25 July 2024
EMA/378464/2024
Committee for Medicinal Products for Human Use (CHMP)

Assessment report

Fymskina

International non-proprietary name: ustekinumab

Procedure No. EMEA/H/C/005805/0000

Note

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

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List of abbreviations

Abbreviation	Description
ACR	American College of Rheumatology
ADA	Anti-drug antibody
ADCC	Antibody-dependent cell mediated cytotoxicity
ADR	Adverse drug reaction
AE	Adverse event
AESI	Adverse event of special interest
ALT	Alanine aminotransferase
ANCOVA	Analysis of covariance
ANOVA	Analysis of variance
AST	Aspartate Aminotransferase
ATC	Anatomical therapeutic chemical
AUC	Area under the serum concentration time curve
$AUC_{0\text{-}inf}$	Area under the serum concentration curve (from time zero to infinity)
BLA	Biologics licence application
BMI	Body mass index
BSA	Body surface area
CCIT	Container Closure Integrity Testing
CD	Crohn's disease
CD4+	Cluster of differentiation 4 positive
CDC	Complement dependent cytotoxicity
CHO	Chinese Hamster Ovary
CI	Confidence interval
CL	Clearance
C_{max}	Maximum serum concentration
CPP	Critical process parameters
CQA	Critical quality attributes
CRP	C-Reactive Protein
CSR	Clinical study report
CTD	Common technical document
C_{trough}	Drug serum concentration immediately before the next dose
CV	Coefficient of variation
DLQI	Dermatology Life Quality Index
DMARD	Disease-modifying anti-rheumatic drug
DRE	Disease-related event
DSP	Downstream process
ECG	Electrocardiogram

ECL	Electrochemiluminescent
EMA	European Medicines Agency
EU	European Union
FAS	Full analysis set
FDA	Food and Drug Administration
GCP	Good Clinical Practice
GLP	Good Laboratory Practice
GMP	Good Manufacturing Practice
HCP	Host cell protein
HIV	Human immunodeficiency virus
HMWS	high molecular weight species
ICH	International Council for Harmonisation of Technical Requirements for Pharmaceuticals for Human Use
Ig	Immunoglobulin
IgG	Immunoglobulin G
IL	Interleukin
IL-12Rβ1	Interleukin-12 receptor, beta 1
IPCs	In process controls
IPTs	In process tests
IQR	Interquartile range
ISI	Integrated Summary of Immunogenicity
I-VAS	Itching Visual Analogue Scale
L	Liter
LMWS	Low molecular weight species
LoQ	Limit of quantification
LS	Least squares
LSD	Late-stage development
MACE	Major adverse cardiovascular event
MAR	Missing at Random
MCB	Master Cell Bank
MedDRA	Medical Dictionary for Regulatory Activities
MMRM	Mixed Model Repeated Measurements
MNAR	Missing not at random
MTX	Methotrexate
NAb	Neutralizing antibody
NK	Natural killer
PASI	Psoriasis Area and Severity Index
PASI 75	≥75% improvement (reduction) in PASI score
PASI 90	≥90% improvement (reduction) in PASI score
PD	Pharmacodynamics

PFS	Prefilled syringe
PGA	Physician's Global Assessment
PI	Prescribing information
PK	Pharmacokinetics
PKS	Pharmacokinetic analysis set
PMDA	Pharmaceuticals and Medical Devices Agency
PPQ	Process Performance Qualification
PPS	Per Protocol Set
Ps	Plaque psoriasis
PsA	Psoriatic arthritis
PT	Preferred Term
PUVA	Psoralen and ultraviolet A
Q	Quartile
QFT-Plus	QuantiFERON-TB Gold Plus
Ref.	Reference
RP	Reference product
RRAS	Re-randomised analysis set
SAE	Serious adverse event
SAF	Safety analysis set
SAP	Statistical analysis plan
SC	Subcutaneous
SD	Standard deviation
SE	Standard error
SmPC	Summary of product characteristics
SOC	System organ class
TB	Tuberculosis
TEAE	Treatment emergent adverse event
Th1	Type 1 helper
Th17	Type 17 helper
T_{max}	Time to maximum serum concentration
TNF	Tumour necrosis factor
ULN	Upper limit of normal
US	United States
USP	Upstream process
UVB	Ultraviolet B
V	Visit
VAS	Visual analog scale
vs.	Versus
WCB	Working cell bank

1. Background information on the procedure

1.1. Submission of the dossier

The applicant Formycon AG submitted on 8 September 2023 an application for marketing authorisation to the European Medicines Agency (EMA) for Ustekinumab Formycon, through the centralised procedure falling within Article 3(1) and point 1 of Annex of Regulation (EC) No 726/2004. During the procedure, the product name was changed to Fymskina.

The applicant applied for the following indications:

Plaque psoriasis

Fymskina 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

Fymskina 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 weigh 60 kg or more and who are inadequately controlled by, or are intolerant to, other systemic therapies or phototherapies (see section 5.1).

Psoriatic arthritis (PsA)

Fymskina, 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

Fymskina 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

Fymskina 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).

1.2. Legal basis, dossier content and multiples

The legal basis for this application refers to:

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

The application submitted is composed of administrative information, complete quality data, appropriate non-

clinical and clinical data for a similar biological medicinal product.

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 45 mg and 90 mg solution for injection and Stelara 130 mg concentrate for solution for infusion.
- Marketing authorisation holder: Janssen Cilag International NV
- Date of authorisation: 15-01-2009
- Marketing authorisation granted by:
  - Union
- Marketing authorisation number: EU/1/08/494/001, 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 45 mg and 90 mg solution for injection and Stelara 130 mg concentrate for solution for infusion.
- Marketing authorisation holder: Janssen Cilag International NV
- Date of authorisation: 15-01-2009
- Marketing authorisation granted by:
  - Union
- Marketing authorisation number: EU/1/08/494/001, 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 comparability tests and studies have been conducted:

- Product name, strength, pharmaceutical form: Stelara 45 mg and 90 mg solution for injection and Stelara 130 mg concentrate for solution for infusion.
- Marketing authorisation holder: Janssen Cilag International NV
- Date of authorisation: 15-01-2009
- Marketing authorisation granted by:
  - Union
- Marketing authorisation number: EU/1/08/494/001, EU/1/08/494/003, EU/1/08/494/004, EU/1/08/494/005.
- Bioavailability study number(s): study FYB202-03-01

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
15 November 2018	EMEA/H/SA/3970/1/2018/III	Stephan Lehr, Rune Kjeken and Jeanette McCallion
16 December 2021	EMA/SA/0000068892	Juha Kolehmainen and Linda Trauffler

The Scientific advice pertained to the following *quality, non-clinical, and clinical* aspects:

- analytical similarity assessment plan, structural and functional characterisation;
- adequacy of non-clinical development programme;
- design of the pivotal pharmacokinetic study, design of the confirmatory efficacy and safety study in patients with moderate to severe plaque psoriasis, extrapolation of indications;
- adjustment for administered dose; comparative immunogenicity assessment; bridging between EU and US reference products; and additional pharmacokinetic study.

1.6. Steps taken for the assessment of the product

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

Rapporteur: Jayne Crowe Co-Rapporteur: Simona Badoi

The application was received by the EMA on	8 September 2023
The procedure started on	28 September 2023
The CHMP Rapporteur's first Assessment Report was circulated to all CHMP and PRAC members on	18 December 2023
The PRAC Rapporteur's first Assessment Report was circulated to all PRAC and CHMP members on	3 January 2024
The CHMP agreed on the consolidated List of Questions to be sent to the applicant during the meeting on	25 January 2024
The applicant submitted the responses to the CHMP consolidated List of Questions on	26 March 2024
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	03 May 2024
The PRAC agreed on the PRAC Assessment Overview and Advice to CHMP during the meeting on	16 May 2024
The CHMP agreed on a list of outstanding issues in writing to be sent to the applicant on	30 May 2024
The applicant submitted the responses to the CHMP List of Outstanding Issues on	24 June 2024
Methodology Working Party experts (as appropriate) were convened to address questions raised by the CHMP on The CHMP considered the views of the Methodology Working Party (as appropriate) as presented in the minutes of this meeting.	3 July 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 July 2024
The PRAC agreed on the PRAC Assessment Overview and Advice to CHMP during the meeting on	11 July 2024
The CHMP, in the light of the overall data submitted and the scientific discussion within the Committee, issued a positive opinion for granting a marketing authorisation to Fymskina on	25 July 2024

2. Scientific discussion

2.1. Problem statement

2.1.1. Disease or condition

Not applicable for biosimilars.

2.1.2. Epidemiology

Not applicable for biosimilars.

2.1.3. Clinical presentation, diagnosis

Not applicable for biosimilars.

2.1.4. Management

Not applicable for biosimilars.

2.2. About the product

Fymskina (FYB202) is a recombinant, fully human immunoglobulin G, subclass 1, κ light chain (IgG1κ) monoclonal antibody (mAb) that binds to the p40 subunit of interleukin (IL)-12 and IL-23. It has been developed as a biosimilar to Stelara. Binding of the antigen-binding fragment (Fab) domain of ustekinumab to the p40 protein subunit of both IL-12 and IL-23 inhibits the cytokines from binding to IL-12 and IL-23 receptor complexes on the surface of natural killer (NK) cells or T cells, thereby preventing initiation of downstream immune-response signalling pathways.

In line with Stelara, with the exception of the paediatric population in the treatment of plaque psoriasis, which includes the restriction of children who weigh 60 kg or more, the therapeutic indications for FYB202, as initially proposed, were:

Plaque psoriasis

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

Paediatric plaque psoriasis

indicated for the treatment of moderate to severe plaque psoriasis in children and adolescent patients from the age of 6 years and older who weigh 60 kg or more, and who are inadequately controlled by, or are intolerant to, other systemic therapies or phototherapies.

Psoriatic arthritis (PsA)

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

Crohn's Disease

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

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.

2.3. Type of application and aspects on development

The legal basis for this application refers to:

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

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).

2.4. Quality aspects

2.4.1. Introduction

Fymskina (also known as FYB202) is a recombinant humanised monoclonal antibody that is being developed as a similar biological medicinal product to the reference medicinal product, Stelara.

Ustekinumab specifically binds to p40, which is a subunit of interleukin (IL)-12 and IL-23 and prevents IL-12 and IL-23 from binding to IL-12Rβ1 receptor of natural killer (NK) and T cells. Thus, FYB202 neutralises IL-12 (Th1) and IL-23 (Th17) mediated cellular responses that are associated with immune-mediated human diseases.

Fymskina is presented in the following pharmaceutical forms, strengths, and pack sizes:

- 45 mg/0.5 mL (90 mg/mL) solution for injection - in a single-dose pre-filled syringe (PFS) with a safety guard for subcutaneous injection (pack size: 1 pre-filled syringe)
- 90 mg/1 mL (90 mg/mL) solution for injection - in a single-dose pre-filled syringe with a safety guard for subcutaneous injection (pack size: 1 pre-filled syringe)

- 130 mg/26 mL (5 mg/mL) concentrate for solution for infusion - in a single-dose vial for intravenous infusion (pack size: 1 vial)

For FYB202 PFS finished product (FP), other ingredients are L-histidine, polysorbate 80, sucrose, water for injections and hydrochloric acid (to adjust pH).

For FYB202 vial FP, other ingredients are EDTA disodium salt dihydrate, L-histidine, L-histidine monohydrochloride monohydrate, L-methionine, polysorbate 80, sucrose and water for injection.

It is available in a 30 mL Type I borosilicate glass vial closed with a butyl rubber stopper for the vial presentation and in a 1-mL Type I borosilicate glass syringe with a 1/2-inch (27 G thin wall) staked stainless steel needle for the PFS presentations.

2.4.2. Active substance

2.4.2.1. General information

Fymskina (FYB202) is a fully human IgG1 monoclonal antibody. Ustekinumab binds with specificity to the shared p40 protein subunit of human cytokines interleukin (IL)-12 and IL-23. Ustekinumab inhibits the bioactivity of human IL-12 and IL-23 by preventing p40 from binding to the IL-12Rβ1 receptor protein expressed on the surface of immune cells. Details of antibody structure, mechanism of action and the amino acid sequence are provided in the dossier.

2.4.2.2. Manufacture, characterisation and process controls

Description of manufacturing process and process controls

The name, address and general responsibility of each manufacturer involved in the active substance (AS) manufacturing process stream and testing have been provided. All sites involved in the manufacture and control of the active substance operate in accordance with EU GMP.

The manufacturing process and controls are considered to be well described. Acceptance criteria, ranges or limits are provided for critical and non-critical parameters. A description of the batch numbering system has been provided. The applicant has provided the batch numbering system for the contract manufacturer and further details on the internal system in place.

Manufacturing starts with cell culture. The downstream process consists of chromatographies, filtrations and additional steps for virus removal/inactivation and formulation of bulk active substance. The manufacturing description for the purification stage is considered acceptable as the main aspects of the process are described. In-process tests (IPTs) and their acceptance criteria have been added to the process description. The reasons for reprocessing have been defined and fully validated. A protocol for reprocessing at a commercial scale has been provided and is acceptable.

An overview of the manufacturing process is shown.

Control of materials

The list of raw materials and their specifications have been provided for both the cell culture and purification stages. Compendial materials are listed with cross-reference to the relevant Pharmacopoeia grade. Non-

compendial raw materials are tested in-house. The in-house specifications proposed are considered sufficient. The qualitative composition of the media powder has been provided and the information is sufficient.

The host is a Chinese Hamster Ovary (CHO) cell line. The characteristics of the major genetic elements of the plasmid are described and amino acid sequence translated from the nucleotide genes are provided. The construction process is described in line with Ph. Eur. 0784 products of recombinant DNA technology and in line with ICH Q5B. The establishment of the Master Cell Bank (MCB) and Working Cell Bank (WCB) was described. The MCB was characterised to ensure the identity, safety, and genetic stability of the cell substrate. Appropriate testing has been done on the WCB and MCB in line with ICH Q5A and ICH Q5D.

A post-production cell bank (PPCB) was established from a commercial-scale batch by the continued passages of cells that were derived from the production bioreactor at the time of harvest. The PPCB was tested in line with the requirements of ICH Q5A.

Control of critical steps and intermediates

The dossier describes the control strategy for the active substance process. The development of the control strategy is well described.

The critical process parameters (CPP) and relevant critical quality attributes (CQA) affected by the process parameter are listed in the dossier. The applicant has clearly defined CPPs, NCPPs, Key Process Parameters (KPPs) and NKPPs. The criticality of process parameters was determined using risk assessments, product knowledge, manufacturing experience and process development/characterisation studies.

The CPPs, IPTs, their acceptance criteria and acceptable ranges are described and are appropriate for a standard mAb process. The consequences of exceeding the acceptable ranges are described and considered acceptable. Additional data to support the viral inactivation and virus filtration parameters are provided. Bioburden and endotoxin are tested for numerous steps throughout the process. Both bioburden and endotoxin levels are tested at AS release, therefore, the testing proposed is acceptable.

