11 (3.9)	7 (2.5)
Gastrointestinal disorders	8 (2.9)	7 (2.5)
General disorders and administration site conditions	8 (2.9)	9 (3.2)
Nervous system disorders	8 (2.9)	13 (4.6)
Vascular disorders	7 (2.5)	8 (2.8)
Reproductive system and breast disorders	6 (2.1)	2 (0.7)
Respiratory, thoracic, and mediastinal disorders	5 (1.8)	6 (2.1)

CSR = clinical study report; MedDRA = Medical Dictionary for Regulatory Activities
Note: Adverse events were coded using MedDRA version 24.1. Only treatment-emergent adverse events were summarized. For each system organ class, subjects were included only once, even if they experienced multiple events in that system organ class.
Source: Modified from Table 14-6.3.2 in the Study 20190232 CSR

The most common individual AEs by PT through week 28 are shown in Table 34. Grade ≥ 3 events occurred in 8 (2.9%) subjects in the ABP 654 treatment group and 5 (1.8%) subjects in the ustekinumab treatment group (Table 41). All reported CTCAE grade ≥ 3 events were single occurrences.

Table 34. Adverse events experienced by ≥ 2% of subjects in any treatment group by preferred term through week 28 (Study 20190232 Safety Analysis Set)

Preferred Term	ABP 654 (N = 280) n (%)	Ustekinumab (N = 282) n (%)
Hypertension	7 (2.5)	6 (2.1)
Nasopharyngitis	7 (2.5)	3 (1.1)
COVID-19	6 (2.1)	5 (1.8)
Headache	6 (2.1)	7 (2.5)
Upper respiratory tract infection	6 (2.1)	7 (2.5)

COVID-19 = coronavirus disease 2019; CSR = clinical study report; MedDRA = Medical Dictionary for Regulatory Activities

Note: Adverse events were coded using MedDRA version 24.1. Only treatment-emergent adverse events were summarized. For each preferred term, subjects were included only once, even if they experienced multiple events in that preferred term.

Source: Modified from Table 14-6.2.2 from the Study 20190232 CSR

Table 35. Grade ≥ 3 treatment-emergent adverse events by preferred term - through week 28 (Safety Analysis Set)

Preferred Term	ABP 654 (N = 280) n (%)	Ustekinumab (N = 282) n (%)
Any adverse event	8 (2.9)	5 (1.8)
Anaphylactic reaction	1 (0.4)	0 (0.0)
COVID-19 pneumonia	1 (0.4)	0 (0.0)
Cholelithiasis	1 (0.4)	0 (0.0)
Femoral neck fracture	1 (0.4)	0 (0.0)
Gastritis	1 (0.4)	0 (0.0)
Intervertebral disc protrusion	1 (0.4)	0 (0.0)
Invasive lobular breast carcinoma	1 (0.4)	0 (0.0)
Uterine leiomyoma	1 (0.4)	0 (0.0)
Ankle fracture	0 (0.0)	1 (0.4)
Bursitis	0 (0.0)	1 (0.4)
COVID-19	0 (0.0)	1 (0.4)
Cardiac failure congestive	0 (0.0)	1 (0.4)
Cartilage injury	0 (0.0)	1 (0.4)
Osteoarthritis	0 (0.0)	1 (0.4)
Presyncope	0 (0.0)	1 (0.4)
Rotator cuff syndrome	0 (0.0)	1 (0.4)

Note: Adverse events were coded using MedDRA version 24.1. Only treatment-emergent adverse events were summarized. For each preferred term, subjects were included only once, even if they experienced multiple events in that preferred term.

Source: 20190232 CSR Table 14-6.2.5.

For re-randomised subjects, AEs occurring post week 28 were reported in 85 (34.4%) subjects in the ABP 654/ABP 654 treatment group, 44 (37.6%) subjects in the ustekinumab/ABP 654 treatment group, and 40 (34.5%) subjects in the ustekinumab/ustekinumab treatment group. A summary is shown in Table 36. The most commonly affected individual SOC was Infections and infestations (46 (18.6%) subjects in the ABP 654/ABP 654 treatment group, 26 (22.2%) subjects in the ustekinumab/ABP 654 treatment group, and 27 (23.3%) subjects in the ustekinumab/ustekinumab treatment group).

Table 36. Overall summary of adverse events post week 28 (Study 20190232 Re-randomised Safety Analysis Set)

Adverse Event Category	ABP 654/ ABP 654 (N = 247) n (%)	Ustekinumab/ ABP 654 (N = 117) n (%)	Ustekinumab/ Ustekinumab (N = 116) n (%)
Any adverse event	85 (34.4)	44 (37.6)	40 (34.5)
Any grade ≥ 3 adverse event	3 (1.2)	1 (0.9)	4 (3.4)
Any fatal adverse event	0 (0.0)	0 (0.0)	0 (0.0)
Any serious adverse event	1 (0.4)	1 (0.9)	3 (2.6)
Any adverse event leading to discontinuation of IP/study	1 (0.4)	0 (0.0)	1 (0.9)
Any EOI	3 (1.2)	0 (0.0)	4 (3.4)
Any adverse event leading to dose delay of IP[a]	1 (0.4)	3 (2.6)	1 (0.9)
Any COVID-19 adverse event	24 (9.7)	16 (13.7)	11 (9.5)

COVID-19 = coronavirus disease 2019; CSR = clinical study report; EOI = event of interest; IP = investigational product

Note: Only treatment-emergent adverse events were summarized by actual treatment received. For each category, subjects were included only once, even if they experienced multiple events in that category.

[a] An adverse event was only to be summarized as leading to dose delay of IP if that was the last action taken with IP for the given event

Sources: Modified from Table 14-6.1.3 and Table 14-6.2.45 in the Study 20190232 CSR

The most common individual AEs reported among re-randomised subjects post week 28 are summarised in Table 37. Most events were maximum CTCAE grade 1 or grade 2; grade ≥ 3 events were reported in 3 (1.2%) subjects in the ABP 654/ABP 654 treatment group, 1 (0.9%) subject in the ustekinumab/ABP 654 treatment group, and 4 (3.4%) subjects in the ustekinumab/ustekinumab treatment group. No grade ≥ 3 AE by preferred term occurred in more than 1 subject in any treatment group.

Table 37. Adverse events experienced by ≥ 2% of subjects in any treatment group by preferred term post week 28 (Study 20190232 Re-randomised Safety Analysis Set)

Preferred Term	ABP 654/ ABP 654 (N = 247) n (%)	Ustekinumab/ ABP 654 (N = 117) n (%)	Ustekinumab/ Ustekinumab (N = 116) n (%)
COVID-19	23 (9.3)	15 (12.8)	11 (9.5)
Nasopharyngitis	9 (3.6)	1 (0.9)	7 (6.0)
Upper respiratory tract infection	6 (2.4)	6 (5.1)	3 (2.6)

COVID-19 = coronavirus disease 2019; CSR = clinical study report; MedDRA = Medical Dictionary for Regulatory Activities

Note: Adverse events were coded using MedDRA version 24.1. Only treatment-emergent adverse events were summarized. For each preferred term, subjects were included only once, even if they experienced multiple events in that preferred term.

Source: Modified from Table 14-6.2.3 in the Study 20190232 CSR

A summary of AEs occurring post week 28 in subjects with dose intensification at week 28 is shown in Table 38.

Table 38. Overall summary of adverse events post week 28 (Study 20190232 Dose Intensification Subjects)

Adverse Event Category	ABP 654 (N = 25) n (%)	Ustekinumab (N = 34) n (%)
Any adverse event	12 (48.0)	9 (26.5)
Any grade ≥ 3 adverse event	1 (4.0)	1 (2.9)
Any fatal adverse event	0 (0.0)	0 (0.0)
Any serious adverse event	1 (4.0)	0 (0.0)
Any adverse event leading to discontinuation of IP/study	0 (0.0)	0 (0.0)
Any EOI	0 (0.0)	0 (0.0)
Any adverse event leading to dose delay of IP[a]	0 (0.0)	0 (0.0)
Any COVID-19 adverse event	5 (20.0)	1 (2.9)

COVID-19 = coronavirus disease 2019; CSR = clinical study report; EOI = event of interest; IP = investigational product

Note: Only treatment-emergent adverse events were summarized by actual treatment received. For each category, subjects were included only once, even if they experienced multiple events in that category.

[a] An adverse event was only to be summarized as leading to dose delay of IP if that was the last action taken with IP for the given event

Sources: Modified from Table 14-6.1.4 and Table 14-6.2.47 in the Study 20190232 CSR

Within the ABP 654 dose intensified treatment group, reported AEs included COVID-19 (5 subjects), nasopharyngitis (2 subjects), hip dysplasia, rhinovirus infection, bronchitis, COVID-19 vaccination complication, abdominal pain, hepatic steatosis, post-traumatic neck syndrome, contusion, skin laceration, and osteoarthritis (1 subject each). A total of 4 subjects in the ABP 654 dose intensified treatment group had AE preferred terms relating to abnormal laboratory results. With the exception of a serious event of grade 3 hip dysplasia, all events were nonserious and grade 1 or 2.

Within the ustekinumab dose intensified treatment group, reported AEs included vertigo, hyperglycaemia, diabetes mellitus, hypercholesterolaemia, cystitis, COVID-19, bacterial vaginosis, upper respiratory tract infection, urinary tract infection, back pain, and forearm fracture. All AEs in the ustekinumab dose intensified treatment group occurred in single subjects and all were nonserious and grade 1 or 2, except for the event of vertigo that was reported as grade 3.

None of the AEs occurring in the dose intensified treatment groups were considered by the investigator to be related to investigational product.