Hold times are registered and supported by data.

Process validation and/or evaluation

Process validation for FYB202 was performed at a commercial scale at the AS manufacturer. Process validation consisted of demonstrating consistency and reproducibility of the manufacturing process. After completing the process validation runs, several adjustments were implemented for commercial manufacturing. The validation has been successfully performed for the upstream and downstream processes.

Minor deviations have been reported in the validation procedure. All CPPs and IPTs remained within the acceptable validation ranges for each step and met the proposed commercial scale criteria.

Impurity clearance of process- and product-related impurities was validated at a commercial scale and supported by small-scale studies. Validation of process-related impurity clearance was sufficiently demonstrated. Other process-related impurities were demonstrated to be adequately cleared to safe levels. Product-related impurities were shown to be cleared effectively by the purification process. Desirable variants were enriched or remained at constant levels throughout the process.

A risk assessment for elemental impurities in the AS was provided. Low risk was attributed to each of the identified potential contributors of EI. The nitrosamine risk associated with the excipients, water for injection (WFI), process materials and primary packaging material was comprehensively assessed for risk.

Scale-down models (SDM) of the downstream process were used, and qualification for the scale-down models was provided. Hold time validation has been performed. Resin lifetime studies were performed on chromatography resins used in the process and the number of resin cycles defined for each chromatography column were determined. An extractable and leachable risk assessment (E/L) was performed for the FYB202 process. Overall, the assessment found that the materials used in the manufacturing process were low risk. The primary container for the AS was found to have no extractable impurities at levels above the Permitted Daily Exposure (PDE) limit.

Reprocessing under certain circumstances was evaluated, and it was demonstrated that it does not have a negative impact on product quality.

For the shipping validation, the applicant has provided an overview of the shipping conditions. Overall, the temperature validation study demonstrated that the temperature of the shipping container can be maintained under worst-case conditions.

Overall, the applicant has provided sufficient data to provide assurance that the manufacturing process is appropriately validated and can produce active substance batches of consistent quality.

Manufacturing process development

The approach to manufacturing process development for FYB202 has been thorough. Different manufacturing processes have been described. The main differences are in scale with appropriate adjustment of process parameters. At each scale, a comparability study was also performed. No significant differences were reported, and step yields for each process were comparable. Product quality attributes (PQAs) tested at each step of the process also showed suitable comparability.

The development studies of the FYB202 AS manufacturing process were used to inform a risk assessment of critical parameters. The approach to assigning criticality was based on risk assessment, experimental studies and process knowledge. The approach was endorsed. The sources of information used to inform the risk assessment come from historical development data as well as generic process knowledge. The applicant has presented the full characterisation study results for each step assessed. The resulting process is adequately controlled and well understood. The assignation of criticality to process parameters has been well described and justified based on the information provided. The ranges for all process parameters, NKPPs and CPPs are well justified based on the data presented in the dossier. The proposed ranges for IPC are also well-supported and endorsed.

Characterisation

Characterisation has been performed on several batches of AS three are from a commercial scale and one from a development scale.

A comprehensive extended characterisation study has been presented to confirm the structure and physicochemical characteristics of the AS and FP presentations. Studies were performed to characterise FYB202 with respect to the primary structure and post-translational modification higher order structure, purity/impurity, charge variants, glycation/glycosylation, and biological activity were characterised. Target binding to IL-23/IL-12 was assessed, as well as target inhibition.

Overall, the characterisation studies have been carried out in a very comprehensive manner and cover all relevant aspects of a monoclonal antibody.

Impurities

A detailed description of the potential product- and process-related impurities has been provided including risk assessments of their criticality to product quality. A comprehensive analysis of all process-related substances was included.

The justification of the identification and classification of product-related impurities can be agreed upon.

For process-related impurities, it has been demonstrated that these are cleared by the process to acceptably low levels.

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

Specifications

The active substance specifications are provided and include tests for characteristics, identity, content, purity, microbial purity and process-related impurities.

Analytical procedures

Compendial analytical procedures include colour, clarity, pH, bacterial endotoxins and bioburden and are performed in accordance with the relevant Ph. Eur. monographs.

In general, the non-compendial method descriptions are sufficiently detailed.

The analytical procedures have been appropriately validated in accordance with ICH Q2(R1). Verification data has been presented for all the compendial methods and the data presented shows that all the verification results met the acceptance criteria, and the methods are considered appropriate for their intended use.

For the non-compendial methods, a summary of the validation results for each method has been submitted and the testing has been performed.

Data supporting an impurity test will be provided post-approval (REC).

Batch analysis

Batch analysis data is provided for batches used in technical development and clinical studies, reference standard and stability. Batch data is also provided for commercial scale batches including PPQ and clinical batches.

Justification of specification

Proposed acceptance limits are deemed acceptable. The applicant has provided sufficient evidence that the specifications for purity are clinically qualified. The applicant has provided a comprehensive summary of the control strategy as part of the justification for specification.

Reference standards

The applicant has established different reference standards throughout the development of FYB202.

A primary reference standard and the current working standard were established from commercial scale, clinical use batches. The qualification and characterisation program for the standards has been extensive. All reference standards have met the applied qualification criteria.

The applicant has provided extensive data from bridging studies for functional methods and physicochemical methods. This approach is acceptable, and the applicant has adequately demonstrated a conscientious and consistent approach to reference potency continuity.

The re-testing and qualification procedure for current and future reference standards, including acceptance criteria and testing, has been adequately described. The procedure is acceptable and is considered in its approach to ensuring continuity in product quality over the foreseeable lifetime.

Overall, the primary and working reference standard are considered to be appropriately characterised and qualified. The information on the requalification, storage and introduction of a new working and primary reference standard is sufficient.

Container closure

The container closure systems for the FYB202 AS are compliant with Ph. Eur. requirements. Leachable studies and stability studies are presented in the dossier. Overall, the information provided on the container closure is acceptable.

2.4.2.4. Stability

Stability studies have been performed in accordance with ICH guidelines in terms of testing frequency and storage conditions. The methods used have been validated and all tests have the same specifications as listed in the respective dossier's section.

Data has been provided for batches manufactured at AS manufacturer at different scales, including clinical and PPQ batches. The proposed shelf-life and storage conditions, based on real-time data, are considered acceptable. The stability data presented are generally within specification for the proposed conditions.

The applicant commits to completing the stability studies according to the protocol provided, which is acceptable. The applicant has committed to notifying the competent authorities of any out-of-specification results during the post-approval stability studies; this is endorsed.

2.4.3. Finished Medicinal Product

2.4.3.1. Description of the Product and Pharmaceutical Development

Fymskina (FYB202) is a biosimilar to Stelara and has two presentations that cover three strengths. The formulation used is identical to the reference medicinal product (RMP). The finished product presentations include a pre-filled syringe (PFS) for subcutaneous injection with Ustekinumab at 90 mg/dose and 45 mg/dose, and a vial containing 5 mg/mL concentrate solution for infusion. Both presentations are a clear, colourless to slightly brown-yellow, sterile and preservative-free solution. There is no overfill.

The composition of the FYB202 PFS FP is Ustekinumab (active substance), L-histidine, polysorbate 80, sucrose, water for injections and hydrochloric acid (to adjust pH).

The composition of FYB202 vial FP is Ustekinumab (active substance), EDTA disodium salt dihydrate, L-histidine, L-histidine monohydrochloride monohydrate, L-methionine, polysorbate 80, sucrose and water for injection.

All excipients are well-known pharmaceutical ingredients and their quality is compliant with Ph. Eur standards. No novel excipients were used in the finished product formulation.

Pharmaceutical development

The applicant has based their formulation development on the reference medicinal product (RMP) for both the PFS and the vial.

For the PFS, the primary container is a syringe barrel made of borosilicate type I glass and a bromobutyl rubber stopper. For the vial presentation, the primary container is a 30R glass vial, a bromobutyl rubber stopper and an aluminium seal with a plastic flip-off cap. The containers are considered standard for biological medicines. No leachables studies were provided and their absence has been justified because no extractables of concern were identified.

A Notified Body opinion has not been provided for the PFS and a major objection has been raised to this issue. During the assessment, the applicant provided a positive Notified Body Opinion to support the FYB202 prefilled syringe with a needle safety device, and the issue was considered solved.

The NBOp states that the device conforms with Chapters I, II and III of Article 117 of (EU) 2017/745 Regulation and the relevant GSPRs of Annex II.

Only minor changes have been made to the manufacturing process of the PFS throughout development. A comparability study demonstrated comparability between the PFS and vial presentations. The PFS batches used for the comparability study were used in clinical studies. Overall, the PFS batches used in the clinical study can be considered comparable to the PPQ vial batches.

2.4.3.2. Manufacture of the product and process controls

Manufacturing process

The PFS finished product manufacturing process consists of thawing, mixing, filtration and aseptic filling into sterile syringes and stoppering. The filled syringes are then visually inspected and secondary packaged (labelled, assembled and packaged into a blister).

The vial finished product manufacturing process is divided into several manufacturing steps, including preparation of equipment/materials, preparation of the container closure, thawing of AS, filtration, aseptic filling, visual inspection and labelling/secondary packaging.

The PFS and vial process is a standard process for monoclonal finished product manufacturing.

For both PFS and vial presentations, the description of the manufacturing processes is acceptable.
The hold times provided are acceptable and have been supported by validation studies.

Process controls

For both presentations, CQAs were assigned based on a risk assessment. Subsequently, data from FYB202 development batches were evaluated and all process steps were assessed to assign criticality of the operational

parameters and process controls based on their potential effects on CQAs. The chosen PPs and IPCs are largely aligned with similar biological products produced using a standard fill/finish manufacturing process and are acceptable.

Process Validation

Manufacturing process validation has been provided for several PPQ PFS batches (45 mg FYB202 batches and 90 mg batches) and PPQ vial batches. All attributes tested met their pre-defined acceptance criteria throughout the manufacturing process validation and all PPQ batches met release specifications in batch analyses. No deviations were reported during manufacturing process validation. For the finished product vial presentation, several changes were introduced following PPQ. The post-PPQ changes are considered minor and are not likely to impact the quality of the FP and are considered acceptable.

Additional validation has been provided from media fill studies, filter validation studies and shipping validation for both presentations. The media fill studies demonstrated no contamination occurred during filling under representative filling conditions covering the intended fill duration and the containers are representative of those used in the manufacturing process. The filter validation demonstrated that the filter is suitable for the intended purpose.

Overall, the control strategy is considered sufficient to produce a finished product of consistent quality for both presentations.

2.4.3.3. Product specification, analytical procedures, batch analysis

Specifications

The FP specification 90 mg/mL solution for injection in PFS includes tests for characteristics identity, content/activity, purity microbial purity.

The FP specification 5 mg/mL concentrate for solution for infusion (vials) includes tests for characteristics identity, content/activity purity, microbial purity.

The release and stability specifications of FYB202 PFS finished product 90 mg/mL solution for injection and the FYB202 vial finished product 5 mg/mL concentrate for solution for infusion are described. The applicant has provided release specifications for both FYB202 FP presentations that cover general tests, identity, content/activity, purity/impurity and microbial content. The panel is in line with ICH Q6B and considered appropriate for routine control of a monoclonal antibody DP. The approach to setting the release specifications is endorsed. The impurities identified are standard impurities associated with the production of monoclonal antibodies. During studies of the vial, the mitigation strategy proposed by the Applicant was not fully endorsed as it is not in line with the 3Rs principles and a major objection was raised. The applicant has proposed an alternative strategy, with the new proposed method suitably validated. This issue was considered solved. The methods used have been suitably described and validated.

For the PFS, batch data has been provided. This includes batches of the 45 mg PFS presentation and batches of the 90 mg PFS presentation. All batch data provided were within the proposed specification in place at the time of testing and demonstrated that the process could produce FYB202 to a consistent quality.

For the vial batch data has been provided. All batch data provided were within the proposed specification in place at the time of testing and demonstrated that the process could produce FYB202 to a consistent quality.

A risk evaluation concerning the presence of nitrosamine impurities in the finished product has been performed in line with the "Questions and answers for marketing authorisation holders/applicants on the CHMP Opinion for the Article 5(3) of Regulation (EC) No 726/2004 referral on nitrosamine impurities in human medicinal products" (EMA/409815/2020) and the "Assessment report- Procedure under Article 5(3) of Regulation EC (No) 726/2004- Nitrosamine impurities in human medicinal products" (EMA/369136/2020). The information provided is acceptable and no additional control measures are deemed necessary.

Reference Materials

The reference standards used for release are the same as those used for AS.

Container closure system

The container closure system for FYB202 FP PFS is comprised of a glass syringe with a staked-in needle preassembled with a rigid needle shield and a bromobutyl rubber stopper. The container closure system for the vial presentation consists of a Type I glass vial, stoppered with a butyl rubber stopper and sealed with an aluminium crimping cap. The materials used to construct the container closure system are Ph. Eur. compliant. Specifications for the container closure systems have been registered in the dossier. Confirmation that the sterilisation method is conducted and validated in accordance with the relevant ISO standards has been provided. The applicant has provided details of the sterilisation cycle used for product contact components.

A notified body opinion has been provided for the PFS.

2.4.3.4. Stability of the product

The shelf-life for the PFS is 36 months when stored at 5 ±3 °C. The PFS may be stored for a single period of up to 30 days at 30 °C within the proposed shelf-life.

The shelf-life for the vial is 24 months when stored at 5 ±3 °C. In-use stability studies have been performed using polypropylene and polyvinylchloride infusion bags. The in-use stability studies support the information provided in the SmPC that the vial should be diluted only in 0.9% NaCl and can be stored at room temperature for up to 8 hours following dilution before use.

Stability studies for both presentations have been carried out in accordance with ICH Q1A and ICH Q5C. All results to date for Long-term stability studies demonstrate that all tested criteria are within specification and no significant trends are observed for most of the data. Data from the accelerated and stressed condition studies support the stability indicating the profile and the suitability of the analytical methods.

2.4.3.5. Biosimilarity

A tabulated overview of the results is summarised in the table below and discussion of the results for PFS and vial has been provided.