2.6.8.3. Serious adverse events, deaths, and other significant events

Deaths

No fatal events were reported in the single dose PK study 20190230. Through week 28 of the Ps study 20190232, a fatal AE of COVID-19 was reported in the ustekinumab treatment group; the event occurred in a 65-year-old white male and was considered unrelated to investigational product or study by the investigator. No fatal AEs were reported post week 28.

Other serious adverse events

In the single dose PK study 20190230, 1 (1.3%) subject each in the ustekinumab (US) and ustekinumab (EU) treatment groups reported a non-fatal SAE. The events were grade 3 Crohn's disease and grade 3 small intestinal obstruction in a 33-year-old white female for ustekinumab (US), and grade 3 perforated appendicitis in an 18-year-old white female for ustekinumab (EU). Both events were considered unrelated to investigational product/study per the investigator.

Through week 28 of the Ps study 20190232, the subject incidence of SAEs was 7 (2.5%) subjects in the ABP 654 treatment group and 5 (1.8%) subjects in the ustekinumab treatment group. These are summarised in Table 37.

The anaphylactic reaction occurred in a 31-year-old Asian female diagnosed with cat allergy, asthma, Ps, and psoriatic arthritis. She experienced an SAE of grade 3 anaphylactic reaction, 38 days after the most recent dose of ABP 654. The subject presented at the emergency department with throat tightness, muffled voice, and hives, received treatment with cetirizine, dexamethasone, and epinephrine. The event was reported as resolved within hours on the same day and was considered unrelated to investigational product by the investigator. Antidrug antibody results for this subject were negative at all time points.

Table 39. Serious adverse events by system organ class and preferred term through week 28 (Study 20190232 Safety Analysis Set)

System Organ Class Preferred Term	ABP 654 (N = 280) n (%)	Ustekinumab (N = 282) n (%)
Number of subjects reporting serious treatment-emergent adverse events	7 (2.5)	5 (1.8)
Neoplasms benign, malignant and unspecified (incl cysts and polyps)	2 (0.7)	2 (0.7)
Invasive lobular breast carcinoma	1 (0.4)	0 (0.0)
Uterine leiomyoma	1 (0.4)	0 (0.0)
Clear cell renal cell carcinoma	0 (0.0)	1 (0.4)
Renal neoplasm	0 (0.0)	1 (0.4)
Hepatobiliary disorders	1 (0.4)	0 (0.0)
Cholelithiasis	1 (0.4)	0 (0.0)
Immune system disorders	1 (0.4)	0 (0.0)
Anaphylactic reaction	1 (0.4)	0 (0.0)
Infections and infestations	1 (0.4)	2 (0.7)
COVID-19 pneumonia	1 (0.4)	0 (0.0)
COVID-19	0 (0.0)	1 (0.4)
Cellulitis	0 (0.0)	1 (0.4)
Injury, poisoning, and procedural complications	1 (0.4)	0 (0.0)
Femoral neck fracture	1 (0.4)	0 (0.0)
Vascular disorders	1 (0.4)	0 (0.0)
Hypertension	1 (0.4)	0 (0.0)
Cardiac disorders	0 (0.0)	1 (0.4)
Cardiac failure congestive	0 (0.0)	1 (0.4)
Cardiac ventricular thrombosis	0 (0.0)	1 (0.4)

COVID-19 = coronavirus disease 2019; CSR = clinical study report; MedDRA = Medical Dictionary for Regulatory Activities

Note: Adverse events were coded using MedDRA version 24.1. Only treatment-emergent adverse events were summarized. For each system organ class and preferred term, subjects were included only once, even if they experienced multiple events in that system organ class or preferred term.

Source: Modified from Table 14-6.3.6 of the Study 20190232 CSR

Among subjects re-randomised at week 28, the subject incidence of SAEs post week 28 was 1 (0.4%) subject in the ABP 654/ABP 654 treatment group, 1 (0.9%) subject in the ustekinumab/ABP 654

treatment group, and 3 (2.6%) subjects in the ustekinumab/ustekinumab treatment group. In the ABP 654/ABP 654 treatment group and the ustekinumab/ABP 654 treatment group, the reported SAEs were grade 3 ovarian cancer and grade 3 intervertebral disc disorder, respectively. In the ustekinumab/ustekinumab treatment group, SAEs included preferred terms of grade 3 acute myocardial infarction and grade 4 COVID-19 in one subject, grade 4 bipolar I disorder and grade 3 infected cyst in one subject, as well as grade 3 postoperative wound infection and grade 3 sepsis in one subject.

Among the dose intensification subjects, one (4.0%) subject in the ABP 654 treatment group experienced an SAE of grade 3 hip arthroplasty (considered by the investigator to be unrelated to investigational product) post week 28. No dose intensification subjects in the ustekinumab treatment group experienced an SAE post week 28.

Events of interest

Single dose PK study 20190230

In the single dose PK study 20190230, 1 (1.3%) subject in the ustekinumab (US) treatment group and 1 (1.3%) subject in the ustekinumab (EU) treatment group experienced an EOI. The subject in the ustekinumab (US) treatment group experienced an EOI identified with the applicant's search strategy for RPLS; the event in question was grade 1 nonserious somnolence. The event of grade 1 somnolence occurred on study day 9 (8 days after receiving study drug) and was reported as resolved on study day 13; the subject did not receive any treatment for the event of somnolence. The event of somnolence was considered by the investigator to be unrelated to study drug and unrelated to study procedure/activity, and upon further medical evaluation, the event was deemed not clinically representative of RPLS.

The subject in the ustekinumab (EU) treatment group experienced an EOI of serious infections (including mycobacterial and salmonella infections) with a PT term of grade 3 appendicitis perforated, serious.

There were no serious systemic hypersensitivity reactions, facial palsy, pustular psoriasis, erythrodermic psoriasis, malignancy, cardiovascular events, serious depression including suicidality, or venous thromboembolism EOIs reported. Apart from the pre-defined EOIs, a review of AEs by SOC does not reveal cases of local injection-related reactions.

Clinical Ps study 20190232

An overall summary of EOIs through week 28 of the clinical Ps study is presented in Table 38. No EOIs of serious systemic hypersensitivity reactions, facial palsy, pustular psoriasis, erythrodermic psoriasis, serious depression including suicidality, or venous thromboembolism were reported through week 28.

Table 40. Overall summary of adverse events of interest through week 28 (Study 20190232 Safety Analysis Set)

Adverse Event of Interest	ABP 654 (N = 280)	Ustekinumab (N = 282)	Risk Difference (%) (95% CI)[a]
Any event of interest	5 (1.8)	7 (2.5)	-0.70 (-3.49, 1.99)
Cardiovascular events[b]	2 (0.7)	2 (0.7)	0.01 (-1.94, 1.97)
Malignancy[c]	2 (0.7)	2 (0.7)	0.01 (-1.94, 1.97)
Serious infections[d]	1 (0.4)	2 (0.7)	-0.35 (-2.26, 1.36)
Reversible posterior leukoencephalopathy syndrome[e]	0 (0.0)	1 (0.4)	-0.35 (-2.04, 1.02)

AMQ = Amgen MedDRA Query; CSR = clinical study report; CTCAE = Common Terminology Criteria for Adverse Events; MedDRA = Medical Dictionary for Regulatory Activities; SMQ = Standardized MedDRA Query; SOC = system organ class

Note: Only treatment-emergent adverse events of interest were summarized. For each adverse event of interest, subjects were included only once, even if they experienced multiple events in that adverse event of interest.

[a] Risk difference (ABP 654 – ustekinumab) and CIs were estimated by Wald asymptotic confidence limits, or exact confidence limits if n < 25 for either treatment group.

[b] Identified using the cardiac disorders SOC

[c] Identified using the malignancies SMQ (narrow) search strategy

[d] Identified using the infections and infestations SOC for CTCAE grade ≥ 3 or serious adverse events

[e] Identified using the reversible posterior leukoencephalopathy syndrome AMQ (narrow) search strategy

Source: Modified from Table 14-6.5.2 in the Study 20190232 CSR

- For cardiovascular events, the reported PTs comprised single occurrences of grade 1 arrhythmia (ABP 654), grade 1 cardiac failure congestive (ABP 654), and grade 1 angina pectoris (ustekinumab). One subject in the ustekinumab group had grade 3 cardiac failure congestive and grade 2 cardiac ventricular thrombosis.
- For malignancies, the reported PTs comprised single occurrences of grade 1 basal cell carcinoma (ABP 654), grade 3 invasive lobular breast carcinoma (ABP 654), grade 2 clear cell renal cell carcinoma (ustekinumab) and grade 2 renal neoplasm (ustekinumab).
- For serious infections, the reported PTs comprised single occurrences of grade 3 COVID-19 pneumonia (ABP 654), grade 5 COVID-19 (ustekinumab) and grade 2 cellulitis (ustekinumab)
- For RPLS, the reported PT in the ustekinumab group was grade 1 somnolence, with no other signs or symptoms suggestive of RPLS.
- Apart from the pre-defined EOIs, a review of AEs by SOC indicates that injection site erythema was reported for one subject in the ABP 654 group, and injection site inflammation was reported for one subject in the ustekinumab group.

EOIs occurring post week 28 among re-randomised subjects are summarised in Table 41.