Quality attribute	Methods	Assessment Approach	Similarity Assessment Result
Structural characterization			
Amino acid sequence	LC-ESI-MS/MS & Edman degradation	Qualitative comparison	Identical

Quality attribute	Methods	Assessment Approach	Similarity Assessment Result
Molecular mass	LC-MS intact mass deglycosylated	Predefined limit based on the theoretical molecular weight	Similar
Secondary structure	FTIR secondary structure	Qualitative comparison of profiles	Similar
	Far-UV CD secondary structure	Qualitative comparison of profiles	Similar
Tertiary structure	Near-UV CD tertiary structure	Qualitative comparison of profiles	Similar
Disulfide linkage	Ellman's assay	Quality range (mean ± X SD)	Outside range (higher than Stelara)
	LC-MS/LC-UV peptide mapping non-reduced	Qualitative comparison of profiles	Similar
Thermodynamic stability	Far-UV CD	Predefined limit	Within range
Product-related substances and impurities			
HMW species	SE-HPLC	Quality range (mean ± X SD)	Outside range (higher than Stelara)
	SV-AUC	Qualitative comparison of profiles	Similar
LMW species	CE-SDS non-reduced	Quality range (mean ± X SD)	Majority outside range (higher than Stelara)
Purity (main variant)	CE-SDS non-reduced	Quality range (mean ± X SD)	Majority outside range (higher than Stelara)
Main peak (charge variants)	icIEF (native)	Quality range (mean ± X SD)	Outside range (higher than Stelara)
	icIEF (DC)	Quality range (mean ± X SD)	Outside range (lower than Stelara)
Acidic variants	icIEF (native)	Quality range (mean ± X SD)	Majority within range (partially lower than Stelara)
	icIEF (DC)	Quality range (mean ± X SD)	Majority outside range (higher than Stelara)
Basic variants	icIEF (native)	Quality range (mean ± X SD)	Outside range (lower than Stelara)
	icIEF (DC)	Quality range (mean ± X SD)	Outside range (higher than Stelara)
Isoaspartate	RP-HPLC Isoaspartate Quantification	Quality range (mean ± X SD)	Within range
C-terminal Lys	LC-MS/MS peptide mapping reduced	Quality range (mean ± X SD)	Outside range (lower than Stelara)
Deamidation Fab domain	LC-MS/MS peptide mapping reduced	Quality range (mean ± X SD)	Within range
Deamidation Fc domain		Quality range (mean ± X SD)	Similarity given as no deamidation was detected.

Quality attribute	Methods	Assessment Approach	Similarity Assessment Result
Oxidation Fab domain	LC-MS/MS peptide mapping reduced	Quality range (mean ± X SD)	Majority within range
Oxidation Fc domain		Quality range (mean ± X SD)	HC-Met254: Majority outside range (higher than Stelara HC-Trp419/Met430: Majority within range (partially higher than Stelara)
			Majority within range (partially higher than Stelara)
C-terminal Pro	LC-MS/MS peptide mapping reduced	Quality range (mean ± X SD)	Outside range (higher than Stelara)
Pyroglutamate	LC-MS/MS peptide mapping reduced	Quality range (mean ± X SD)	Within range
Glycation	LC-MS subunit mass	Quality range (mean ± X SD)	Outside range (higher than Stelara)
Glycosylation			
High Mannose	N-Glycans RapiFluor HILIC-UPLC	Quality range (mean ± X SD)	Within range
Total afucosylation		Quality range (mean ± X SD)	Majority within range (partially lower than Stelara)
Terminal galactosylation		Quality range (mean ± X SD)	Majority within range (partially lower than Stelara)
Sialylation		Quality range (mean ± X SD)	Outside range (lower than Stelara)
Sum α-galactose		Quality range (mean ± X SD)	Outside range (lower than Stelara)
Monosaccharides	HPAEC-PAD	Quantitative comparison	Levels of fucose, galactosamine, glucosamine, galactose and mannose are comparable
N-Glycan occupancy	CE-SDS reduced	Quality range (mean ± X SD)	Outside range (higher than Stelara)
General properties			

Quality attribute	Methods	Assessment Approach	Similarity Assessment Result
Concentration	Protein concentration (UV280)	Quality range (mean ± X SD)	Majority within range (partially higher than Stelara)
Extractable volume	Extractable volume	Quality range (mean ± X SD)	Within range
Dose	Extractable Volume and Concentration	Quality range (mean ± X SD)	50% within range (50% higher than Stelara)
Relative Dose	Extractable Volume and Concentration	Quality range (mean ± X SD)	Majority within range (partially higher than Stelara)
Total pI	icIEF (native)	Quality range (mean ± X SD)	Within range
Biological function			
Neutralization of p40	NK92 IL-12 potency assay	Quality range (mean ± X SD)	Within range
	IL-12 Potency Assay (ELISA)	Quality range (mean ± X SD)	Within range
	IL-12 binding kinetics (SPR)	Quality range (mean ± X SD)	Within range
	iLite IL-23 Potency Assay	Quality range (mean ± X SD)	Within range
	IL-23 Potency Assay (ELISA)	Quality range (mean ± X SD)	Within range
	IL-23 binding kinetics (SPR)	Quality range (mean ± X SD)	Within range
	Cytokine release	Qualitative comparison	Similar
	STAT 3, 4 signaling	Qualitative comparison	Similar
Binding to FcRn	FcRn binding kinetics (BLI)	Quality range (mean ± X SD)	Within range
Binding to Fcγ panel	FcγRI binding kinetics using (SPR)	Quality range (mean ± X SD)	Majority outside range (lower and higher than Stelara)
	FcγRIIIA(V) binding kinetics using (SPR)	Quality range (mean ± X SD)	Majority within range (partially lower and higher than Stelara)
Binding to C1q	C1q (ELISA)	Quantitative comparison	Similar
Effector functions (ADCC, CDC)	ADCC (cell-based)	Qualitative comparison	Similar
	CDC (cell-based)	Qualitative comparison	Similar
Non-binding to related proteins	IL-6R non-binding (ELISA)	Qualitative comparison	Similar

The comparative analytical assessment consists of the following three elements:

• Characterisation.

• Forced degradation studies.

• Stability studies

Analytical similarity of FYB202 (PFS & vial) was assessed in a comprehensive similarity exercise using EU-sourced Stelara as a reference medicinal product. US Stelara was included as supportive information. The similarity assessment was generally performed in line with the relevant EU guidelines on the development of similar biological medicinal products (CHMP/437/04 Rev 1 & EMA/CHMP/BWP/247713/2012).

The criticality assignment for the QAs is considered acceptable. The similarity assessment was performed by comparing the proposed biosimilar FYB202 to Stelara EU by defining the QA to be tested by quantitative or qualitative data. compared to the same analysis approach to demonstrate similarity will be applied for both the PFS and the vial. Overall, the approach is considered appropriate.

The applicant has provided tables which summarises the number of RMP batches and what attributes the batch was used to assess in the biosimilarity exercise. Sufficient information has been provided for all batches of Stelara EU and FYB202 regarding their shelf-life at the time of testing for each attribute.

For the vial similarity exercise, as for the PFS, adequate information has been provided on the age of the batches for both the Stelara EU and FYB202.

Analytical methods

The analytical methods proposed for the testing of each QA have been listed. The methods selected are considered comprehensive and state-of-the-art analytical methods that cover primary and higher order structure, post-translational modifications, size and charge variants, protein concentration, as well as Fab and Fc-mediated biological functions of ustekinumab. Qualification data has been provided for most of the methods, and for those methods, they are considered suitable for their intended purpose.

Initial characterisation

Structural characterisation

The applicant has used a side-by-side comparison between the FYB202 and EU Stelara to demonstrate similarity. The first step was to demonstrate similarity at a structural level by comparing the primary and higher-order structures. Overall, appropriate testing was performed to evaluate the structural characterisation of FYB202 and Stelara and the results support a conclusion of biosimilarity.

Product-related substances and impurities

The LMW species were higher for FYB202, but the Applicant considers the risk of immunogenicity to be low and there were no safety issues during the clinical studies. Given the low levels and the lack of impact on immunogenicity, the differences can be accepted. Given the small differences and the overall levels of HMW, the levels are considered minor and do not preclude similarity.

Charge variants were analysed and a different pattern was identified between both products. The applicant has adequately shown that the differences in charged variants are due to the different cell line and the results are not considered to preclude the claim of biosimilarity.

Post-translational modifications

In PTM analysis, differences were observed for some of the variants, which were adequately justified due to the different cell lines used.

Glycosylation

The applicant has investigated the glycosylation profile of FYB202 and Stelara. Some differences in the glycosylation profile of FYB202 and Stelara EU, which are not unexpected given the difference in host cell expression system, but are not expected to have an adverse impact on immunogenicity, and it is agreed it does not preclude biosimilarity.

General properties

The general properties of FYB202 and Stelara EU were tested to demonstrate similarity, and this included the determination of extinction coefficient, protein concentration, extractable volume, and total pI. Overall, both products are considered highly similar with respect to these parameters.

Biological function

The applicant has studied the biological activity of FYB202 and Stelara EU using a number of different methods. For all the methods, the results showed that FYB202 fell within the similarity range of Stelara EU.

Forced Degradation Studies PFS

An extensive forced degradation study has been performed which has investigated the similarity of degradation pathways in FYB202 pre-filled syringe (PFS) and Stelara 90 mg/mL PFS. The stress conditions applied were considered to be harsher than the conditions the product will experience during long-term storage; hence, they are deemed appropriate for testing the degradation pathway.

The applicant has presented supportive data showing the overall degradation profiles are similar between the two products. There were some differences identified, but these issues are not considered to impact the claim for biosimilarity between FYB202 and EU Stelara.

Accelerated Stability Studies

The similarity of the stability profiled was investigated between the FYB202 90 mg/mL solution for injection in PFS and Stelara 90 mg/mL solution for injection in PFS under accelerated (25 °C ± 2°C /60 % ± 5 % RH) and stress (40 °C ± 2°C/75 % ± 5 % RH) storage conditions. Minor differences were observed but are not considered to impact pharmacokinetics, efficacy, immunogenicity and safety. Overall, the stability profiles were considered to be similar.

Vial Biosimilarity

The results are consistent with those presented already for the PFS and support the similarity of FYB202 and Stelara EU. Minor differences were noted between the vial and PFS batches, and an adequate justification was provided.

Forced Degradation Studies Vial

The applicant has performed a forced degradation study for the vial FYB202 and Stelara EU batches which has been done in the exact same manner as described for the PFS study.

The applicant has presented supportive data showing the overall degradation profiles are similar between the two products. There are some differences noted, but these are not deemed to impact the claim for biosimilarity between FYB202 and EU Stelara.

Accelerated Stability Studies

The similarity of the stability profiled was investigated between the FYB202 vial and Stelara vial under accelerated (25 °C ± 2°C /60 % ± 5 % RH) and stress (40 °C ± 2°C/75 % ± 5 % RH) storage conditions. For the majority of the attributes tested, the effects observed were the same as for the PFS study. and it can be concluded that the stability behaviour is similar.

Conclusion on biosimilarity

Overall, a comprehensive analytical similarity exercise has been performed for both the PFS and the vial presentations of FYB202 against the EU reference product, Stelara. The results of the individual tests generally support a conclusion of biosimilarity.

2.4.3.6. Adventitious agents

No raw materials of biological origin are used routinely in the manufacturing process. The applicant provides an adequate overview of the strategy to minimise the risk of contamination by adventitious agents. The strategy consists of controlling potential sources of virus contamination both to the cell bank system and the production process, and viral clearance processes.

Testing for sterility and mycoplasma on the MCB and WCB are performed in accordance with the Ph. Eur. 2.6.1 and 2.6.7, respectively, and details, including the results of the testing, have been provided. GMP batches were tested for mycoplasma, bioburden, endotoxin and viral adventitious agents and all were found to be free from non-viral and viral adventitious agents.

The testing performed on the MCB, WCB and PPCB is considered to be in accordance with the ICH Q5A (R1). Testing is performed routinely for the unprocessed bulk in line with the requirements in ICH Q5A. Testing results for GMP batches showed that no viruses were detected.

A summary of the viral clearance studies has been provided and, in general, is acceptable and complies with ICH Q5A. The methods used for viral validation and screening of cell banks are considered suitable for their intended purpose. The virus validation studies have been performed and are considered acceptable.

The level of viral clearance and the safety calculated per dose are considered acceptable.

2.4.4. Discussion on chemical, pharmaceutical and biological aspects

Active substance

The active substance manufacturing process is standard for the production of monoclonal antibodies. Details of developmental genetics and the establishment of the MCB and WCB are described and acceptable. The control strategy for the active substance is comprehensive, with sufficient control of each manufacturing step. The manufacturing process has been appropriately validated. The lists of raw materials have been provided and are acceptable. The characterisation data presented was comprehensive. The panel of release tests covers relevant aspects of purity, potency, and safety. Batch data provided demonstrate that the commercial process

is capable of manufacturing a consistent active substance. Reference standards are sufficiently described. The container closure systems for the AS are detailed and the AS shelf life proposed is supported by sufficient real-time data.

Finished Product

FYB202 has two presentations covering three strengths. DMB PFS is provided as 45 mg/0.5 mL and 90 mg/1.0 mL of ustekinumab solution for injection as a single-use PFS. FYB202 vial FP is presented as a single-use vial containing 5 mg/mL in approximately 27 mL concentrate solution for infusion of ustekinumab for intravenous infusion. The formulations used are identical to the reference medicinal product. Nitrosamine risk assessments are provided and are acceptable.

There have been minimal changes throughout the development of the manufacturing process of the PFS. Comparability has been provided between the clinical lots of the PFS and the PPQ batches of the vial. The comparability study is acceptable and it is agreed that the finished product from both processes are comparable. The manufacturing process for both the PFS and vial are standard processes for FP manufacturing of a monoclonal antibody biological medicine. Overall, it can be concluded that both the PFS and vial FP manufacturing processes can consistently produce FP that meets the required CQAs using the current control strategy. The manufacturing processes are considered suitably validated. For both presentations, the proposed panel of tests is in line with the ICH Q6B and Ph. Eur. 2031 and is considered appropriate for routine control of a monoclonal antibody. The container closure systems are well described.

Upon request during the assessment, the Applicant has provided a positive NBOp to support the FYB202 prefilled syringe with a needle safety device. The NBOp states that the device conforms with Chapters I, II and III of Article 117 of (EU) 2017/745 Regulation and the relevant GSPRs of Annex II.

In addition, the applicant also provided an alternative mitigation strategy, in line with the 3Rs principles, as requested during the assessment. The proposed shelf-life for the PFS is 36 months and the proposed shelf-life for the vial is 24 months. The proposed out of fridge time listed in the SmPC has been suitably supported with data. The in-use period for the diluted vial listed in the SmPC is supported with data and is considered acceptable.

The claim of biosimilarity is supported.

2.4.5. Conclusions on the chemical, pharmaceutical and biological aspects

Information on the development, manufacture and control of the active substance and finished product has been presented in a satisfactory manner. The results of tests carried out indicate consistency and uniformity of important product quality characteristics, and these, in turn, lead to the conclusion that the product should have a satisfactory and uniform performance in clinical use. 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 has been presented to give reassurance on viral/TSE safety. Comparability to Stelara has been sufficiently demonstrated.

Post-approval, the applicant is recommended to provide data supporting an impurity test when available (REC).

2.4.6. Recommendation(s) for future quality development

In the context of the obligation of the MAHs to take due account of technical and scientific progress, the CHMP recommends further points for investigation:

1. The applicant is recommended to provide data supporting an impurity test when available (REC).

2.5. Non-clinical aspects

2.5.1. Introduction

Fymskina (FYB202) has been developed as a biosimilar product to Stelara (ustekinumab).