Table 41. Summary of adverse events of interest post week 28 (Study 20190232 Re-randomised Safety Analysis Set)

Adverse Event of Interest	ABP 654/ ABP 654 (N = 247)	Ustekinumab/ ABP 654 (N = 117)	Ustekinumab/ Ustekinumab (N = 116)	Risk Difference (%) (95% CI)[a]	Risk Difference (%) (95% CI)[b]
Any event of interest	3 (1.2)	0 (0.0)	4 (3.4)	-2.23 (-7.57, 1.03)	-3.45 (-8.59, -0.04)
Serious infections[c]	1 (0.4)	0 (0.0)	3 (2.6)	-2.18 (-7.13, 0.37)	-2.59 (-7.47, 0.82)
Cardiovascular events[d]	1 (0.4)	0 (0.0)	3 (2.6)	-2.18 (-7.13, 0.37)	-2.59 (-7.47, 0.82)
Malignancy[e]	1 (0.4)	0 (0.0)	0 (0.0)	0.40 (-3.04, 2.35)	- (-, -)

- = Not available
AMQ = Amgen MedDRA Query; CSR = clinical study report; CTCAE = Common Terminology Criteria for Adverse Events; MedDRA = Medical Dictionary for Regulatory Activities; SMQ = Standardized MedDRA Query; SOC = system organ class
Note: Only treatment-emergent adverse events of interest were summarized. For each adverse event of interest, subjects were included only once, even if they experienced multiple events in that adverse event of interest.
[a] Risk difference (ABP 654/ABP 654 vs ustekinumab/ustekinumab) and CIs were estimated by Wald asymptotic confidence limits, or exact confidence limits if n < 25 for either treatment.
[b] Risk difference (ustekinumab/ABP 654 vs ustekinumab/ustekinumab) and CIs were estimated by Wald asymptotic confidence limits, or exact confidence limits if n < 25 for either treatment.
[c] Identified using the infections and infestations SOC for CTCAE grade ≥ 3 or serious adverse events
[d] Identified using the cardiac disorders SOC
[e] Identified using the malignancies SMQ (narrow) search strategy
Source: Modified from Table 14-6.5.3 in the Study 20190232 CSR

- For serious infections, the reported PTs comprised single occurrences of grade 3 Helicobacter infection (ABP 654/ABP654), grade 4 COVID-19 (ustekinumab/ustekinumab) and grade 3 infected cyst (ustekinumab/ustekinumab). One subject in the ustekinumab/ustekinumab group had a grade 3 postoperative wound infection and a grade 3 sepsis.
- For cardiovascular events, the reported PTs comprised single occurrences of grade 1 cardiac hypertrophy (ABP 654/ABP 654), grade 3 acute myocardial infarction (ustekinumab/ustekinumab), grade 2 cardiac failure congestive (ustekinumab/ustekinumab), and grade 1 tachycardia (ustekinumab/ustekinumab).
- For malignancies, the reported PT in the ABP 654/ABP 654 group was grade 3 ovarian cancer.

2.6.8.4. Laboratory findings

Clinical laboratory assessments

Through week 28 of the clinical Ps study, changes in mean values for both haematology and clinical chemistry parameters were minimal in both treatment groups.

Individual post-baseline grade ≥ 3 haematology values through week 28 included lymphocyte count decreased (1 [0.4%] subject in the ABP 654 treatment group and 0 [0.0%] subjects in the ustekinumab treatment group) and neutrophil count decreased (0 [0.0%] and 1 [0.4%] subject, respectively). The subject in the ABP 654 treatment group with lymphocyte count decreased had baseline grade 3 and maximum post-baseline grade 3. The subject in the ustekinumab treatment group with neutrophil count decreased had a shift from baseline grade 0 to maximum post-baseline grade 3.

Individual post-baseline grade ≥ 3 clinical chemistry values through week 28 included AST increased (1 [0.4%] subject in the ABP 654 treatment group and 0 [0.0%] subjects in the ustekinumab treatment group), creatinine increased (1 [0.4%] and 0 [0.0%] subjects, respectively), hyperkalaemia (1 [0.4%] and 1 [0.4%] subjects, respectively), and hyponatraemia (1 [0.4%] and 1 [0.4%] subjects, respectively). The subjects in the ABP 654 treatment group with AST increased, with creatinine increased, and with hyponatraemia, and the subjects in the ustekinumab treatment group with hyperkalaemia and with hyponatraemia had shifts from baseline grade 0 to maximum postbaseline grade 3. The subject in the ABP 654 treatment group with hyperkalaemia had a shift from baseline grade 1 to maximum postbaseline grade 3.

There were no notable differences between the ABP 654 treatment group and the ustekinumab treatment group in median changes from baseline for urinalysis values through week 28, and changes were overall minimal. One subject in the ABP 654 treatment group had a shift in urine protein from baseline grade 2 to maximum postbaseline grade 3; no other subjects had postbaseline grade ≥ 3 urine protein values through week 28.

Vital signs and other observations

No relevant changes in vital signs (systolic and diastolic blood pressure, heart rate, respiratory rate, body temperature) were noticed in either study. ECG assessments were not routinely performed in the studies.

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 for biosimilars.

2.6.8.7. Immunological events

Frequencies of ADAs and NAbs

Single dose PK study 20190230

In the PK study 20190230, blood samples for ADA analysis were collected prior to dosing on day 1, day 11, day 35, and day 112/EOS. All samples were screened in a single ECL-based bridging immunoassay to detect anti-drug antibodies. Samples confirmed to be positive for binding antibodies were subsequently tested in a neutralising antibody assay. The number and percentage of subjects developing binding and neutralising ADAs were tabulated by treatment, and results are summarised in Table 42.

Table 42. Antidrug antibody results (Study 20190230 Safety Analysis Set)

Variable	ABP 654 (N = 78) n (%)	Ustekinumab (US) (N = 79) n (%)	Ustekinumab (EU) (N = 80) n (%)
Subjects with an on-study result[a]	78	79	80
Total antibody incidence, n (%)			
Binding antibody positive anytime	13 (16.7)	30 (38.0)	30 (37.5)
Neutralizing antibody positive anytime	2 (2.6)	10 (12.7)	6 (7.5)
Subjects with a result at baseline	78	79	80
Pre-existing antibody incidence, n (%)			
Binding antibody positive at or before baseline	1 (1.3)	0	1 (1.3)
Neutralizing antibody positive at or before baseline	0	0	0
Subjects with a postbaseline result through day 11	77	77	77
Treatment boosted antibody incidence, n (%)			
Binding antibody positive at baseline with a ≥ 4x increase in magnitude postbaseline	1 (1.3)	0	0
Developing antibody incidence, n (%)			
Binding antibody positive postbaseline with a negative or no result at baseline	6 (7.8)	22 (28.6)	18 (23.4)
Neutralizing antibody positive postbaseline with a negative or no result at baseline	0	1 (1.3)	0
Subjects with a postbaseline result through day 35	78	79	80
Treatment boosted antibody incidence, n (%)			
Binding antibody positive at baseline with a ≥ 4x increase in magnitude postbaseline	1 (1.3)	0	0
Developing antibody incidence, n (%)			
Binding antibody positive postbaseline with a negative or no result at baseline	9 (11.5)	25 (31.6)	23 (28.8)
Neutralizing antibody positive postbaseline with a negative or no result at baseline	0	1 (1.3)	1 (1.3)
Subjects with a postbaseline result through EOS	78	79	80
Treatment boosted antibody incidence, n (%)			
Binding antibody positive at baseline with a ≥ 4x increase in magnitude postbaseline	1 (1.3)	0	0
Developing antibody incidence, n (%)			
Binding antibody positive postbaseline with a negative or no result at baseline	12 (15.4)	30 (38.0)	29 (36.3)
Transient[b]	8 (10.3)	14 (17.7)	10 (12.5)
Neutralizing antibody positive postbaseline with a negative or no result at baseline	2 (2.6)	10 (12.7)	6 (7.5)
Transient[b]	0	1 (1.3)	0

CSR = clinical study report; EOS = end-of-study; EU = European Union; US = United States
Note: Baseline was defined as the last non-missing assessment taken prior to the first dose of study investigational product. Percentages were calculated using the corresponding category count as the denominator.
[a] Subjects considered on-study after signing informed consent.
[b] Negative result at the subject's last time point tested within the study period.
Source: Modified from Table 14-10.1 in the Study 20190230 CSR

Clinical Ps study 20190232

In the Ps study 20190232, blood samples for ADA analysis were collected prior to dosing on day 1/week 0 (baseline), and weeks 4, 12, 28, 32, 40, and 52/EOS. All samples were screened for binding ADAs, and samples confirmed positive for binding ADAs were also tested for neutralising activity. The number and percentage of subjects developing binding and neutralising ADAs were tabulated by treatment. Results through week 28 (i.e., before re-randomisation) are depicted in Table 43.

Table 43. Antidrug antibody results through week 28 (Study 20190232 Safety Analysis Set)

Variable	ABP 654 (N = 280)	Ustekinumab (N = 282)
Subjects with an on-study result[a]	280	282
Total antibody incidence, n (%)		
Binding antibody positive anytime	70 (25.0)	112 (39.7)
Neutralizing antibody positive anytime	25 (8.9)	50 (17.7)
Subjects with a result at baseline	276	280
Pre-existing antibody incidence, n (%)		
Binding antibody positive at or before baseline	18 (6.5)	8 (2.9)
Neutralizing antibody positive at or before baseline	1 (0.4)	0 (0.0)
Subjects with a postbaseline result through week 4	276	280
Treatment boosted antibody incidence, n (%)		
Binding antibody positive at baseline with a ≥ 4 times increase in magnitude postbaseline	1 (0.4)	0 (0.0)
Developing antibody incidence, n (%)		
Binding antibody positive postbaseline with a negative or no result at baseline	26 (9.4)	71 (25.4)
Neutralizing antibody positive postbaseline with a negative or no result at baseline	4 (1.4)	11 (3.9)
Subjects with a postbaseline result through week 12	279	280
Treatment boosted antibody incidence, n (%)		
Binding antibody positive at baseline with a ≥ 4 times increase in magnitude postbaseline	1 (0.4)	2 (0.7)
Developing antibody incidence, n (%)		
Binding antibody positive postbaseline with a negative or no result at baseline	41 (14.7)	92 (32.9)
Neutralizing antibody positive postbaseline with a negative or no result at baseline	14 (5.0)	35 (12.5)
Subjects with a postbaseline result through week 28	279	280
Treatment boosted antibody incidence, n (%)		
Binding antibody positive at baseline with a ≥ 4 times increase in magnitude postbaseline	1 (0.4)	2 (0.7)
Developing antibody incidence, n (%)		
Binding antibody positive postbaseline with a negative or no result at baseline	52 (18.6)	104 (37.1)
Transient[b]	24 (8.6)	50 (17.9)
Neutralizing antibody positive postbaseline with a negative or no result at baseline	24 (8.6)	50 (17.9)
Transient[b]	3 (1.1)	6 (2.1)

CSR = clinical study report
Note: Baseline was defined as the last non-missing assessment taken prior to the first dose of study investigational product. Percentages are calculated using the corresponding category count as the denominator.
[a] Subjects considered on-study after signing informed consent.
[b] Negative result at the subject's last time point tested within the study period.
Source: Modified from Table 14-10.1.1 in the Study 20190232 CSR

ADA results post week 28 for subjects re-randomised at week 28 are displayed in Table 44. Overall, relatively few subjects developed new onset ADAs post week 28. The same observation holds true for the limited number of subjects whose dose was intensified at week 28 (data not shown for brevity).