The active ingredient ustekinumab, is a fully human immunoglobulin G 1K monoclonal antibody (IgG1κ). It binds with high affinity and specificity to the 40 kDa human protein (p40) which is a subunit of IL-12 and IL-23. Binding of ustekinumab to p40 prevents IL-12 and IL-23 from binding to IL-12Rβ1 receptor protein which is expressed on the surface of natural killer (NK) and T cells. Thus, ustekinumab neutralises IL-12 (Th1) and IL-23 (Th17) mediated cellular responses that are associated with immune-mediated human diseases.

As with EU-approved Stelara, Fymskina has been developed for subcutaneous and intravenous administration.

The non-clinical development programme included in vitro primary pharmacodynamic (PD) studies and a GLP compliant single dose comparative pharmacokinetic study performed in female Göttingen minipigs to assess the similarity of the proposed biosimilar Fymskina (FYB202), US-licensed Stelara, and EU-authorised Stelara.

2.5.2. Pharmacology

2.5.2.1. Primary pharmacodynamic studies

The pharmacology programme of FYB202 was focused on comparative in vitro primary pharmacodynamic studies with the reference product EU-Stelara.

To cover all relevant aspects of the well-established MoA of ustekinumab, this was investigated through binding to target antigen bioassays. Fab-associated function tests have also been performed.

Binding to representative isoforms of the Fc gamma receptors (FcγRI and FcγRIII), FcRn and complement C1q has been investigated. Ustekinumab cannot bind to IL-12 or IL-23 that is already bound to IL-12Rβ1 cell surface receptors. Thus, ustekinumab is not likely to contribute to complement- or antibody-mediated cytotoxicity of cells with IL-12 and/or IL-23 receptors. However, in support of a comprehensive non-clinical package, binding to the FcγRs (with the exception of FcγRIIa-H131, FcγRIIa-R131), was assayed.

FYB202 and EU-approved Stelara had similar biological activities in terms of Fab function in IL-12/IL-23 p40 binding activity, cell-based IL-12 or IL-23 binding inhibition activity, signaling inhibition activity and IFN-γ secretion inhibition activity.

The assessment of biosimilarity was primarily based on the quality assessment of the appropriateness and acceptability of the in vitro comparability studies conducted.

2.5.2.2. Secondary pharmacodynamic studies

No secondary PD studies were conducted. The lack of secondary PD studies is acceptable for an application under Article 10(4) of Directive 2001/83/EC and in accordance with EMEA/CHMP/BMWP/42832/2005 Rev1 guideline.

2.5.2.3. Safety pharmacology programme

Safety pharmacology studies are not required for an application under Article 10(4) of Directive 2001/83/EC and in accordance with the EMEA/CHMP/BMWP/403543/2010 guideline.

2.5.2.4. Pharmacodynamic drug interactions

No PD drug interactions studies were conducted. The lack of PD drug interactions studies is acceptable for an application under Article 10(4) of Directive 2001/83/EC and in accordance with EMEA/CHMP/BMWP/42832/2005 Rev1 guideline.

2.5.3. Pharmacokinetics

One comparative single-dose PK study was performed in female Göttingen minipigs over 9 weeks under GLP conditions. The PK study included separate groups of animals with 8 animals per treatment group to comparatively assess FYB202 in three different formulations with US-licensed Stelara, and EU-authorised Stelara. For all but one PK parameter, FYB202-RF (reference formulation, same buffer formulation as Stelara) was superior to FYB202-F1 and FYB202-F3 (alternative buffer formulations) in terms of similarity of measured values when compared to the RP. The PK consequences of using different formulation buffers are well described in the study report.

It is noteworthy that in this study, anti-drug antibodies (ADAs) were evident in all treatment groups and the number of ADA-positive test animals increased over time.

2.5.4. Toxicology

2.5.4.1. Single dose toxicity

No single-dose toxicity study was performed, which is in line with Guideline EMEA/CHMP/BMWP/42832/2005 Rev1. The single-dose PK study in Minipigs described above under PK – Absorption, however, included some safety endpoints.

Animals were observed before and after administration for any signs of behavioural changes, reaction to treatment, or illness. Analysis of local tolerance, behaviour, external appearance, faeces, mortality, body weight and body weight gain, food and drinking water consumption, ophthalmological and auditory

examinations, haematological parameters, biochemical parameters, and urinary parameters did not reveal any test or reference item-related changes.

These data are consistent with results from pivotal safety studies of the reference product, which did not detect clinically relevant safety alerts in nonclinical studies for ustekinumab.

2.5.4.2. Repeat dose toxicity

No repeat dose toxicity studies were performed, which is in line with the applicable guideline ICH S6 (R1).

2.5.4.3. Genotoxicity

No genotoxicity or mutagenicity studies were performed, which is in line with the applicable guideline ICH S6 (R1). It is noted that the range and type of genotoxicity studies routinely conducted for pharmaceuticals are not applicable to biotechnology-derived pharmaceuticals because large proteins would not be expected to pass through cell membranes and interact directly with DNA or other chromosomal material.

2.5.4.4. Carcinogenicity

No carcinogenicity studies were performed, which is in line with the applicable guidelines (EMEA/CHMP/BMWP/42832/2005 Rev1 and ICH S6 (R1)). It is noted that studies regarding carcinogenicity are not required for non-clinical testing of biosimilars.

2.5.4.5. Reproductive and developmental toxicity

No reproductive and developmental studies were performed, which is in line with the applicable guideline (EMEA/CHMP/BMWP/42832/2005 Rev1).

2.5.4.6. Toxicokinetic data

No toxicokinetic studies were performed, which is in line with the applicable guideline ICH S6 (R1).

2.5.4.7. Local Tolerance

Analysis of local tolerance (injection sites) was performed as part of the single-dose PK study and revealed no toxicologically significant differences in injection site findings between animals administered FYB202, EU-Stelara or US-Stelara.

2.5.4.8. Other toxicity studies

No other toxicity studies were performed.

2.5.5. Ecotoxicity/environmental risk assessment

Fymskina (FYB202) is a monoclonal antibody and is classified as a protein. Therefore, an environmental risk assessment (ERA) is not required for this medicinal product in accordance with Article 8(3) of Derivative 2001/83/EC and the guideline (EMEA/CHMP/SWP/4447/00).

An expert statement justifying the absence of an ERA has been submitted by the applicant. 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, ustekinumab is not expected to pose a risk to the environment. This is in line with the Guideline on the environmental risk assessment of medicinal products for human use (EMEA/CHMP/SWP/4447/00 corr 2).

2.5.6. Discussion on non-clinical aspects

An abridged nonclinical package has been provided to support the MAA for Fymskina. This is acceptable to the CHMP considering the legal basis of this application for a proposed biosimilar of Stelara, in line with the EMA Guideline (EMA/CHMP/BMWP/403543/2010).

A comprehensive comparative analytical assessment strategy using a stepwise approach was performed to demonstrate biosimilarity, in accordance with EMA overarching "Guideline on Similar Biological Medicinal Products (CHMP/437/04 Rev. 1). The comparative analytical assessment was designed to assess the physicochemical and functional similarity with the reference product and to ensure the understanding, of whether any differences observed between FYB202 and the reference product had the potential to impact clinical performance, consistent with EMA guidelines. The analytical biosimilarity programme showed comparability between the proposed biosimilar and its reference medicinal product, as concluded in the Quality part of the assessment report. Sections 4.6 and 5.3 of the SmPC are in line with the reference product.

In the comparative single-dose PK study performed in minipigs, ADAs were evident in all treatment groups and the number of ADA-positive test animals increased over time. However, usually *in vivo* PK studies are not requested for biosimilar applications as per the relevant EMA Guidelines (Guideline on Similar biological medicinal products containing biotechnology-derived proteins as active substance: non-clinical and clinical issues (EMEA/CHMP/BMWP/42832/2005 Rev1) and the guideline on Similar biological medicinal products containing monoclonal antibodies: non-clinical and clinical issues (EMA/CHMP/BMWP/403543/2010). Hence, the minipig comparative PK study has limited utility in the biosimilarity assessment between FYB202 and Stelara and could be regarded as supportive. Furthermore, the minipig is not a relevant species, as no target binding occurs. Considering the limitations of the animal model, in the GLP-compliant, comparative single-dose PK study in minipigs, no relevant differences in safety and pharmacokinetic parameters were noted between FYB202 and Stelara.

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, ustekinumab is not expected to pose a risk to the environment.

2.5.7. Conclusion on the non-clinical aspects

The design of the non-clinical development programme for Fymskina is appropriate for a biosimilar application of Stelara and in line with the relevant guidance. Overall, the available non-clinical data are

adequate to support the biosimilarity of Fymskina versus the EU reference product Stelara from a non-clinical perspective.

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**

Table 1 Phase 1 studies

Study identifier	Study design	Population (incl number of subjects, healthy vs patient and gender ratio)	Dosing regimen	Main PK parameters
FYB202-01-01 (EudraCT 2019-001272-12	Randomised, double-blind, single-dose, 3-arm, parallel-group phase 1 study in healthy subjects. Subjects received either a single subcutaneous injection of FYB202 (test), Stelara EU (reference 1) or Stelara US (reference 2) [allocation ratio 1:1:1]. PK samples were taken up to day 112.	Number of subjects dosed: 315 Completed the study: 306 Included in the final statistical PK analysis: 313	45 mg (90 mg/mL) ustekinumab in 0.5 mL solution Single dose	AUC0-inf, Cmax Secondary AUC0-t, tmax, t1/2, CL, Kel, Vz AUC0-t, tmax, t1/2, CL, Kel, Vz
FYB202-01-02 (EudraCT 2022-000832-43	Multi-centre, randomised, double-blind, single-dose, 3-arm, parallel-group phase 1 study in healthy subjects. Subjects received either a single subcutaneous injection of FYB202 (test), Stelara EU(reference 1) or Stelara US (reference 2) [allocation ratio 1:1:1]. PK samples were taken up to day 112	Number of subjects: Dosed: Completed the study: Included in the final statistical PK analysis: 491 486 478	45 mg (90 mg/mL) ustekinumab in 0.5 mL solution Single/Multiple dose: Single dose	AUC0-inf, Cmax Secondary AUC0-t, tmax, t1/2, CL, Kel, Vz AUC0-t, tmax, t1/2, CL, Kel, Vz

Table 2 Phase III study

Study ID	Enrolment status Start date Total enrolment/ enrolment goal	Design Control type	Study & control drugs Dose, route of administration and duration Regimen	Population Main inclusion/ exclusion criteria
FYB202-03-01	Study has been completed. Start date: 23-Sep-2020 Completion date: Until and including Week 28: 14-Oct2021	Phase III A multicentre, double-blind, parallel-group, randomised Phase 3 study designed to	**Study & control drugs:** FYB202 (proposed biosimilar) Stelara **Dose and Route of administration:**	

	Until end of study: 21-Mar-2022 The study was conducted at 27 sites in 4 countries: Estonia (23 [5.9%] patients), Georgia (49 [12.5%] patients), Poland (212 [54.1%] patients) and Ukraine (108 [27.6%] patients).	demonstrate the clinical similarity of FYB202 compared with Stelara in patients with moderate-to-severe plaque psoriasis regarding efficacy, safety, and immunogenicity.	45mg via subcutaneous injection (SC) **Duration:** Week 0 -week 52 **Regimen:** Patients were randomised 1:1 to receive SC injections of either FYB202 or Stelara 45 mg at Weeks 0 and 4 and at 12-week intervals thereafter (Weeks 16, 28, and 40); the end-of-study visit took place at Week 52.	

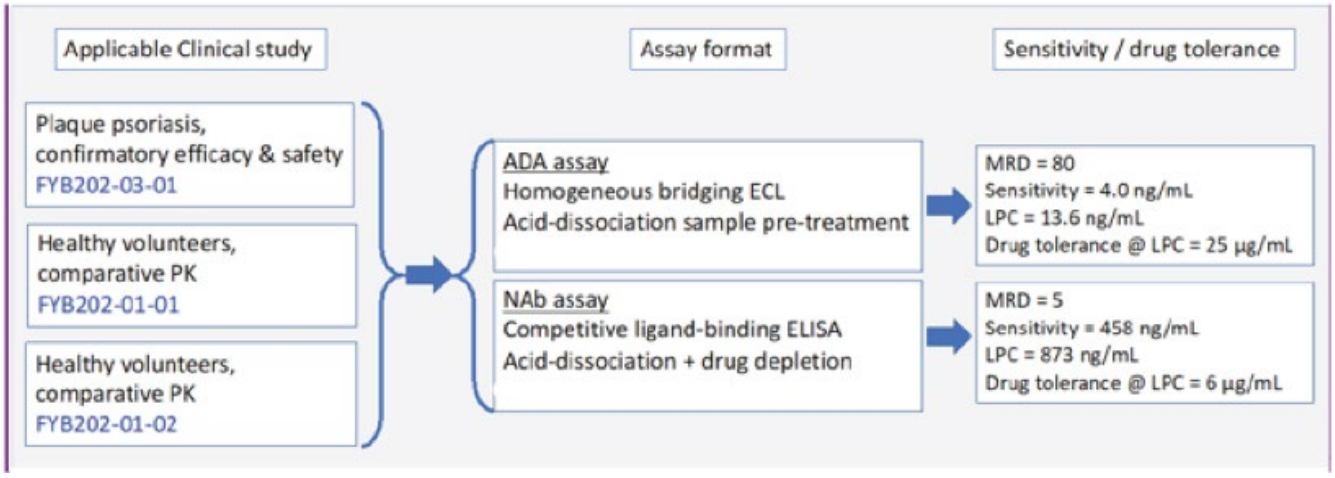
2.6.2. Clinical pharmacology

2.6.2.1. Pharmacokinetics

Bioanalytical methods

The analytical methods applied during the clinical development include methods for measuring human serum levels of ustekinumab and detecting anti-drug antibodies (ADAs) and neutralising antibodies (NAbs) against ustekinumab. **Figure 1** summarises the assay formats used and validated performance characteristics.

Figure 1 Overview of bioanalytical assays



The applicant has employed a sandwich ELISA approach for the detection and quantitation of ustekinumab in Human plasma. The applicant has presented three standard operating procedure (SOP) reports, a method development report and two validation reports. The SOPs outlined the method procedure. The assay has

been validated in accordance with the EMA guideline on Bioanalytical method validation (EMEA/CHMP/EWP/192217/2009) and ICH M10.

The applicant has developed an electrochemiluminescence (ECL) immunoassay for determination of anti-ustekinumab antibodies (ADA) in human serum study samples which is in accordance with the Guideline on Immunogenicity assessment of biotechnology-derived therapeutic proteins (EMEA/CHMP/BMWP/14327/2006 Rev.1), and uses 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 NAb method is a competitive ligand-binding assay platform and the approach to validation is in line with relevant standards.