Table 44. Antidrug antibody results post week 28 (Study 20190232 Re-randomised Safety Analysis Set)

Variable	ABP 654/ ABP 654 (N = 247)	Ustekinumab/ ABP 654 (N = 117)	Ustekinumab/ Ustekinumab (N = 116)
Subjects with a postbaseline result post week 28	246	116	115
Developing antibody incidence, n (%)			
Binding antibody positive postbaseline with a negative or no result prior to the first dose in this study period	11 (4.5)	4 (3.4)	2 (1.7)
Transient[a]	9 (3.7)	2 (1.7)	2 (1.7)
Neutralizing antibody positive postbaseline with a negative or no result prior to the first dose in this study period	5 (2.0)	1 (0.9)	1 (0.9)
Transient[a]	1 (0.4)	1 (0.9)	0 (0.0)
Subjects with a postbaseline result through week 32	246	116	115
Developing antibody incidence, n (%)			
Binding antibody positive postbaseline with a negative or no result prior to the first dose in this study period	5 (2.0)	0 (0.0)	2 (1.7)
Neutralizing antibody positive postbaseline with a negative or no result prior to the first dose in this study period	3 (1.2)	1 (0.9)	0 (0.0)
Subjects with a postbaseline result through week 40	246	116	115
Developing antibody incidence, n (%)			
Binding antibody positive postbaseline with a negative or no result prior to the first dose in this study period	11 (4.5)	2 (1.7)	2 (1.7)
Neutralizing antibody positive postbaseline with a negative or no result prior to the first dose in this study period	3 (1.2)	1 (0.9)	1 (0.9)
Subjects with a postbaseline result through week 52	246	116	115
Developing antibody incidence, n (%)			
Binding antibody positive postbaseline with a negative or no result prior to the first dose in this study period	11 (4.5)	4 (3.4)	2 (1.7)
Neutralizing antibody positive postbaseline with a negative or no result prior to the first dose in this study period	5 (2.0)	1 (0.9)	1 (0.9)

CSR = clinical study report
Note: Percentages are calculated using the corresponding category count as the denominator.
[a] Negative result at the subject's last time point tested within the study period.
Source: Modified from Table 14-10.1.2 in the Study 20190232 CSR

ADA results over the entire study period for re-randomised subjects who were treated post re-randomisation are displayed in Table 45.

Table 45. Antidrug Antibody Results – Entire Study (Study 20190232 Re-randomised Safety Analysis Set)

Variable	ABP 654/ ABP 654 (N = 247)	Ustekinumab/ ABP 654 (N = 117)	Ustekinumab/ Ustekinumab (N = 116)
Subjects with an on-study result[a]	247	117	116
Total antibody incidence, n (%)			
Binding antibody positive anytime	70 (28.3)	54 (46.2)	42 (36.2)
Neutralizing antibody positive anytime	25 (10.1)	21 (17.9)	18 (5.5)
Subjects with a result at baseline	243	117	115
Pre-existing antibody incidence, n (%)			
Binding antibody positive at or before baseline	16 (6.6)	4 (3.4)	3 (2.6)
Neutralizing antibody positive at or before baseline	1 (0.4)	0 (0.0)	0 (0.0)
Subjects with a post-baseline result through week 4	244	117	116
Treatment boosted antibody incidence, n (%)			
Binding antibody positive at baseline with a ≥ 4 times increase in magnitude post-baseline	1 (0.4)	0 (0.0)	0 (0.0)
Developing antibody incidence, n (%)			
Binding antibody positive post-baseline with a negative or no result at baseline	22 (9.0)	32 (27.4)	24 (20.7)
Neutralizing antibody positive post-baseline with a negative or no result at baseline	2 (0.8)	2 (1.7)	4 (3.4)
Subjects with a post-baseline result through week 12	247	117	116
Treatment boosted antibody incidence, n (%)			
Binding antibody positive at baseline with a ≥ 4 times increase in magnitude post-baseline	1 (0.4)	1 (0.9)	1 (0.9)
Developing antibody incidence, n (%)			
Binding antibody positive post-baseline with a negative or no result at baseline	34 (13.8)	41 (35.0)	31 (26.7)
Neutralizing antibody positive post-baseline with a negative or no result at baseline	11 (4.5)	12 (10.3)	11 (9.5)

Table 45. cont'd Antidrug antibody results –entire study (Study 20190232 Re-randomised Safety Analysis Set)

Variable	ABP 654/ ABP 654 (N = 247)	Ustekinumab/ ABP 654 (N = 117)	Ustekinumab/ Ustekinumab (N = 116)
Subjects with a post-baseline result through week 28	247	117	116
Treatment boosted antibody incidence, n (%)			
Binding antibody positive at baseline with a ≥ 4x increase in magnitude post-baseline	1 (0.4)	1 (0.9)	1 (0.9)
Developing antibody incidence, n (%)			
Binding antibody positive post-baseline with a negative or no result at baseline	43 (17.4)	46 (39.3)	37 (31.9)
Neutralizing antibody positive post-baseline with a negative or no result at baseline	19 (7.7)	20 (17.1)	17 (14.7)
Subjects with a post-baseline result through week 32	247	117	116
Treatment boosted antibody incidence, n (%)			
Binding antibody positive at baseline with a ≥ 4x increase in magnitude post-baseline	1 (0.4)	1 (0.9)	1 (0.9)
Developing antibody incidence, n (%)			
Binding antibody positive post-baseline with a negative or no result at baseline	48 (19.4)	46 (39.3)	39 (33.6)
Neutralizing antibody positive post-baseline with a negative or no result at baseline	22 (8.9)	21 (17.9)	17 (14.7)
Subjects with a post-baseline result through week 40	247	117	116
Treatment boosted antibody incidence, n (%)			
Binding antibody positive at baseline with a ≥ 4x increase in magnitude post-baseline	2 (0.8)	1 (0.9)	1 (0.9)
Developing antibody incidence, n (%)			
Binding antibody positive post-baseline with a negative or no result at baseline	54 (21.9)	48 (41.0)	39 (33.6)
Neutralizing antibody positive post-baseline with a negative or no result at baseline	22 (8.9)	21 (17.9)	18 (15.5)

Table 45. cont'd Antidrug antibody results – entire study (Study 20190232 Re-randomised Safety Analysis Set)

Variable	ABP 654/ ABP 654 (N = 247)	Ustekinumab/ ABP 654 (N = 117)	Ustekinumab/ Ustekinumab (N = 116)
Subjects with a post-baseline result through week 52	247	117	116
Treatment boosted antibody incidence, n (%)			
Binding antibody positive at baseline with a ≥ 4x increase in magnitude post-baseline	2 (0.8)	1 (0.9)	1 (0.9)
Developing antibody incidence, n (%)			
Binding antibody positive post-baseline with a negative or no result at baseline	54 (21.9)	50 (42.7)	39 (33.6)
Transient[b]	40 (16.2)	34 (29.1)	26 (22.4)
Neutralizing antibody positive post-baseline with a negative or no result at baseline	24 (9.7)	21 (17.9)	18 (15.5)
Transient[b]	9 (3.6)	8 (6.8)	5 (4.3)

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CSR = clinical study report
Note: Percentages are calculated using the corresponding category count as the denominator.
[a] Negative result at the subject's last time point tested within the study period.
Source: Modified from Table 14-10.1.3 in the Study 20190232 CSR

The applicant postulates that the presence of non-human glycans enhances immune reactivity to the protein backbone of Stelara, and the immunogenicity differences detected between the ABP 654 and Stelara (ustekinumab) treatment groups in both Study 20190230 and Study 20190232 are due to these in glycan profiles which result from the use of different expression systems for the respective treatment products (ABP 654 expressed in CHO vs Stelara [ustekinumab] expressed in Sp2/0). Specifically, Stelara contains galactose-α-1,3-galactose (α-gal) and N-glycolylneuraminic acid, while ABP 654 does not contain either of these non-human glycans. The presence of these non-human glycans on proteins can enhance their immunogenicity, and the development of ADAs in Stelara-treated subjects in Study 20190230 and Study 20190232 is therefore not unexpected. The mechanism behind this enhanced immunogenicity is the presence of pre-existing and/or developing anti-glycan antibodies that result in immune complex formation and enhanced uptake by antigen presenting cells through Fc receptor interactions.

Impact of ADA on PK

In the study 20190230, percent changes in CL/F by binding ADA status subgroup were 15.95%, 35.35%, and 24.23% for subjects in the ABP 654, ustekinumab (US), and ustekinumab (EU) treatment groups, respectively; percent changes in $t_{1/2}$ by binding ADA status subgroup were -12.14%, -32.42% and -19.97%, respectively (see Table 46).

Table 46. Percent change in clearance and half-life between ABP 654 and ustekinumab by developing binding antidrug antibody status (Study 20190230 PK parameter analysis set)

Parameter	ADA Subset	n	ABP 654 GeoMean (Geo CV [%])	n	Ustekinumab (US) GeoMean (Geo CV [%])	n	Ustekinumab (EU) GeoMean (Geo CV [%])
CL/F (L/h)	Negative	64	0.00809 (33.7)	47	0.00761 (35.3)	48	0.00718 (34.4)
	Positive	11	0.00938 (76.1)	29	0.0103 (32.9)	28	0.00892 (30.9)
	% Change in CL/F[a]		15.95		35.35		24.23
$t_{1/2}$ (h)	Negative	64	582.566 (22.2)	47	611.198 (23.0)	48	608.321 (20.2)
	Positive	11	511.854 (32.9)	29	413.050 (43.7)	28	486.863 (34.6)
	% Change in $t_{1/2}$[a]		-12.14		-32.42		-19.97

ADA = antidrug antibody; CL/F = apparent clearance; CSR = clinical study report; EU = European Union; Geo CV = geometric coefficient of variation; GeoMean = geometric mean; n = number of subjects with non-missing values; NA = not applicable; PK = pharmacokinetic; $t_{1/2}$ = half-life; US = United States.
[a] The % change is calculated as (geometric mean in positive ADA subgroup - geometric mean in negative ADA subgroup)/geometric mean in ADA negative subgroup.
Source: Modified from Table 14-9.a.1.1 and Table 14-9.2.3 of the Study 20190230 CSR

For CL/F, there was no significant interaction effect between treatment and binding ADA status(p = 0.5299) . For $t_{1/2}$, the effect of interaction between treatment and binding ADA status was significant (p = 0.0373). The magnitude of the impact of developing positive binding ADA on $t_{1/2}$ was statistically significantly different between the ABP 654 and ustekinumab (US) treatment groups(p=0.0172); however, the magnitude of the impact was not statistically significantly different between the ABP 654 and ustekinumab (EU) treatment groups (p=0.3953) (see Table 47).

Table 47. Analysis of clearance (Study 20190230 PK parameter analysis set)

	Estimate	95% Confidence Interval	p-value
Treatment			
Ustekinumab (US) vs ABP 654	0.9412	(0.8238, 1.0752)	0.3705
Ustekinumab (EU) vs ABP 654	0.8878	(0.7777, 1.0135)	0.0779
ADA Status			
B vs A	1.1601	(0.9252, 1.4547)	0.1972
Treatment by ADA Status Interaction			0.5299
(Ustekinumab (US) vs ABP 654) x (ADA status B vs ADA status A)	1.1663	(0.8821, 1.5421)	0.2789
(Ustekinumab (EU) vs ABP 654) x (ADA status B vs ADA status A)	1.0701	(0.8088, 1.4159)	0.6337

ADA = antidrug antibody; ANCOVA = analysis of covariance; EU = European Union; PK = pharmacokinetic; US = United States
ADA status: A = Binding negative; B = Binding positive. Binding positive refers to subjects with a binding antibody positive result post-baseline with a negative or no result at baseline.
An ANCOVA model was fit with the natural logarithm of clearance as the response and treatment (ABP 654, ustekinumab US, ustekinumab EU), ADA status (binding negative, binding positive), and treatment by ADA status interactions in the model.
Source: Modified from Table 14-9.a.4.1

Table 48. Analysis of half-life (Study 20190230 PK parameter analysis set)

	Estimate	95% Confidence Interval	p-value
Treatment			
Ustekinumab (US) vs ABP 654	1.0491	(0.9467, 1.1626)	0.3583
Ustekinumab (EU) vs ABP 654	1.0442	(0.9429, 1.1565)	0.4046
ADA Status			
B vs A	0.8786	(0.7379, 1.0462)	0.1454
Treatment by ADA Status Interaction			0.0373
(Ustekinumab (US) vs ABP 654) x (ADA status B vs ADA status A)	0.7692	(0.6201, 0.9540)	0.0172
(Ustekinumab (EU) vs ABP 654) x (ADA status B vs ADA status A)	0.9109	(0.7340, 1.1304)	0.3953

ADA = antidrug antibody; ANCOVA = analysis of covariance; EU = European Union; PK = pharmacokinetic; US = United States

ADA status: A = Binding negative; B = Binding positive. Binding positive refers to subjects with a binding antibody positive result post-baseline with a negative or no result at baseline.

An ANCOVA model was fit with the natural logarithm of half-life as the response and treatment (ABP 654, ustekinumab US, ustekinumab EU), ADA status (binding negative, binding positive), and treatment by ADA status interactions in the model.

Source: Modified from Table 14-9.a.4.2

In the study 20910232, overall, subjects who developed binding ADAs exhibited reduced trough PK concentrations at each study visit through week 28; the magnitude of the impact of positive binding ADA on PK was similar between the ABP 654 and ustekinumab treatment groups (see Table 49).

Table 49. Through PK concentrations (ng/ml) by developing binding ADA status and visit -through week 28 (Study 20190232 Safety analysis set)

	Positive Binding ADA Status[a]		Negative Binding ADA Status[b]	
Visit Statistic	ABP 654 (N = 52)	Ustekinumab (N = 104)	ABP 654 (N = 209)	Ustekinumab (N = 168)
Week 4				
n	52	104	206	168
m	51	103	204	160
Geometric LS mean	2108.87	2018.98	3216.36	3243.32
Ratio of geometric LS mean (ABP 654 /Ustekinumab)	1.0445		0.9917	
90% CI for ratio of geometric LS mean	(0.8097, 1.3474)		(0.9282, 1.0596)	
Week 12				
n	50	100	203	166
m	49	95	200	163
Geometric LS mean	1264.56	1321.02	2063.08	1816.18
Ratio of geometric LS mean (ABP 654 /Ustekinumab)	0.9573		1.1359	
90% CI for ratio of geometric LS mean	(0.7468, 1.2271)		(1.0132, 1.2735)	
Week 28				
n	52	99	205	164
m	46	84	203	163
Geometric LS mean	342.15	395.65	693.00	624.06
Ratio of geometric LS mean (ABP 654 /Ustekinumab)	0.8648		1.1105	
90% CI for ratio of geometric LS mean	(0.6501, 1.1504)		(0.9791, 1.2595)	

ANCOVA = analysis of variance; LS = least squares; m = number of subjects with a non-zero concentration; n = number of subjects with non-missing values

Note: Lower limit of quantification was 20.0 ng/mL. Pharmacokinetic concentrations below the lower limit of quantification were assigned a value of 0 and were excluded from the calculations of geometric LS mean, geometric mean ratio, and 90% CI (calculated only if m ≥ 5).

The geometric LS mean, ratio of geometric LS means, and 90% CI were estimated based on ANCOVA model adjusted for the actual stratification factors of prior biologic use for psoriasis, baseline body weight group, and geographic region.

[a] Developing Binding Positive is defined as binding antibody positive at a post-baseline visit through Week 28 with a negative or no result at baseline.

[b] Developing Binding Negative is defined as binding antibody negative at all post-baseline visits through Week 28 with a negative or no result at baseline.

Source: Modified from Table 14-9.af.3

Impact of ADA on efficacy

To further evaluate the potential impact of ADA on efficacy in Study 20190232, the applicant conducted additional analyses of the primary efficacy endpoint (PASI percent improvement from baseline to week 12) according to subject developing binding ADA status; results are provided in Table 47. For each of the developing ADA status subgroups (positive and negative), the 95% CI of the mean difference in PASI percent improvement between treatment groups fell within the prespecified similarity margin for the primary efficacy endpoint of (-15, +15). The findings for PASI percent improvement were consistent between the developing ADA positive and negative subgroups. Thus, the applicant has concluded that the numerical difference in binding and neutralising ADAs between treatment groups in Study 20190232 did not translate into imbalances in treatment response.

Table 50. Analysis of PASI percent improvement from baseline to week 12 by developing binding ADA status through week 28 (Study 20190232 Full Analysis Set)

	ABP 654 (N = 281)		Ustekinumab (N = 282)	
Statistic	PASI Score	PASI Percent Improvement from Baseline	PASI Score	PASI Percent Improvement from Baseline
Positive Binding ADA Status[a]				
n	50	50	101	101
Mean (SD)	4.27 (5.102)	79.65 (19.519)	4.00 (5.007)	80.16 (22.585)
95% CI of mean	(2.82, 5.72)	(74.10, 85.20)	(3.01, 4.99)	(75.71, 84.62)
Difference between means[b]		0.12		
90% CI[b]		(-6.09, 6.32)		
95% CI[b]		(-7.27, 7.51)		
Negative Binding ADA Status[c]				
n	204	204	166	166
Mean (SD)	3.73 (4.826)	82.59 (19.877)	3.56 (4.229)	82.90 (17.825)
95% CI of mean	(3.07, 4.40)	(79.85, 85.34)	(2.91, 4.20)	(80.17, 85.63)
Difference between means[b]		-0.23		
90% CI[b]		(-3.48, 3.01)		
95% CI[b]		(-4.11, 3.64)		

ADA = antidrug antibody; ANCOVA = analysis of covariance; CSR = clinical study report; MI = multiple imputation; PASI = Psoriasis Area and Severity Index

Note: The summary statistics by each visit was derived based on observed data. Multiple imputation was only applied for the point estimate and CI of the mean difference between the 2 groups.