2.6.2.1.1.1. Bioequivalence

Clinical Phase I study

Period of study: Study initiation date (first subject enrolled): 08-OCT-2019

Study completion date (last subject completed): 16-NOV-2020

Study centres: Germany

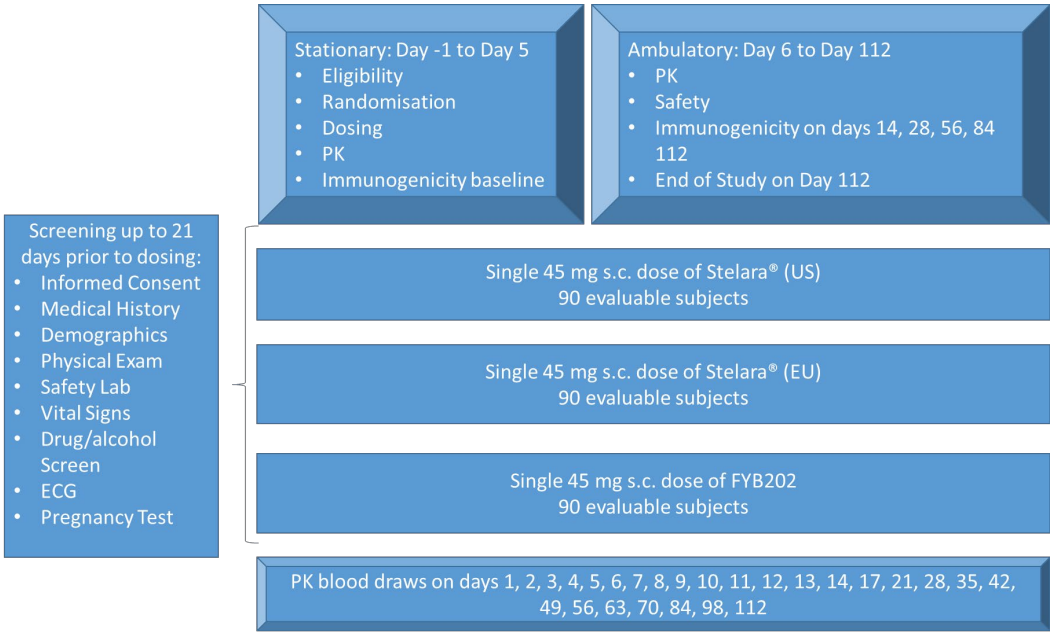
Methodology

The study was a randomised, double-blind, 3- arm, single-dose, parallel-group study of 105 subjects, each receiving a single SC dose of 45 mg of FYB202, EU-approved or US-licensed Stelara®.

Study period of 112 days

Overall study design and plan

The study schema is shown in the Figure below.



Selection of study population

Main criteria for inclusion:

1. The subject was male or female and 18 to 55 years of age, inclusive [screening]
2. The subject was healthy as determined by their medical history [screening and Day -1], a physical examination [screening], vital signs [screening and Day -1], an ECG [screening and Day -1] and clinical laboratory testing [screening and Day -1]
3. The subject had a BMI within the range of 20.5 to 28.0 kg/m^2, inclusive [screening]
4. The subject had a body weight within the range of 60 to 90 kg, inclusive [screening]
5. The subject had provided written, informed consent prior to any clinical study-specific procedures.
6. Male subject and his female spouse/partner who was of childbearing potential had to be using two acceptable methods for contraception (one of which had to be a barrier method) during the study and for 4 months after study drug administration.
7. Male subject agreed not to donate sperm starting from screening and throughout the clinical study period and for 4 months after study drug administration.
8. Female subject of childbearing potential had a negative pregnancy test [screening and Day -1].
9. Female subject had to be categorised by at least one of the following:

- Post-menopausal (defined as at least 1 year without any menses) prior to screening; or
- Surgically sterile or having undergone a hysterectomy at least 1 month prior to screening; or
- had a negative pregnancy test [screening and Day -1] and was using a highly effective contraception. All females of childbearing potential were required to use highly effective contraception starting at screening and throughout the clinical study period and for 4 months after study drug administration.

Main exclusion criteria

A subject was excluded from participation if any of the following applied:

1. Any known exposure to ustekinumab or biosimilar to ustekinumab
2. Known or suspected hypersensitivity to ustekinumab, or any components of the formulation used (L-histidine, sucrose, polysorbate 80).
3. Known or suspected hypersensitivity to latex.
4. Female subject who had been pregnant within 6 months prior to screening or breastfeeding or lactating within 3 months prior to screening.
5. Creatinine and/or ALT 1.1 x above the ULN; AST, ALP, GGT and/or TBL 1.2x above the ULN. In such a case, the assessment might be repeated once. [screening and Day-1]

6. Any clinically significant history of allergic conditions (including drug allergies, asthma, eczema, or anaphylactic reactions, but excluding untreated, asymptomatic, seasonal allergies at the time of dosing).

7. Any history or evidence of any clinically significant cardiovascular, gastrointestinal endocrinologic, haematologic, hepatic, immunologic, metabolic, urologic, pulmonary, neurologic, dermatologic, psychiatric, renal, and/or other major disease or malignancy, as judged by the Investigator.

Treatments administered

The 3 investigational medicinal products (IMPs) were administered in random order according to the randomisation scheme. IMP administration took place in the morning with appropriate intervals between subjects to allow for sample collection and any necessary additional clinical observations.

Subjects were administered a single subcutaneous injection of either 45 mg FYB202, EU-approved or US-licensed Stelara.

Table 3 Study Interventions

ARM Name	Arm 1	Arm 2	Arm 3
Intervention Name	FYB202	EU-approved Stelara®	US-licensed Stelara®
Type	Biologic (Monoclonal antibody)	Biologic (Monoclonal antibody)	Biologic (Monoclonal antibody)
Dose Formulation	Solution for injection in a pre-filled syringe. Each syringe contained 45 mg (90 mg/mL) ustekinumab in 6.6 mM L-Histidine (pH 6.0), 7.6 % (w/v) Sucrose and 0.004 % (w/v) polysorbate 80.	Solution for injection in a pre-filled syringe. Each syringe contained 45 mg (90 mg/mL) ustekinumab in 6.6 mM L-Histidine (pH 6.0), 7.6 % (w/v) Sucrose and 0.004 % (w/v) polysorbate 80.	Solution for injection in a pre-filled syringe. Each syringe contained 45 mg (90 mg/mL) ustekinumab in 6.6 mM L-Histidine (pH 6.0), 7.6 % (w/v) Sucrose and 0.004 % (w/v) polysorbate 80.
Unit Dose Strength(s)	90 mg/mL	90 mg/mL	90 mg/mL
Dosage Level(s)	Single 45 mg dose (0.5 mL)	Single 45 mg dose (0.5 mL)	Single 45 mg dose (0.5 mL)
Route of Administration	Subcutaneous injection	Subcutaneous injection	Subcutaneous injection
IMP and NIMP	IMP	IMP	IMP
Marketing Authorisation Holder	N.A.	Janssen-Cilag International NV	Janssen Biotech Inc.
Expiry Date	AUG-2020	AUG-2020	AUG-2020
Sourcing	Bulk provided centrally by the Sponsor.	Authorised wholesaler	Authorised wholesaler

Packaging and Labelling	Each pre-filled syringe was labelled as required per country requirement.	Each pre-filled syringe was labelled as required per country requirement.	Each pre-filled syringe was labelled as required per country requirement.
Current Name	Ustekinumab (Biosimilar to Stelara®)	Ustekinumab (Stelara®)	Ustekinumab (Stelara®)

N.A. = not applicable

Method of assigning subjects to treatment groups
Subjects were randomly assigned in a [1:1:1] ratio to receive study intervention. Randomisation was stratified according to body weight for each of three weight categories (60.0 kg to 69.9 kg; 70.0 kg to 79.9 kg; 80.0 kg to 90.0 kg) to ensure a balanced distribution across each study arm.

Blinding
The investigative team was not present whilst the intervention was in the dosing room. The subject was also prevented from seeing the intervention by wearing a mask fitted over the eyes.

Objectives

Primary objective:

To compare the PK of FYB202 with EU- and US- Stelara and the PK of EU- Stelara with US- Stelara in terms of Cmax and AUC0-inf following a single 45 mg/0.5 mL SC injection in healthy subjects.

Outcomes/endpoints

Primary endpoints

- Maximum serum concentration (Cmax) AND area under the serum concentration-time curve from time zero extrapolated to infinity (AUC0-inf).

Secondary endpoints:

- Secondary PK Endpoints
    - Area under the concentration-time curve from time zero to the last quantifiable concentration (AUC last)
    - Area under the concentration-time curve from time zero to 264 hours (AUC0-264h)
    - Time to reach Cmax (Tmax)
    - Apparent volume of distribution during the terminal phase (Vz/F)
    - Terminal rate constant (λz)
    - Terminal half-life (t1/2)
    - Apparent clearance (CL/F)
    - Percentage of AUC inf due to extrapolation from time of last measurable concentration (Tlast) to infinity (%AUC extrap).

Timing of assessments

The following time windows were defined to clarify that blood sample timing divergences did not necessarily constitute a protocol deviation:

- ± 30 min from the nominal time for Day 1, 12h;
- ± 1 hour as of Day 2 until Day 5 (included);
- ± 8 hours on Day 6 until Day 14;
- ± 1 day after Day 14 until Day 112.

Disposition of subjects

315 subjects (136 female and 179 male) signed the informed consent form and were randomised. The first subject signed the ICF on 08-OCT-2019 and was screened on 09-OCT-2019. The last subject signed the ICF and was screened on 15-JUL-2020.9 subjects discontinued the study:

- 2 subjects due to protocol non-compliance (one subject [EU-approved Stelara] after the scheduled end of the study, one subject [EU-approved Stelara] on Day 12).
- 1 subject due to death (on Day 101, this subject received EU-approved Stelara)
- 4 subjects due to the Covid-19 situation: 2 subjects [FYB202], and one subject [US-licensed Stelara] could not attend the End of Study visit and terminated the study after the scheduled end of the study. In addition, one subject [FYB202] did not come to the study site after the scheduled end of the study.
- 1 subject for private reason ([EU-approved Stelara] on Day 112).
- 1 subject was lost to follow-up ([FYB202], after the scheduled end of the study).

All other 306 subjects completed the study.

Table 4 Subject disposition

		FYB202 (N=105)	Stelara EU (N=105)	Stelara US (N=105)
No. of subjects randomised and treated	n	105	105	105
No. of subjects completing the study	n	101	101	104
No. of subjects with premature termination	n	4	4	1
Reason for premature termination: Protocol non-compliance		-	2	-
Death		-	1	-
Other		3	1	1
Lost to follow-up		1	-	-

Randomisation

Randomisation to FYB202, EU-approved Stelara, or US-licensed Stelara was performed in a 1:1:1 ratio.

Overall, 38 protocol deviations were classified as 'major/important' and related to thirty-eight (38) subjects being re-screened, as the time between their ICF signature and rescreening examination had exceeded 30 days. Of those, 22 subjects were randomised. The scientific integrity of the trial and the subjects' safety and well-being were not compromised. Thus, all affected subjects remained in the Safety Analysis Set (SAS) and the Pharmacokinetic Analysis Set (PKS).

Three amendments were made and all of these related to adjusting the sample size, which could have had an impact on the conclusions.

Outcomes and estimation

Ustekinumab serum concentrations

The mean serum concentration vs. nominal time curves on the linear and semi-logarithmic scale for the PKS are presented for pairwise comparisons of all study treatment groups comparison of FYB202 and EU-sourced Stelara, comparison of FYB202 and US-sourced Stelara, and comparison of EU-sourced Stelara and US sourced Stelara). This assessment report focuses on the comparison of FYB202 and EU-sourced Stelara.

Pharmacokinetic evaluation

315 subjects who were randomised and dosed were included in the Safety Set. Further information on the number of subjects per treatment group is provided in the Table below.

313 subjects were included in the PK Set. 2 subjects (one who received [FYB202] and another who received EU-approved Stelara]) had an insufficient PK profile for calculation of the primary endpoints $AUC_{0\text{-}inf}$ and C_{max} and were therefore excluded from the PK Set. Further information on the number of subjects per treatment group and within subgroups is provided in **Table 4**.

Table 5 Description of the Analysis Populations

Population	Description	Number of subjects within the analysis
Pharmacokinetic Set	All subjects assigned to study intervention and who were dosed with study intervention and provided sufficient samples to allow calculation of the primary endpoints, $AUC_{0\text{-}inf}$ and C_{max}. This population was used for analysis of pharmacokinetics.	N=313 subjects (FYB202: 104 subjects, Stelara EU: 104 subjects; Stelara US: 105 subjects)
	Subgroup of ADA-positive subjects	N=89 subjects (FYB202: 15 subjects, Stelara EU: 38 subjects; Stelara US: 36 subjects)
	Subgroup of NAB-reactive subjects	N= 58 subjects (FYB202: 9 subjects, Stelara EU: 24 subjects; Stelara US: 25 subjects)
	Subgroup of ADA-negative subjects	N=224 subjects (FYB202: 89 subjects, Stelara EU: 66 subjects; Stelara US: 69 subjects)
	Subgroup of NAB-negative subjects	N=255 subjects (FYB202: 95 subjects, Stelara EU: 80 subjects; Stelara US: 80 subjects)

FYB202: FYB202, single 45 mg dose (0.5 mL); Stelara EU: EU-approved Stelara®, single 45 mg dose (0.5 mL); Stelara US: US-licensed Stelara®, single 45 mg dose (0.5 mL); N = number of subjects in the population under consideration.

Demographic and other baseline characteristics

Table 6 Demographics (Safety Set, all subjects, N = 315)

	Treatment			
	FYB202 (N=105)	**Stelara EU (N=105)**	**Stelara US (N=105)**	**Overall (N=315)**
Age [years]				
Mean ± SD	37.0 ± 10.89	37.4 ± 10.38	38.9 ± 10.07	37.8 ± 10.45
Min; Max	19; 55	20; 55	19; 55	19; 55
Height [cm]				
Mean ± SD	173.1 ± 7.89	173.6 ± 8.80	173.2 ± 8.39	173.3 ± 8.34
Min; Max	155; 190	156; 194	157; 191	155; 194
Weight [kg]				
Mean ± SD	73.80 ±	73.75 ±	73.99 ±	73.85 ±
Min; Max	60.1; 90.0	60.1; 89.6	60.0; 89.9	60.0; 90.0

BMI [kg/m^2] Mean ± SD	24.60 ± 2.117	24.47 ± 2.153	24.62 ± 1.904	24.56 ± 2.055
Min; Max	20.6; 28.0	20.6; 28.0	20.5; 28.0	20.5; 28.0
Sex	n (%)	n (%)	n (%)	n (%)
Female	44 (41.9)	45 (42.9)	47 (44.8)	136 (43.2)
Male	61 (58.1)	60 (57.1)	58 (55.2)	179 (56.8)
Race	n (%)	n (%)	n (%)	n (%)
Black or African American	1 (1.0)	2 (1.9)	2 (1.9)	5 (1.6)
White	104 (99.0)	103 (98.1)	103 (98.1)	310 (98.4)
Ethnicity Not Hispanic or Latino	n (%) 105 (100.0)	n (%) 105 (100.0)	n (%) 105 (100.0)	n (%) 315 (100.0)
Not Japanese	104 (99.0)	105 (100.0)	105 (100.0)	314 (99.7)
Japanese	1 (1.0)	0 (0.0)	0 (0.0)	1 (0.3)

FYB202: FYB202, single 45 mg dose (0.5 mL); Stelara EU: EU-approved Stelara®, single 45 mg dose (0.5 mL); Stelara US: US-licensed Stelara®, single 45 mg dose (0.5 mL); N = number of subjects in the population under consideration. n = number of cases.