[a] Positive Binding ADA is defined as binding antibody positive at a post-baseline visit through Week 28 with a negative or no result at baseline.

[b] Estimated using ANCOVA model adjusted for baseline PASI value, and the stratification factors of prior biologic use for psoriasis, baseline body weight group, and geographic region. Multiple imputation was performed using PROC MI in 2 steps: the Markov Chain Monte Carlo was used for data with sporadic missing values to create imputed datasets with monotone missing pattern, and then for the resulting datasets the regression method was used to generate complete datasets for final analysis.

[c] Negative Binding ADA is defined as binding antibody negative at all post-baseline visits through Week 28 with a negative or no result at baseline.

Source: Modified from Table 14-4.af.1.1.1

Impact of ADA on safety

The applicant has concluded that there were no clinically impactful effects resulting from ADAs on the safety profile of ABP 654 or ustekinumab (US and EU) in the single dose PK study 20190230. This conclusion is based on the following findings:

- no events of anaphylaxis were reported
- no events of cytokine release syndrome were reported
- no events of serious or grade ≥ 3 hypersensitivity (SMQ) were reported
- no events of injection site reaction were reported

The applicant has also conducted a review of the AEs that occurred in the comparative clinical Ps study, Study 20190232. Based on the review, the applicant has concluded that there were no clinically

impactful effects resulting from ADAs on the safety profile of ABP 654 or ustekinumab (EU) in Study 20190232. This conclusion is based on the following findings:

- no events of anaphylaxis associated with investigational product were reported (1 event of anaphylaxis without temporal association to investigational product administration was reported)
- no events of cytokine release syndrome were reported
- no events of serious or grade ≥ 3 hypersensitivity (SMQ) were reported
- the number of injection site reactions that were reported was low (1 event of injection site erythema for a subject in the ABP 654 treatment group and 1 event of injection site inflammation for a subject in the ustekinumab (EU) treatment group)

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

Not applicable for biosimilars.

2.6.8.9. Discontinuation due to adverse events

As this was a single-dose study, there were no AEs leading to discontinuation of study medication in the PK study 20190230.

Through week 28 of the clinical Ps study, discontinuation of investigational product or study due to one or more AEs occurred in 2 (0.7%) and 4 (1.4%) subjects in the ABP 654 group and ustekinumab treatment groups, respectively. Adverse events resulting in discontinuation of investigational product or study included 1 (0.4%) subject each for grade 1 cardiac failure congestive and grade 3 invasive lobular breast carcinoma in the ABP 654 treatment group and 1 (0.4%) subject each for grade 5 COVID-19, grade 2 clear cell renal cell carcinoma, grade 2 psoriatic arthropathy, and grade 1 purpura in the ustekinumab treatment group.

Among subjects re-randomised at week 28, discontinuation of investigational product or study post week 28 due to one or more AEs was reported by 1 (0.4%) subject in the ABP 654/ABP 654 treatment group (grade 1 alanine aminotransferase increased) and 1 (0.9%) subject in the ustekinumab/ustekinumab treatment group (grade 4 bipolar I disorder).

2.6.8.10. Post marketing experience

Not applicable.

2.6.9. Discussion on clinical safety

The applicant has provided safety data from two clinical studies: a pivotal Phase 3 study (20190232) in Ps patients, and a Phase 1 PK study (20190230) in healthy adult subjects. Within the development programme, a total of 799 subjects, either healthy subjects or subjects with moderate to severe Ps, received any amount of ABP 654 or Stelara. Of the 799 subjects who received investigational product, 475 received ABP 654.

For the development of ABP 654, EMA Scientific Advice was received in December 2019 and June 2021. Further, the global development of ABP 654 has been discussed with the FDA. From the safety perspective, it is noted that CHMP in the Scientific Advice expressed reservations concerning the switching procedure after 28 weeks and emphasised that the switching of patients from Stelara to ABP 654 to assess efficacy and safety should be done in such a way that allows follow up of sufficient numbers of patients for one year to compare the proposed biosimilar to Stelara. Considering that there

are 112 subjects with continuous exposure to Stelara (EU) for the full duration of the study in the clinical Ps study (not accounting for subjects who received dose intensification), this concern is considered addressed. Consequently, the design of the conducted Phase 3 study as well as the safety assessments included in the clinical studies are sufficiently aligned with the EMA Scientific Advice and adequate to the CHMP.

The safety evaluations were planned according to the known safety profile of ustekinumab, considering the adverse reactions presented in the SmPC and other available clinical information. The safety analyses were performed on the safety analysis sets, consisting of all subjects receiving at least 1 dose of either ABP 654 or Stelara. Within the application documentation, the safety data has been presented by individual study and has not been pooled; in light of the different study populations, this is acceptable to the HCMP. Overall, the safety analyses are considered adequate by the CHMP.

In the clinical Ps study, there were no notable differences between the treatment groups in terms of exposure, and attrition rates were generally quite low. While the switch at week 28 decreases the sample size for the Stelara group and thereby decreases the discriminatory power of the study to evaluate potential differences at later stages, is the CHMP noted that 112 subjects completed IP in the study (not accounting for subjects who received dose intensification) and thereby have continuous exposure to Stelara for the full duration of the study. As already stated above, this size of the safety database is considered sufficient to allow a meaningful comparison of safety and immunogenicity between ABP 654 and Stelara in the context of a biosimilar MAA. Of note, only Stelara (EU) was used in the clinical Ps study.

Per protocol in the Ps study, week 28 non-responders (i.e., subjects not achieving PASI 50 response or better) were considered to have completed the study and completed the end of study procedures (i.e., procedures planned for week 52) at week 28. These subjects should have been followed up for safety and immunogenicity although treatment was stopped. However, as such non-responders were few (2 and 3 subjects in the ABP 654 and Stelara (EU) treatment groups, respectively), the omission of these subjects from the safety follow-up is not considered to adversely impact safety analyses.

Overall, the adverse event profiles of ABP 654 and Stelara were comparable in both the single dose PK study and the clinical Ps study in terms of nature, frequency and severity of the adverse events. In the Ps study, both products seemed to be generally well tolerated; most reported AEs were grade 1 or 2, and no unexpected clustering of events was seen. Discontinuations due to AEs were overall infrequent, and no clear differences could be seen between the treatment groups.

The clinical programme was ongoing at the time of the COVID-19 pandemic, and as can be expected, COVID-related AEs were reported in both groups in the clinical Ps study. A single fatal COVID-19 infection was reported in the Stelara (EU) group. Among the dose-intensification subjects, COVID-related events were more frequent in the ABP 654 group (5 subjects vs. 1 subject), however these were grade 1 or 2, and a slight imbalance in frequency can plausibly be explained by the dynamic nature of the pandemic.

Serious adverse events and events of interest were overall infrequent in the clinical Ps study, and the nature, severity and frequency of such events was comparable between the treatment groups. Most events were single occurrences, with no clustering discernible. Relevant to immunogenicity and ADA formation, the absence of serious systemic hypersensitivity reactions is noted (the anaphylactic reaction occurred 38 days after the most recent dose of study medication and is thereby not captured in the EOI search).

In the clinical Ps study, changes in laboratory parameters were overall minimal. Individual clinically significant changes were infrequent, and no concerning trend can be identified in either group.

In both the PK study and the clinical Ps study, ADAs were observed more frequently in subjects receiving Stelara than in subjects receiving ABP 654; this holds true for both binding antibodies as well as neutralising antibodies. A potential reason for the apparently lower immunogenicity of ABP 654 is the use of different expression systems in manufacturing of ABP 654 vs. Stelara, resulting in the absence of non-human glycans in ABP 654. However, as per relevant guidance (Guideline on similar biological medicinal products containing monoclonal antibodies – non-clinical and clinical issues, EMA/CHMP/BMWP/403543/2010), a lower immunogenicity for the biosimilar mAb is a scenario that does not preclude biosimilarity if the efficacy of the biosimilar and the reference mAb are in principle similar when not impacted by an immune response.

When viewed over the entire study period, subjects in the Ustekinumab/ABP 654 treatment arm, i.e. subjects who switched from Stelara to ABP 654 at week 28 had higher ADA incidence compared to the other groups. However, this difference was already seen at week 4 and 12 and is therefore a chance finding which does not indicate increased immunogenicity due to switching. Overall, the development of new onset ADAs after week 28 was infrequent.

In both studies 20190230 and 20190232, the presence of binding ADAs reduced systemic exposure to ABP 654 and reference/comparator products by increasing CL/F and decreasing $t_{1/2}$. In study 20190230, the impact on the PK parameter CL/F was similar between treatment groups and the impact on the PK parameter $t_{1/2}$ differed statistically significantly only between Stelara (US) and ABP 654. In study 20190232, subjects, who were ADA positive had reduced trough concentrations to a similar extent in both treatment arms. The impact of positive binding ADA on PK was similar between the ABP 654 and Stelara treatment groups, when present. As a conclusion, there are no meaningful differences between ABP 654 and Stelara (EU) in terms of the magnitude of effect of ADA presence on PK parameters.

Based on the analysis of PASI response in the ADA negative subgroup, the efficacy of ABP 654 and Stelara seems similar when not impacted by an immune response. Moreover, there was no notable difference in efficacy between ABP 654 and Stelara in either the ADA negative or ADA positive subgroup. Based on the results provided, binding ADAs are considered to have a limited impact on efficacy, as mean percent improvements in PASI scores in the ADA positive subgroups were almost as high as in the ADA negative subgroups. Furthermore, the low frequency of potentially immune-mediated AEs in either group supports the view that ADAs do not play any major role as regards the safety profile of either ABP 654 or the reference product.