Other baseline characteristics

All subjects fulfilled the inclusion criteria and none of the exclusion criteria was present.

All serum pregnancy tests in female subjects were negative, except for one subject who had an increased beta-HCG level on Day 112 up to 1279 IU/L (upper reference range: 5.3 IU/L), which was documented as a TEAE. The subject was asked to consult her gynaecologist for further clarification, and she was confirmed as not pregnant, on Day 140.

Prior medication

Prior medication was defined as any medication which had been stopped prior to the first dose of the study intervention. Ten subjects took prior medication (ibuprofen or herbal cough and cold remedies).

Concomitant medication

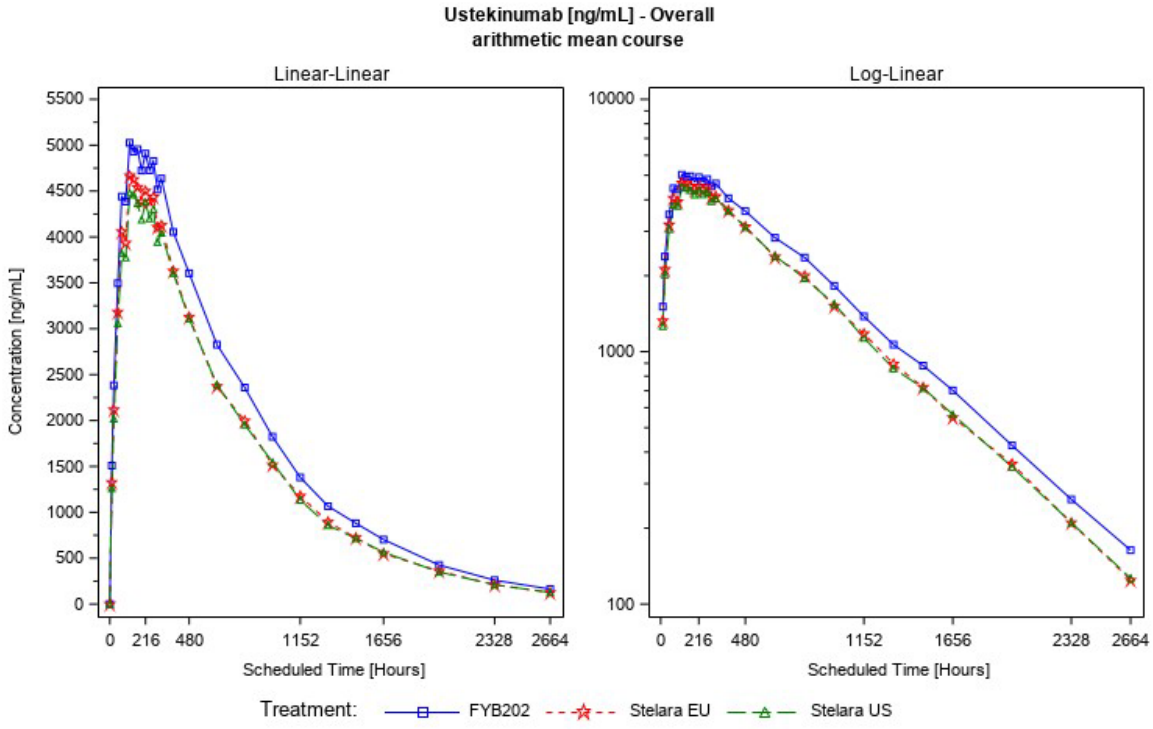
Concomitant medication was defined as any medication that was taken at or after the time of starting the study medication, regardless of whether it had started prior to the study or not.

In this study, 118 subjects took concomitant medication. In most cases, these were contraceptives or oral pain relievers for the treatment of AEs (ibuprofen, paracetamol). As outlined in the study protocol paracetamol and ibuprofen were permitted for use at any time during the study. Oral, injectable, or topical contraceptives were also permitted as they were acceptable methods of contraception. Other concomitant medication might be considered on a case-by-case basis by the Investigator in consultation with the Sponsor if required. No concomitant medication was considered to influence the endpoints or the outcomes of the study.

Serum concentration data
All subjects

All pre-dose concentrations were below LLOQ (i.e. <40 ng/mL) for all treatment groups. Arithmetic mean serum concentrations of ustekinumab increased after subcutaneous injection and received a peak at 120 hours after dosing (on Day 6) for all treatments. After administration of EU-approved Stelara or US-licensed Stelara, all subjects had serum concentrations of ustekinumab above LLOQ at least until Day 35 (816 hours post-dose), after administration of FYB202 at least until Day 49 (1152 hours post-dose. The ustekinumab arithmetic mean serum concentration vs. time curves following administration of a single 45 mg dose (0.5 mL) of FYB202, Stelara EU and Stelara US are shown in **Figure 2**.

Figure 2 Mean-concentration-time profiles of ustekinumab (ng/mL; PK Set, all subjects, N = 313)



Pharmacokinetic parameters

Evaluation for all subjects

- Geometric means for $AUC_{0\text{-}t}$ and $AUC_{0\text{-}inf}$ were about 17% to 19% higher after administration of FYB202 compared to EU-approved Stelara or US-licensed Stelara, whereas geometric means for $AUC_{0\text{-}t}$ and $AUC_{0\text{-}inf}$ were similar between EU-approved Stelara and US-licensed Stelara (**Table 6**).
- Whereas geometric means for partial AUCs in the second and third interval (i.e. from Day 28 to Day 56 and from Day 56 to Day 84) were about 25% to 28% higher after administration of FYB202 compared to EU-approved Stelara or US-licensed Stelara, the difference was less pronounced in the first interval until Day 28.
- The geometric mean AUC0-Day 28 was about 13% to 16% higher after administration of FYB202 compared to EU-approved Stelara or US-licensed Stelara.
- Geometric means for C_{max} were about 8% higher after administration of FYB202 compared to EU-

approved Stelara and about 12% higher compared to US-licensed Stelara (**Table 6**). Geometric means for Cmax were similar between EU-approved Stelara and US-licensed Stelara.

- Median tmax was reached later after administration of FYB202 (193 hours) compared to EU-approved Stelara and US-licensed Stelara (both 168 hours). The geometric mean t1/2 was longer after treatment with FYB202 (about 463 hours) compared to EU-approved Stelara and US-licensed Stelara (about 417 and 423 hours).

Table 7 FYB202-01-01: Summary of the PK parameters for ustekinumab (PK Set, all subjects, N = 313)

		FYB202 (N=104)	Stelara EU (N=104)	Stelara US (N=105)
AUC_{0-t} (h*ng/mL)[a]	Geom. Mean (CV%)	4303129.8 (30.9)	3686369.0 (39.9)	3620244.9 (36.6)
AUC_{0-inf} (h*ng/mL)[b]	Geom. Mean (CV%)	4419884.8 (31.8)	3782006.9 (40.2)	3717019.4 (37.2)
C_{max} (ng/mL)[c]	Geom. Mean (CV%)	5253 (34.3)	4844 (38.3)	4691 (35.8)
t_{max} (h)[c]	Median	192.83	168.35	168.30
	Min-Max	72.0 - 483.7	24.0 - 478.7	72.0 - 383.8
CL/f (mL/h)[b]	Geom. Mean (CV%)	10.181 (31.8)	11.898 (40.2)	12.106 (37.2)
Vz/f (mL)[b]	Geom. Mean (CV%)	6771.6 (30.6)	7198.8 (37.4)	7365.2 (30.7)
Kel (1/h)[d]	Geom. Mean (CV%)	0.00150 (25.9)	0.00166 (35.2)	0.00164 (39.3)
$t_{1/2}$ (h)[d]	Geom. Mean (CV%)	462.94 (25.9)	417.32 (35.2)	422.76 (39.3)
Partial AUC from 0 to Day 28 (h*ng/mL)	Geom. Mean (CV%)	2458338.1 (31.5)	2182134.5 (36.3)	2126483.1 (34.1)
Partial AUC from Day 28 to Day 56 (h*ng/mL)	Geom. Mean (CV%)	1208958.4 (29.5)	971044.1 (60.1)	950776.9 (57.0)
Partial AUC from Day 56 to Day 84 (h*ng/mL)	Geom. Mean (CV%)	441402.6 (53.1)	345539.4 (72.3)	345835.5 (80.5)

a: n = 99 for FYB202, n = 98 for Stelara EU, n = 100 for Stelara US
b: n = 98 for FYB202, n = 98 for Stelara EU, n = 100 for Stelara US
c: n = 104 for FYB202, n = 103 for Stelara EU, n = 103 for Stelara US
d: n = 103 for FYB202, n = 103 for Stelara EU, n = 105 for Stelara US
FYB202: FYB202, single 45 mg dose (0.5 mL); Stelara EU: EU-approved Stelara®, single 45 mg dose (0.5 mL); Stelara US: US-licensed Stelara®, single 45 mg dose (0.5 mL);
CV = coefficient of variation; Geom. = geometric; Max = maximum; Min = minimum, N = number of subjects in the population under consideration, n = number of cases, SD = standard deviation.
Partial AUCs were calculated irrespective of missing values.

Statistical Analysis of Pharmacokinetic Similarity

A summary of the statistical analysis of the primary PK endpoints AUC0-inf and Cmax after applying **ANCOVA**

for all subjects is provided in **Table 7**.

Table 8 Summary of the statistical analysis for the primary PK endpoints (PK Set; all subjects N=313; [FYB202: N = 104, Stelara EU: N = 104; Stelara US: N = 105])

Parameter	Ratio (%)	90% Confidence interval
	FYB202 \ Stelara EU	
$AUC_{0\text{-}inf}$[a]	117.44	108.32;127.32
C_{max}[b]	108.52	100.48;117.19
	FYB202 \ Stelara US	
$AUC_{0\text{-}inf}$[a]	118.82	109.65;128.77
C_{max}[b]	111.82	103.54;120.76
	Stelara EU \ Stelara US	
$AUC_{0\text{-}inf}$[a]	101.18	93.36;109.65
C_{max}[b]	103.04	95.40;111.30
Parameter	**Inter-subject CV (%)**	
$AUC_{0\text{-}inf}$[a]	35.29	
C_{max}[b]	34.50	

a: n = 98 for FYB202, n = 98 for Stelara EU, n = 100 for Stelara US

b: n = 104 for FYB202, n = 103 for Stelara EU, n = 103 for Stelara US

CV = coefficient of variation; N = number of subjects in the population under consideration, n = number of cases.

FYB202: FYB202, single 45 mg dose (0.5 mL); Stelara EU: EU-approved Stelara®, single 45 mg dose (0.5 mL); Stelara US: US-licensed Stelara®, single 45 mg dose (0.5 mL)

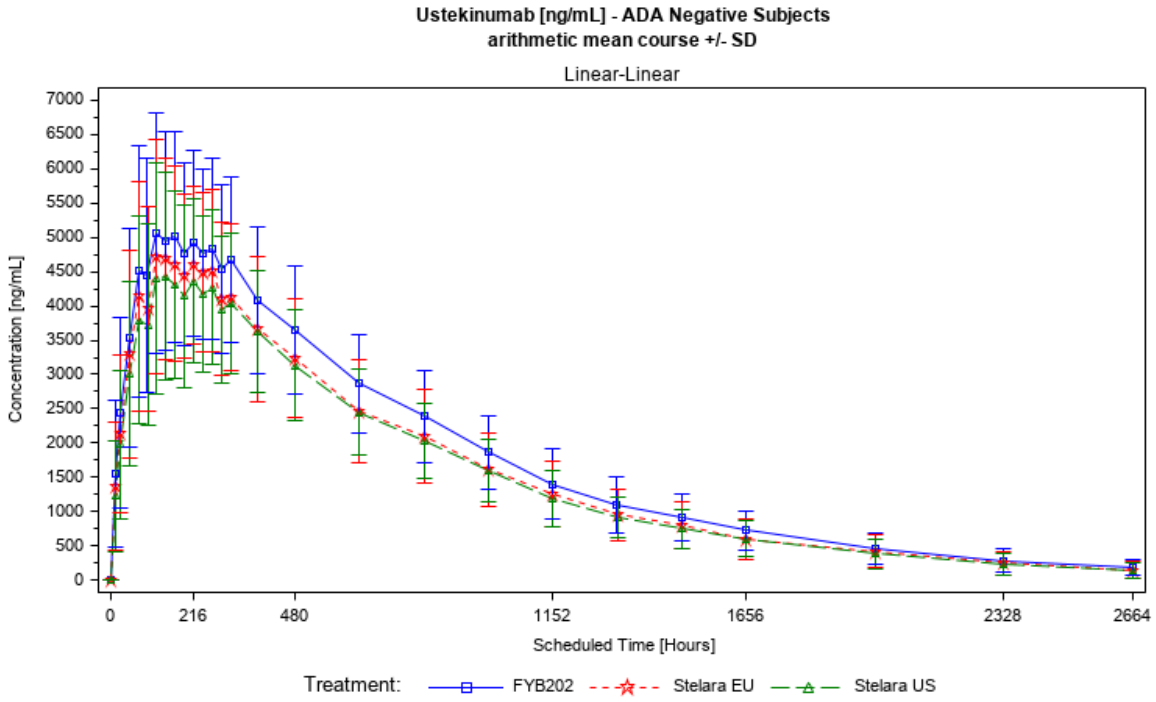
Partial AUCs: No formal statistical analysis of the partial AUCs was conducted. Instead, summary statistics were provided*.*

Subgroup analyses

ADA-negative subjects

There were **224 subjects** of the PK set who did not have or develop any ustekinumab ADAs during the whole course of the study, i.e., they were 'ADA-negative'. There were **89 ADA-negative** subjects after administration of FYB202, **66 subjects** after administration of EU-approved Stelara and **69 subjects** after administration of US-licensed Stelara. As depicted in **Figure 3**, the arithmetic mean serum concentration curves for ustekinumab were slightly higher after administration of FYB202 compared to EU-approved Stelara or US-licensed Stelara treatment.

Figure 3 Mean-concentration-time profiles of ustekinumab (ng/mL; PK Set, ADA-negative subjects, N = 224)



FYB202: FYB202, single 45 mg dose (0.5 mL); Stelara EU: EU-approved Stelara®, single 45 mg dose (0.5 mL); Stelara US: US-licensed Stelara®, single 45 mg dose (0.5 mL) N = number of subjects in the population under consideration, ADA = anti-drug antibody, SD = standard

ADA-negative subjects

Geometric mean $AUC_{0\text{-}t}$, $AUC_{0\text{-}inf}$ and partial AUCs were higher after the administration of FYB202 compared to EU-approved Stelara or US-licensed Stelara, whereas AUCs were similar between EU-approved Stelara and US-licensed Stelara.

The geometric mean C_{max} was higher after the administration of FYB202.

Median t_{max} was reached later after administration of FYB202 (193 hours) compared to EU-approved Stelara (168 hours) and US-licensed Stelara (180 hours) administrations. Geometric mean $t_{1/2}$ was longer for FYB202 (485 hours) compared to EU-approved Stelara (467 hours) and US-licensed Stelara (469 hours). Summary statistics of the PK parameters for ustekinumab are given for the main parameters in **Table 8**.

A summary of the statistical analysis of ustekinumab for the primary PK endpoints is provided in **Table 10**.

Table 9 Summary of the PK parameters for ustekinumab (PK Set, ADA-negative subjects, N = 224)

		FYB202 (N=89)	Stelara EU (N=66)	Stelara US (N=69)
AUC_{0-t} (h*ng/mL)[a]	Geom. Mean (CV%)	4369715.9 (31.8)	3908571.9 (31.8)	3811787.7 (26.9)
AUC_{0-inf} (h*ng/mL)[a]	Geom. Mean (CV%)	4495362.7 (32.5)	4019325.8 (32.7)	3919332.8 (27.7)
C_{max} (ng/mL)[b]	Geom. Mean (CV%)	5300 (34.7)	4987 (32.8)	4671 (32.6)
t_{max} (h)[b]	Median	193.05	168.37	180.10
	Min-Max	72.0 - 483.7	72.0 - 384.6	72.0 - 383.8
CL/f (mL/h)[a]	Geom. Mean (CV%)	10.010 (32.5)	11.196 (32.7)	11.482 (27.7)
Vz/f (mL)[a]	Geom. Mean (CV%)	6990.1 (26.6)	7549.3 (25.5)	7775.1 (23.8)
Kel (1/h)[c]	Geom. Mean (CV%)	0.00143 (18.5)	0.00148 (21.7)	0.00148 (22.5)
$t_{1/2}$ (h)[c]	Geom. Mean (CV%)	485.04 (18.5)	467.19 (21.7)	469.21 (22.5)
Partial AUC from 0 to Day 28 (h*ng/mL)	Geom. Mean (CV%)	2479077.6 (31.9)	2248334.7 (30.2)	2150891.1 (30.0)
Partial AUC from Day 28 to Day 56 (h*ng/mL)	Geom. Mean (CV%)	1228604.9 (30.1)	1067185.9 (33.8)	1051048.9 (29.2)
Partial AUC from Day 56 to Day 84 (h*ng/mL)	Geom. Mean (CV%)	461579.7 (44.1)	392600.6 (51.7)	380941.0 (48.1)

a: n = 84 for FYB202, n = 62 for Stelara EU, n = 66 for Stelara US

b: n = 89 for FYB202, n = 65 for Stelara EU, n = 68 for Stelara US

c: n = 89 for FYB202, n = 65 for Stelara EU, n = 69 for Stelara US

FYB202: FYB202, single 45 mg dose (0.5 mL); Stelara EU: EU-approved Stelara®, single 45 mg dose (0.5 mL); Stelara US: US-licensed Stelara®, single 45 mg dose (0.5 mL)

ADA = anti-drug antibody, CV = coefficient of variation; Geom. = geometric; Max = maximum; Min = minimum, N = number of subjects in the population under consideration, n = number of cases, SD = standard deviation. Partial AUCs were calculated irrespective of missing values.

NAB-negative subjects.

There were 255 subjects of the PK set who did not have or develop any ustekinumab neutralising antibodies during the whole course of the study, i.e. they were 'NAB-negative'. There were 95 NAB-negative subjects after administration of FYB202, 80 subjects after administration of EU-approved Stelara and 80 subjects after administration of US-licensed Stelara.

Geometric mean AUC0-t, AUC0-inf and partial AUCs were higher after the administration of FYB202 compared to EU-approved Stelara or US-licensed Stelara administrations, whereas AUCs were similar between EU-approved Stelara and US-licensed Stelara. Geometric mean Cmax was higher after administration of FYB202 (**Table 9**).

Median tmax was reached later after administration of FYB202 (215 hours) compared to EU-approved Stelara (168 hours) and US-licensed Stelara (169 hours) administrations. Geometric mean t1/2 was comparable for FYB202 (472 hours) compared to EU-approved Stelara (457 hours) and US-licensed Stelara (462 hours).

Table 10 Summary of the PK parameters for ustekinumab (PK Set, NAB-negative subjects, N = 255)

		FYB202 (N=95)	Stelara EU (N=80)	Stelara US (N=80)
AUC_{0-t} (h*ng/mL)[a]	Geom. Mean (CV%)	4311534.7 (32.1)	3863169.6 (31.9)	3750917.2 (29.3)
AUC_{0-inf} (h*ng/mL)[a]	Geom. Mean (CV%)	4430433.1 (32.8)	3969041.9 (32.7)	3854636.5 (30.0)
C_{max} (ng/mL)[b]	Geom. Mean (CV%)	5241 (35.3)	4997 (36.0)	4627 (36.7)
t_{max} (h)[b]	Median	215.25	167.87	168.82
	Min-Max	72.0 - 483.7	72.0 - 478.7	72.0 - 383.8
CL/f (mL/h)[a]	Geom. Mean (CV%)	10.157 (32.8)	11.338 (32.7)	11.674 (30.0)
Vz/f (mL)[a]	Geom. Mean (CV%)	6896.2 (28.7)	7493.0 (27.2)	7782.9 (27.0)
Kel (1/h)[c]	Geom. Mean (CV%)	0.00147 (21.7)	0.00152 (22.4)	0.00150 (23.1)
$t_{1/2}$ (h)[c]	Geom. Mean (CV%)	472.25 (21.7)	457.06 (22.4)	462.02 (23.1)
Partial AUC from 0 to Day 28 (h*ng/mL)	Geom. Mean (CV%)	2452047.8 (32.4)	2249939.3 (32.1)	2120044.5 (33.9)
Partial AUC from Day 28 to Day 56 (h*ng/mL)	Geom. Mean (CV%)	1216650.9 (30.1)	1058909.4 (33.4)	1030909.8 (30.4)
Partial AUC from Day 56 to Day 84 (h*ng/mL)	Geom. Mean (CV%)	453024.2 (44.5)	387119.7 (52.6)	371987.7 (48.9)

a: n = 90 for FYB202, n = 75 for Stelara EU, n = 76 for Stelara US

b: n = 95 for FYB202, n = 79 for Stelara EU, n = 78 for Stelara US

c: n = 95 for FYB202, n = 79 for Stelara EU, n = 80 for Stelara US

FYB202: FYB202, single 45 mg dose (0.5 mL); Stelara EU: EU-approved Stelara®, single 45 mg dose (0.5 mL); Stelara US: US-licensed Stelara®, single 45 mg dose (0.5 mL)

CV = coefficient of variation; Geom. = geometric; Max = maximum; Min = minimum, N = number of subjects in the population under consideration, n = number of cases, NAB = neutralising antibody, SD = standard deviation. Partial AUCs were calculated irrespective of missing values.

Table 11 Summary of the statistical analysis of ustekinumab for the primary PK endpoints (PK Set); subgroup analyses for ADA-negative and NAB-negative subjects

ADA-negative subjects, N = 224 (FYB202: N = 89, Stelara EU: N = 66; Stelara US: N = 69)		
Parameter	**Ratio (%)**	**90% Confidence interval**
	FYB202 \ Stelara EU	
$AUC_{0\text{-}inf}$[a]	112.48	103.59;122.12
C_{max}[b]	106.23	97.54;115.69
	FYB202 \ Stelara US	
$AUC_{0\text{-}inf}$[a]	114.73	105.83;124.38
C_{max}[b]	113.56	104.39;123.53
	Stelara EU \ Stelara US	
$AUC_{0\text{-}inf}$[a]	102.00	93.52;111.26
C_{max}[b]	106.90	97.63;117.04
Parameter	**Inter-subject CV (%)**	
$AUC_{0\text{-}inf}$[a]	30.39	
C_{max}[b]	32.46	

NAB-negative subjects, N = 255 (FYB202: N = 95, Stelara EU: N = 80; Stelara US: N = 80)		
Parameter	**Ratio (%)**	**90% Confidence interval**
	FYB202 \ Stelara EU	
$AUC_{0\text{-}inf}$[c]	112.12	103.79;121.12
C_{max}[d]	104.84	96.42;114.00
	FYB202 \ Stelara US	
$AUC_{0\text{-}inf}$[c]	114.80	106.30;123.98
C_{max}[d]	112.95	103.85;122.84
	Stelara EU \ Stelara US	
$AUC_{0\text{-}inf}$[c]	102.39	94.48;110.96
C_{max}[d]	107.73	98.68;117.61
Parameter	**Inter-subject CV (%)**	
$AUC_{0\text{-}inf}$[c]	30.59	
C_{max}[d]	34.24	

a: n = 84 for FYB202, n = 62 for Stelara EU, n = 66 for Stelara US

b: n = 89 for FYB202, n = 65 for Stelara EU, n = 68 for Stelara US

c: n = 90 for FYB202, n = 75 for Stelara EU, n = 76 for Stelara US

d: n = 95 for FYB202, n = 79 for Stelara EU, n = 78 for Stelara US

ADA = anti-drug antibody; CV = coefficient of variation; N = number of subjects in the population under consideration, n = number of cases; NAB = neutralising antibody.

FYB202: FYB202, single 45 mg dose (0.5 mL); Stelara EU: EU-approved Stelara®, single 45 mg dose (0.5 mL); Stelara US: US-licensed Stelara®, single 45 mg dose (0.5 mL)

Subgroup analysis for ADA-positive and NAB-reactive subjects.

All results have to be interpreted with caution due to the high inter-subject variabilities (especially for AUC0-inf [44.72% for ADA-positive subjects; 51.46% for NAB-reactive subjects]) and the small and unbalanced sample sizes of the treatment groups within the subgroup.

The portion of ADA-positive and NAB-reactive subjects was about 2-fold higher in the reference intervention groups compared to the FYB202 intervention group (ADA-positive subjects: N=15 for FYB202, N=38 for EU-approved Stelara and N=36 for US-licensed Stelara; NAB reactive subjects: N=9 for FYB202, N=24 for EU-approved Stelara and N=25 for US-licensed Stelara).

Statistical Analyses

Different post-hoc analyses were performed to verify the validity of the assumptions and the appropriateness of the statistical analysis model:

- Additional ANCOVAs, including additional covariates (BMI, age) and factors (gender)
- Additional ANCOVA based on the arithmetic mean ratios and CIs according to Fieller (Jaki et al, 2010[1])
- ANCOVA with values after protein content correction

The protein content, as well as the extractable volume of the three study intervention batches, were assessed *post hoc*, head-to-head, by the release method based on UV spectroscopy at the release site, and the pharmacopeial method for measuring extractable volume. Next, the protein content was multiplied by the extractable volume in order to obtain the closest possible approximation to the administered dose. The results are presented in **Table 11**.

Table 12 Content, extractable volume and dose of study intervention batches

Batch	Content determined via UV release method [mg/mL]	Extractable volume [mL]	Dose [mg]
Stelara US	88.30	0.5330	47.06
Stelara EU	89.20	0.5248	46.81
FYB202	92.30	0.5320	49.10

Dose: calculated by multiplying content and extractable volume

To support the investigation on the potential impact of the difference in content, an exploratory ANCOVA based on protein content adjusted concentrations was performed on the ln-transformed pharmacokinetic parameters Cmax and AUC0-inf with ln-transformed weight as covariate and treatment as fixed effect. For simplicity, the content correction was applied linearly to the full extent not taking into account the impact of a lower relative bioavailability following a s.c. administration. The results are provided in **Table 12**.

[1] Jaki, et al, 2010 [9]: Jaki, T., Wolfsegger, M.J., and Lawo, J.P., Establishing bioequivalence in complete and incomplete data designs using AUCs. J Biopharm Stat, 2010. 20(4): p. 803- 20.

Table 13 Summary of the statistical analysis for the primary PK endpoints (PK Set; all subjects N=313, ANCOVA with protein content adjusted concentrations

Parameter	Ratio (%)	90% Confidence interval
	FYB202 \ Stelara EU	
AUC_{0-inf}[a]	113.50	104.69;123.04
C_{max}[b]	104.87	97.11;113.26
	FYB202 \ Stelara US	
AUC_{0-inf}[a]	113.67	104.90;123.19
C_{max}[b]	106.97	99.06;115.52
	Stelara EU \ Stelara US	
AUC_{0-inf}[a]	100.16	92.42;108.54
C_{max}[b]	102.00	94.44;110.18
Parameter	**Inter-subject CV (%)**	
AUC_{0-inf}[a]	35.29	
C_{max}[b]	34.50	

a: n = 98 for FYB202, n = 98 for Stelara EU, n = 100 for Stelara US
b: n = 104 for FYB202, n = 103 for Stelara EU, n = 103 for Stelara US
CV = coefficient of variation; N = number of subjects in the population under consideration, n = number of cases.
FYB202: FYB202, single 45 mg dose (0.5 mL); Stelara EU: EU-approved Stelara®, single 45 mg dose (0.5 mL); Stelara US: US-licensed Stelara®, single 45 mg dose (0.5 mL)

Root Cause Analysis

Following the results of clinical study FYB202-01-01, in which PK similarity of FYB202 for the area under the curve (AUC_{inf}) to the two RMPs was not shown, an extensive root cause analysis (RCA) was performed investigating all aspects of study set-up, study conduct, product characteristics, analytical methods, and impact of anti-drug antibodies (ADAs)/neutralising antibodies (NAbs). The root cause analysis confirmed that the study set-up, study conduct and bioanalytical methods of FYB202-01-01 were adequate.

However, it was found that the single administered dose relative to FYB202 was approximately 4.9%-6.6% lower for Stelara EU and 3.5%-5.2% lower for Stelara US. The batch numbers, protein concentration, mean extractable volume and protein dose relative to the label claim of the test drug (FYB202) and comparator drugs (Stelara EU and Stelara US) are presented in the table below.