2.6.10. Conclusions on clinical safety

A comprehensive analysis of safety data from the ABP 654 development programme has been provided. The size of the safety database is sufficient to enable a reasonable analysis of comparability between ABP 654 and Stelara (EU). No concerning differences are identified.

While ABP 654 seems to elicit a lower degree of immunogenicity than the reference product, this is acceptable per applicable guidance and is not considered to adversely impact determination of biosimilarity. Overall, the immunogenicity data provided in the application support the view that binding ADAs have a very limited impact on the efficacy or safety profile of Stelara.

Overall, the CHMP concluded that biosimilarity of ABP 654 and Stelara (EU) from the safety perspective has been shown.

2.7. Risk management plan

2.7.1. Safety Specification

Summary of safety concerns

Table 51. Summary of 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 Exposure during pregnancy
Missing information	Long-term safety in paediatric psoriasis patients 6 years and older Long-term impact on growth and development in paediatric psoriasis patients 6 years and older Long-term safety in adult patients with moderately to severely active Crohn's disease

2.7.2. Pharmacovigilance plan

No additional pharmacovigilance activities.

2.7.3. Risk minimisation measures

No additional risk minimisation measures.

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

No full user consultation with target patient groups on the package leaflet has been performed on the basis of a bridging report. The PLs of WEZENLA 130 mg concentrate for solution for infusion and 45 mg & 90 mg solution for injection in pre-filled syringe were compared for design and layout with the PL of Kyprolis 10, 30, 60 mg powder for solution for infusion. The PL of WEZENLA 45 mg solution for injection in vial was compared for design and layout with the PL of Parsabiv 2.5, 5, 10 mg solution for injection. WEZENLA package leaflets were compared for key safety messages with reference product Stelara (130 mg concentrate for solution for infusion, 45 mg solution for injection in vial, 45 mg and 90 mg solution for injection in pre-filled syringe).

The bridging report submitted by the applicant has been found acceptable.

2.9.2. Additional monitoring

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

- It contains a new active substance which, on 1 January 2011, was not contained in any medicinal product authorised in the EU;
- It is a biological product that is not covered by the previous category and authorised after 1 January 2011

Therefore, the summary of product characteristics and the package leaflet includes a statement that this medicinal product is subject to additional monitoring and that this will allow quick identification of new safety information. The statement is preceded by an inverted equilateral black triangle.

3. Biosimilarity assessment

3.1. Comparability exercise and indications claimed

ABP 654 is being developed as a biosimilar candidate to Stelara (ustekinumab). The proposed indications for ABP 654 are as follows:

- Moderate to severe plaque psoriasis (Ps) in adult patients and paediatric patients 6 years of age and older
- Active psoriatic arthritis in adults
- Moderately to severely active Crohn’s disease

Quality programme

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. CHMP scientific advice has been followed in the presented similarity exercise. ABP 654, ustekinumab (EU) and ustekinumab (US) have been compared. Comparability studies between ustekinumab (US) and (EU) have not been presented and the similarity is assessed between ABP 654 and ustekinumab (EU).

ABP 654 has the same formulations, dosage forms, presentations, and product strengths as the reference product. Clinical studies 20190230 and 20190232 included the use of only the PFS

presentations. Batches of vial presentations were not used in clinical studies. The 45 mg vial has the same formulation, dosage, and recommended administration as the 45 mg PFS presentation. The 130 mg vial has the same AS but different formulation and administration route compared to PFS presentations. Comparability at quality level between SC PFS presentations and 130 mg vial (IV) has been demonstrated. Hence, the FP material used in the analytical biosimilarity studies is considered representative of the material used in clinical trials.

Similarity data were generated using (1) side-by-side testing, (2) independent testing, and/or (3) age-dependent testing. The quality range was defined as reference product (mean) ± 3SD using minimum of 10 batches of ustekinumab (EU) (unless otherwise noted).

The comparative testing included analysis of biological activity, primary structure, higher order structure, particles and aggregates, product-related substances and impurities, general properties and thermal stability and degradation studies. Appropriate analytical methods have been utilised to ensure an understanding of the ustekinumab (EU) product profile and the ABP 654 product developed.

Non-clinical programme

The non-clinical programme supporting the similarity of ABP 654 to Stelara (ustekinumab) includes several *in vitro* pharmacological studies investigating the functional activity of ABP 654 compared to Stelara on mode of action -relevant endpoints.

Clinical programme

The clinical programme supporting the similarity of ABP 654 to Stelara (ustekinumab) includes one completed randomised, double-blind, single-dose, 3-arm, parallel-group PK similarity study in healthy adult subjects comparing ABP 654 to ustekinumab (Study 20190230); and one completed randomised, double-blind, active-controlled clinical study in adult subjects with moderate to severe Ps (Study 20190232).

The safety profiles of ABP 654 and the reference product were assessed in the clinical PK study as well as the clinical Ps study through a comparative, descriptive analysis of adverse events, laboratory data and immunogenic potential. For both clinical studies, the safety analyses were performed on the safety analysis set which included all randomised subjects who received any investigational product.

The clinical development followed the applicable guidelines Guideline on similar biological medicinal products (EMEA/CHMP/42832/2005 Rev. 1) and Guideline on Similar Biological Medicinal Products Containing Monoclonal Antibodies - Non-Clinical and Clinical Issues (EMA/CHMP/BMWP/403543/2010).

3.2. Results supporting biosimilarity

Quality

Similarity between ABP 654 and ustekinumab (EU) has been demonstrated for the following physicochemical and biological properties:

- Primary structure (including glycosylation)
- Higher order structure
- Particles and aggregates
- Product-related substances and impurities
- Thermal stability and degradation studies
- General properties including protein concentration and volume

- Biological activity:
  - Inhibition of IL-12 and IL-23 -mediated Signalling
  - IL-23 and IL-12 Receptor-ligand Binding
  - Lack of Binding to Receptor-bound IL-23 and IL-12 on Cell Surface
  - IL-23 and IL-12 Binding Kinetics and Affinity
  - Binding Specificity Against IL-6, IL-35, and IL-39 (lack of binding)
  - FcRn Binding
  - FcγRIa, FcγRIIa (131R), FcγRIIb, FcγRIIIb and FcγRIIIa (158V) Binding
  - C1q Binding
  - Lack of ADCC / ADCP / CDC Activity

Non-clinical

In the pharmacology studies assessing inhibition of IL-23-induced STAT-3 signalling, IL-12-induced STAT-4 signalling, IL-23 induced IFN-γ release and IL-12-induced IFN-γ release in activated T-cells from healthy human donors, ABP 654 was demonstrated to be quite similar with Stelara (EU), supporting biosimilarity.

Clinical

Pharmacokinetics

In the comparison of PK data (pivotal PK study 20190230) for the ABP 654 group with ustekinumab (EU) and ustekinumab (US) groups, the 90% CIs of the GMRs for the primary PK endpoints AUC_{inf} and C_{max} (also for the AUC_{last}) were within the BE criteria of 0.80 to 1.25 in all comparisons of ABP 654 vs ustekinumab (EU), ABP 654 vs ustekinumab (US) and ustekinumab (US) vs ustekinumab (EU): ratio of LS geometric means (90% CI) of ABP 654 vs ustekinumab EU was 0.9391 (0.8620, 1.0232) for AUC_{inf} and 0.9452 (0.8779, 1.0175) for $C_{max.}$

Also, the secondary PK endpoints (i.e., t_{max}, $t_{½}$, CL/F and MRT) were shown to be similar between ABP654, ustekinumab (EU) and ustekinumab (US).

The PK results of the sensitivity/subgroup analyses performed in the study 20190230 were similar to the primary PK results.

In the comparative efficacy and safety study (i.e., 20190232) in patients with moderate to severe plaque psoriasis, the trough concentrations were comparable at different timepoints between ABP 654 and ustekinumab (EU).

Clinical efficacy

The primary efficacy endpoint was PASI percent improvement from baseline to week 12. The point estimate of the mean difference in PASI percent improvement from baseline to week 12 between the treatment groups was 0.14 with a 2-sided 95% CI of (-3.16, 3.43). The 95% CI was within the prespecified similarity margin of (-15, +15).

Sensitivity analyses showed that results were consistent over different analysis sets (FAS and PP) and regardless of choice of imputation method for missing values (LOCF or MMRM).

Subgroup analyses were performed for the following subgroups: prior biologic use for psoriasis (yes, no), baseline BW group (≤ 100 kg vs > 100 kg), geographic region (North America vs Europe), age (< 65 years vs ≥ 65 years), race (white vs non-white), sex (female vs male), and disease duration (< 1 year vs ≥ 1 year). Clinical comparability was concluded in all subgroups, including patients with BW >100kg and patients aged ≥ 65 years.

All secondary efficacy endpoints supported similarity (PASI percent improvement at other timepoints, PASI 75 and PASI 100 response throughout the study, Static Physician's Global Assessment (sPGA) response and Body surface area (BSA) change from baseline at week 12 and week 52).

There was no notable difference in efficacy between ABP 654 and the reference product in either the ADA negative or ADA positive subgroup.

Clinical safety

The analysis of adverse event data and laboratory data support the view that the safety profiles of ABP 654 and ustekinumab are comparable:

- In the single dose PK study
  - AEs were reported for 22 subjects (28%) in the ABP 654 group vs. 18 subjects (23%) for ustekinumab (US) and 29 subjects (36%) for ustekinumab (EU).
  - The most commonly reported AE was headache [9 subjects (11%) ABP 654, 3 subjects (4%) ustekinumab (US), 9 subjects (11%) ustekinumab (EU)].
  - Grade ≥ 3 AEs were reported in 1 subject each in the ustekinumab (US) and ustekinumab (EU) treatment groups. Each of the grade ≥ 3 AEs were also identified as SAEs and considered not related to study drug.
- In the clinical Ps study
  - Through week 28, AEs were reported by 106 subjects (38%) in the ABP 654 treatment group and 99 subjects (35%) in the ustekinumab treatment group. For both treatment groups, the highest subject incidence rates of AEs were in the SOC of Infections and infestations (40 subjects (14.3%) ABP 654 vs. 31 subjects (11.0%) ustekinumab). The most common individual AEs by PT were hypertension (7 subjects (3%) ABP 654 vs. 6 subjects (2%) ustekinumab), nasopharyngitis (7 subjects (3%) ABP 654 vs. 3 subjects (1%) ustekinumab), COVID-19 (6 subjects (2%) ABP 654 vs. 5 subjects (2%) ustekinumab), headache (6 subjects (2%) ABP 654 vs. 7 subjects (3%) ustekinumab), and upper respiratory tract infection (6 subjects (2%) ABP 654 vs. 7 subjects (3%) ustekinumab).
  - Through week 28, most AEs were maximum CTCAE grade 1 or 2; grade ≥ 3 events occurred in 8 subjects (3%) in the ABP 654 treatment group and 5 subjects (2%) in the ustekinumab treatment group. All reported CTCAE grade ≥ 3 events were single occurrences.
  - Through week 28, a single fatal event of COVID-19 was reported in the ustekinumab treatment group. The subject incidence of SAEs was 7 subjects (3%) in the ABP 654 treatment group and 5 subjects (2%) in the ustekinumab treatment group.
  - Post week 28, COVID-19 was the most commonly reported AE by PT in all groups (23 subjects (9%) ABP 654/ABP 654, 15 subjects (13%) ustekinumab/ABP 654, 11 subjects (10%) ustekinumab/ustekinumab). No fatal events were reported post week 28; the subject incidence of non-fatal SAEs post week 28 was 1 subject (0.4%) in the ABP 654/ABP 654 treatment group, 1 subject (0.9%) in the ustekinumab/ABP 654 treatment group, and 3 subjects (3%) in the ustekinumab/ustekinumab treatment group.
  - An analysis of reported EOIs identified no concerning trends. The total number of potential EOIs was 5 (1.8%) for ABP 654 vs. 7 (2.5%) for ustekinumab (risk difference -0.70 (95%

CI -3.49, 1.99), with no event type being reported for more than 2 subjects in either group.

- Changes in mean values for both haematology and clinical chemistry parameters were minimal in both treatment groups. Individual post-baseline changes grade 3 or greater were overall very infrequent and identified no concerning trends.

The immunogenic potential of ABP 654 appeared lower than that of the reference product, potentially due to different expression systems used in their respective manufacturing processes:

- In the single dose PK study, developing antibody incidence for binding ADAs through end of study was 15% for ABP 654, 38% for ustekinumab (US) and 36% for ustekinumab (EU). For neutralising ADAs, the incidences were 3%, 13% and 8%, respectively.
- In the clinical Ps study, developing antibody incidence for binding ADAs through week 28 was 19% for ABP 654 and 37% for ustekinumab. For neutralising ADAs, the incidences were 9% and 18%, respectively. Few subjects developed new onset ADAs post week 28.
- Based on data analyses in the ADA negative and ADA positive subgroups, ADAs only had a minor impact on pharmacokinetics, and no appreciable effect on the efficacy or safety profile. Thus, in the clinical Ps study, mean (SD) PASI percent improvement from baseline to week 12 for binding ADA positive vs. binding ADA negative was 79.6 (19.52) vs. 82.6 (19.88) in the ABP 654 group, and 80.2 (22.58) vs. 82.9 (17.82) in the ustekinumab group. Furthermore, the frequency of potentially immune-mediated AEs in either group was overall very low.

3.3. Uncertainties and limitations about biosimilarity

Quality

None.

Non-clinical

None

Clinical

Pharmacokinetics

None.

Clinical efficacy

None.

Clinical safety

The size of the safety database is limited and effectively precludes the detection of any rare adverse effects.

3.4. Discussion on biosimilarity

Quality

The totality of the presented biological and physiochemical data supports the claim of biosimilarity for ABP 654 and ustekinumab (EU). Most biological activities relevant to the primary mechanism of action, including IL-23 receptor ligand binding, IL-12 receptor ligand binding and inhibition of IL-12 and IL-23 mediated signalling are similar. A lower binding activity of ABP 654 to FcγRIIIa (158V) and FcγRIIIb

compared to ustekinumab (EU) was observed and attributed to lower levels for afucosylated glycans in ABP 654. The difference is considered to result from the cell line change and not considered to be clinically meaningful based on the similar lack of ADCC activity for both ABP 654 and ustekinumab. Differences were also observed in charge variant levels (38% lower level of basic peaks and 27% higher level of acidic peaks). Lower level of basic peaks in ABP 654 is primarily due to a lower level of unprocessed HC C-terminal lysine variants. Higher acidic peak level is due to lower level of basic peaks and slightly higher level of sialic acid-containing species in ABP 654. C-terminal lysine variants and sialylation are both non-critical quality attributes. The differences between ABP 654 and ustekinumab (EU) 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 glycan map analysis, post-translational modifications, basic peaks in cIEF profiles and size variants in ABP 654 compared to reference product. All observed differences are well discussed and justified, are not considered to be clinically meaningful, and are unlikely to have an impact on PK, efficacy, or safety.

Non-clinical

The *in vitro* pharmacology data investigating the functional activity of ABP 654 compared to Stelara demonstrates the biosimilarity of the products.

Clinical

Pharmacokinetics

The PK biosimilarity in the pivotal PK study 20190230 using healthy adult subjects has been formally demonstrated between ABP 654 and ustekinumab (EU) and ustekinumab (US) as for the primary PK parameters AUC_{inf}, C_{max} and AUC_{last}, the 90% CI for the ratio of test-to reference/comparator fell within the acceptance range of 80.00-125.00% (including 100%).

From a PK perspective, the potential immunogenicity difference between ABP 654 and the reference product(s) is not considered clinically relevant because all evidence points to the direction that in ADA positive subjects the elimination is faster. Therefore, a potentially lower ADA formation rate with ABP 654 does not implicate higher ustekinumab exposure.

The additional PK data obtained in the efficacy/safety study 20190232 supported PK similarity.

The PK results obtained with the sc presentations can be extrapolated to the iv presentations.

Clinical efficacy

Results from the pivotal study on efficacy and safety (study 20190232) support comparability of efficacy of ABP 654 and ustekinumab (EU). The primary endpoint, PASI percent improvement from baseline to week 12, was similar between the treatment arms. No relevant difference was seen between treatment arms in PASI improvement up to week 52, regardless of whether the treatment was switched at week 28 or continued as initially randomised. Secondary endpoints, subgroup analyses and sensitivity analyses confirmed the robustness of the result. Switching from Ustekinumab (EU) to ABP 654 did not lead to a change in efficacy or safety. As the study was well designed and no major flaws in conduct were detected, the CHMP concluded that the efficacy of ABP 654 is similar to that of Ustekinumab (EU) in subjects with moderate to severe Ps.

The study also included an extra study arm where a subgroup of patients, who achieved PASI 50 response or better by week 28 but did not achieve PASI 75 response, could continue with an intensified dose, not authorised in the EU. This dose intensification came with no apparent benefit in either treatment arm.

Clinical safety

The analysis of adverse event data and laboratory data support the view that the safety profiles of ABP 654 and ustekinumab are comparable. The reported adverse event profiles seem similar in terms of nature, frequency and severity, no unexpected events or clustering was seen, and both products were generally well tolerated. The immunogenic potential of ABP 654 seems to be lower than that of the reference product, potentially due to different expression systems used in their respective manufacturing processes. However, this is permissible per applicable guidance and is not considered to adversely impact determination of biosimilarity as long as the biosimilar and the reference mAb are in principle similar when not impacted by an immune response. Similarity in this respect may be concluded based on available data in the ADA negative subgroup; overall, binding ADAs seem to have limited effect on the efficacy or safety profile.

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 Ps patients can overall be considered to support a determination of biosimilarity.

3.5. Extrapolation of safety and efficacy

Amgen is seeking approval for ABP 654 for the same indications approved for the reference medicinal product Stelara except for the UC indication. Approval is sought for all the same dosage forms, strengths and presentations as approved for Stelara in the EU (see section 2.2). In the present MAA, 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 MOA, PK, expected toxicities, and any other factor that may affect safety and efficacy.

No PK data was available for iv administration and no plans were presented for generating data on iv administration. Extrapolation of data generated with sc administration to iv administration is acceptable as the applicant demonstrated comparability in both absorption and elimination for the sc route by computing the partial AUC GMRs with corresponding 90% CIs. The applicant provided adequate ad hoc analyses to enable extrapolation of the PK results obtained with the sc presentations to the respective iv presentations.

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 ABP 654 and Stelara (ustekinumab) have the same MOA, which is common for each of the originator indications (Ps, paediatric Ps, PsA, CD, UC).

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 20190232 in patients with Ps to all other approved indications of Stelara not studied in the clinical programme of ABP 654.

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

Hence, the totality of evidence presented in this application is supportive of the conclusion that ABP 654 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, biosimilarity of Wezenla (also referred to as ABP 654) to Stelara has been demonstrated and thus, the benefit/risk balance is comparable to the reference product.

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 WEZENLA is favourable in the following indication(s):

Plaque psoriasis

WEZENLA 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

WEZENLA 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)

WEZENLA, 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

WEZENLA is indicated for the treatment of adult patients with moderately to severely active Crohn's

disease who have had an inadequate response with, lost response to, or were intolerant to either conventional therapy or a TNFα antagonist or have medical contraindications to such therapies.

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.

Conditions or restrictions with regard to the safe and effective use of the medicinal product to be implemented by the Member States

Not applicable.