Protein concentration, mean extractable volume, and administered dose of the drug product batches used in FYB202 clinical studies

Investigati-onal Product Identity, 45 mg (PFS)	Batch no.	Concen-tration (mg/mL)	Extract-able volume (mL)	Administered dose (mg), a product of conc. and ext. vol.	Dose % relative to label claim (45 mg)
Study FYB202-01-01 (first phase 1 study)					
FYB202	Batch 1	92.2	0.53/0.54*	48.9/49.8*	109/111*
Stelara EU	Batch 1	89.4	0.52	46.5	103
Stelara US	Batch 2	89.1	0.53	47.2	105
Study FYB202-03-01 (phase 3 study)					
FYB202	Batch 2	93.5	0.54	50.5	112
	Batch 3	94.1	0.54	50.8	113
Stelara EU	Batch 3	88.1	0.52	45.8	102
	Batch 4	89.8	0.52	46.7	104
Study FYB202-01-02 (second phase 1 study)					
FYB202	Batch 4	89.9	0.52	46.7	104
Stelara EU	Batch 5	91.5	0.53	48.5	108
	Batch 6	89.8	0.52	46.7	104
Stelara US	Batch 7	88.3	0.53	46.8	104
	Batch 8	89.7	0.53	47.5	106

Source: Summary root cause analysis report 2.7.1.4.4.Table 3

* While the extractable volume values in the table were all generated by the applicant there is also a release value of 0.54 mL from the manufacturer for this FYB202 batch.

A higher dose of FYB202 compared to Stelara EU and US RMPs was administered to participants in studies FYB202-01-01 and FYB202-03-01. This results from the fact that different setpoints for protein concentration and fill volume were used during the development and production of FYB202 drug substance and drug product batches.

Batches included in clinical studies FYB202-01-01 and FYB202-03-01 were produced with slightly higher process setpoints for protein concentration compared to batches included in study FYB202-01-02. Also, the drug product fill volume limits were adjusted starting with the drug product validation campaign and prior to the repeat phase 1 clinical study FYB202-01-02. This adjustment led to drug product batches with extractable volume ranges overall more in line with the data obtained for Stelara. Batches included in clinical studies FYB202-01-01 and FYB202-03-01 were produced with slightly higher fill volume limits and thus higher extractable volume compared to the batch included in study FYB202-01-02.

Both factors led to between-group differences in the actual protein dose of ustekinumab administered to subjects treated in the first phase 1 comparative PK study, FYB202-01-01, which were 4 % to 6 % lower for Stelara EU/US relative to FYB202 when calculating the dose ratios from the label claims. The between-group difference increased to 6 % to 8 % if the extractable volume release value generated at the drug product manufacturer for this FYB202 batch was used. In all other instances, the extractable volume values generated by Formycon and the release values from the manufacturer gave the same results. In the comparative efficacy, safety, and immunogenicity study, FYB202-03-01, the dose when calculated from the label claims was 8 % to 11 % lower for Stelara EU relative to FYB202.

The incidences of ADAs and NAbs were more than 2-fold higher in subjects of the two Stelara groups compared to the FYB202 group. In line with that – when only considering the subgroups of ADA-negative and NAb-negative subjects – all geometric mean ratios and the corresponding 90 % CIs were fully contained within the range of 80.00–125.00 % for both primary endpoints, AUC0-inf and Cmax.

The findings of the trial FYB202-01-01 and the design of a repeat phase 1 trial were discussed with regulatory authorities (EMA and US-FDA). The following adjustments were made for the repeat phase 1 PK trial FYB202-01-02:

- To ensure that the ustekinumab dose was similar in all three groups, the setpoints for drug substance concentration and drug product filling volume were adjusted for FYB202 to be more aligned with the RMP Stelara.
- In accordance with the advice from the authorities, the sample size was planned more conservatively considering the results of the first phase 1 PK trial FYB202-01-01 (**Table 13**).

Table 14 Sample size consideration for the repeat phase 1 trial FYB202-01-02

Design aspects	Planned	Assumptions
Variability (CV%)	36 %	Variability for $AUC_{0\text{-}inf}$ and C_{max} similar to that in the first phase 1 trial
Ratio	0.91–1.099	Potential maximum difference in exposure of up to 10 % considered
Power	94.6 % for each comparison, 85 % overall	Increased power for each comparison compared to first phase 1 trial (93 %), 5 % larger power overall

Corrective actions taken

As no issues in study conduct were observed, no action needed to be taken in this respect.

The fact that the data were not log-normally distributed and that an imbalance in ADA and Nab incidence may have led to data which were not adequately analysed on the log-scale. Instead of changing the analysis to the original scale, this fact was mitigated by the larger sample size in the repeat phase 1 study. The sample size was increased to increase the power of the study thereby also reducing the risk of outliers which may negatively impact the analysis.

Overall, the following adaptations (see below Table) were made regarding the sample size calculation for study FYB202-01-02.

Table 15 Assumptions for sample size estimation for repeat study FYB202-01-02 in comparison to study FYB202-01-01

Design aspect	FYB202-01-01	FYB202-01-02
Expected ratio	0.95 – 1/0.95	0.91 – 1/0.91
Variability (CV%)	38%	36%
Power	93% for each comparison (80% overall)	94.6% for each comparison (85% overall)
Resulting sample size	90 evaluable subjects/group	156 evaluable subjects/group

The results of study FYB202-01-02 showed that the initial process setpoints/limits prior to the validation campaigns were at least partly responsible for differences in PK between FYB202 and Stelara observed in studies FYB202-01-01 and FYB202-03-01: when protein concentration and fill weight (and thus extractable volume) were adjusted prior FYB202-01-02, both primary PK endpoints were met.

For the manufacturing of commercial batches, the same setpoints/limits for protein concentration and fill volume (and thus extractable volume) are intended to be used for the production of the FYB202 batch used in the successful clinical study FYB202-01-02.

2nd PK Study (FYB202-01-02 – RUSTIC Study)

RUSTIC is a randomised, double-blind, single-dose, 3-arm, parallel-group phase 1 study to demonstrate pharmacokinetic equivalence of FYB202 and EU-approved or US-licensed Stelara (ustekinumab) administered as a single 45 mg subcutaneous (SC) injection to healthy volunteers. 491 subjects. The present RUSTIC study was designed to provide sufficient power to demonstrate pharmacokinetic similarity between FYB202, EU-approved Stelara and US-licensed Stelara based on the observed results from the first phase 1 study.

The clinical study was conducted in Germany in 4 clinical trial sites.

Overall, the study design and plan were the same as FYB202-01-01 but there were a couple of differences. Subjects had to be male and female healthy volunteers aged 18–55 years and a weight of 60 to 90 kg and a BMI within the range of 20.5 to 30.0 kg/m2.

Each subject was observed for up to 112 days.

Study objectives are in line with study FYB202-01-01.

Samples for pharmacokinetic assessment

Serum samples were collected for measurement of serum concentrations of ustekinumab as specified in the SoA (TT 4): pre-dose, day 1 (2 times), day 2 (2 times), and on days 3, 4, 5, 6, 7, 8, 9, 10, 12, 14, 17, 21, 28, 35, 42, 49, 56, 63, 70, 84, 98, 112 (in total 27 times).

Drug concentration information that unblinded the study was not reported to investigative sites or blinded personnel until the study had been unblinded.

Any changes in the timing or addition of time points for any planned study assessments were documented and approved by the relevant study team member and then archived in the sponsor and site study files but did not constitute a protocol amendment.

Samples for immunogenicity assessments

A serum sample was collected from all subjects at time points listed in the SoA (TT 4) for evaluation of antibodies to ustekinumab (ADAs): pre-dose, day 3, 7, 10, 14, 28, 56, 84, and 112 (in total 9 times).

The inclusion criteria and exclusion criteria were the same as FYB202-01-01.

Treatments

Table 16 Protein concentration, mean extractable volume, and administered dose of the drug product batches used in FYB202 clinical studies.

Investigational Product Identity, 45 mg (PFS)	Batch no.	Concentration (mg/mL)	Extractable volume (mL)	Administered dose (mg), a product of conc. and ext. vol.	Dose % relative to label claim (45 mg)
Study FYB202-01-01 (first phase 1 study)					
FYB202	Batch 1	92.2	0.53/0.54*	48.9/49.8*	109/111*
Stelara EU	Batch 1	89.4	0.52	46.5	103
Stelara US	Batch 2	89.1	0.53	47.2	105
Study FYB202-03-01 (phase 3 study)					
FYB202	Batch 2	93.5	0.54	50.5	112
	Batch 3	94.1	0.54	50.8	113
Stelara EU	Batch 3	88.1	0.52	45.8	102
	Batch 4	89.8	0.52	46.7	104
Study FYB202-01-02 (second phase 1 study)					
FYB202	Batch 4	89.9	0.52	46.7	104
Stelara EU	Batch 5	91.5	0.53	48.5	108
	Batch 6	89.8	0.52	46.7	104
Stelara US	Batch 7	88.3	0.53	46.8	104
	Batch 8	89.7	0.53	47.5	106

While the extractable volume values in the table were all generated by the applicant, there is also a release value of 0.54 mL from the manufacturer for this FYB202 batch.

The table shows that a higher dose of FYB202 compared to Stelara EU and US RMPs was administered to participants in studies FYB202-01-01 and FYB202-03-01. This results from the fact that different setpoints for

protein concentration and fill volume were used during the development and production of FYB202 drug substance and drug product batches.

Batches included in clinical studies FYB202-01-01 and FYB202-03-01 were produced with slightly higher fill volume limits and, thus, higher extractable volume compared to the batch included in study FYB202-01-02. The results of study FYB202-01-02 showed that the initial process setpoints/limits prior to the validation campaigns were at least partly responsible for differences in PK between FYB202 and Stelara observed in studies FYB202-01-01 and FYB202-03-01: when protein concentration and fill weight (and thus extractable volume) were adjusted prior FYB202-01-02, both primary PK endpoints were met. For the manufacturing of commercial batches, the same setpoints/limits for protein concentration and fill volume (and thus extractable volume) are intended to be used for the production of the FYB202 batch used in the successful clinical study FYB202-01-02.

Method of assigning subjects to treatment groups
Subjects were randomly assigned in a [1:1:1] ratio to receive study intervention.

Randomisation was stratified according to the study site, body weight for each of three weight categories (60.0 kg to 69.9 kg; 70.0 kg to 79.9 kg; 80.0 kg to 90.0 kg) and sex to aim for a balanced distribution across each study arm in the entire study.

Selection of doses in the study
A single subcutaneous fixed dose of 45 mg had been chosen for this study,

Blinding was the same as FYB202-01-01.

Determination of sample size
The coefficient of variation (%CV) for exposure parameters was estimated to be approximately 36% for AUC0-inf and Cmax in healthy subjects, based on data from the previous phase 1 study with FYB202 and Stelara.

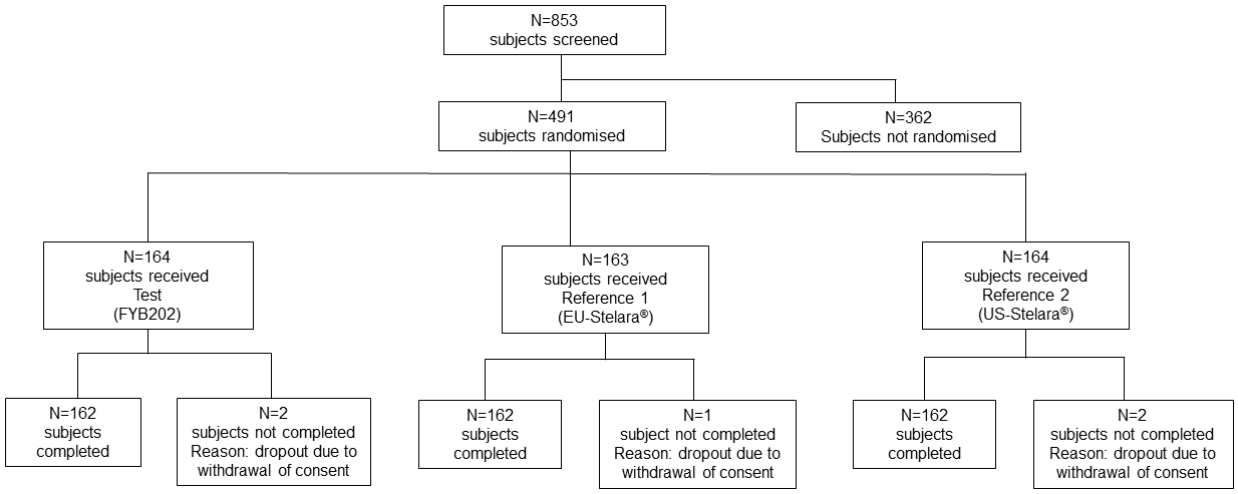
The sample size calculation was based on the following assumptions:

- Significance level: 5%
- Test/Reference ratio 0.91 to 1/0.91 for AUC0-inf and Cmax
- Equivalence limits: 0.8000 – 1.2500
- Randomisation ratio: 1:1

Using these assumptions, a sample size of 156 evaluable subjects per arm provided a power of 94.6% for a single comparison. In the current study with 3 pairwise comparisons, the overall power for the comparisons was approximately 85% if all comparisons were considered independent. Assuming a dropout rate of 5%, 165 subjects per arm were intended to be randomised.

Disposition:
In Study FYB202-01-02, the population of healthy volunteers (N=491) had a mean (SD) age of 37.7 (9.9) years (median: 37.0). 481 volunteers were white, and the majority of all randomised subjects were white (97.96%). 4 were black, and 6 were Asian. Approximately equal proportions of male and female volunteers were included (48.95% females and 50.51% males) with a mean BMI of 24.75 (2.30) kg/m2 (median: 24.50).

Subject flow:



All 491 randomised subjects received the planned IMP dose and were thus included in the SAS. The dropout rate was low: only 5 out of 491 subjects prematurely dropped out during the study (reason: withdrawal of consent).

Five (5) subjects were stratified manually.

Five (5) subjects did not complete the study.

Overall, only 13 subjects (including the 5 dropouts) were excluded from the PKS due to major protocol deviations (2 pregnancies, 11 subjects with ≥ 2 missing subsequent blood samples). All other deviations were minor and not relevant to the primary outcome of the trial.

All 491 randomised subjects were assigned to the SAS as for all IMP administration was documented. Notably, according to the protocol, 495 subjects were intended to be randomised. However, for 1 subject who was assigned to a subject number and treatment, dosing was not performed due to bilirubin being out of the normal range. Thus, only 491 subjects were randomised and dosed (SAS).

With regard to medical history, 242 events were reported in 167 of 491 subjects (34.01%). COVID-19 was most frequently reported (121 subjects [24.64%]). A total of 124 cases, by 77 of 491, subjects (15.68%) were reported in the category "surgeries". Appendicectomy (13 subjects [2.65%]) and adenoidectomy (7 subjects [1.43%] were most frequently reported.

Adjustments for covariates

The ANCOVA of the PK parameters $AUC_{0\text{-}inf}$ and C_{max} was performed using body weight as a covariate.

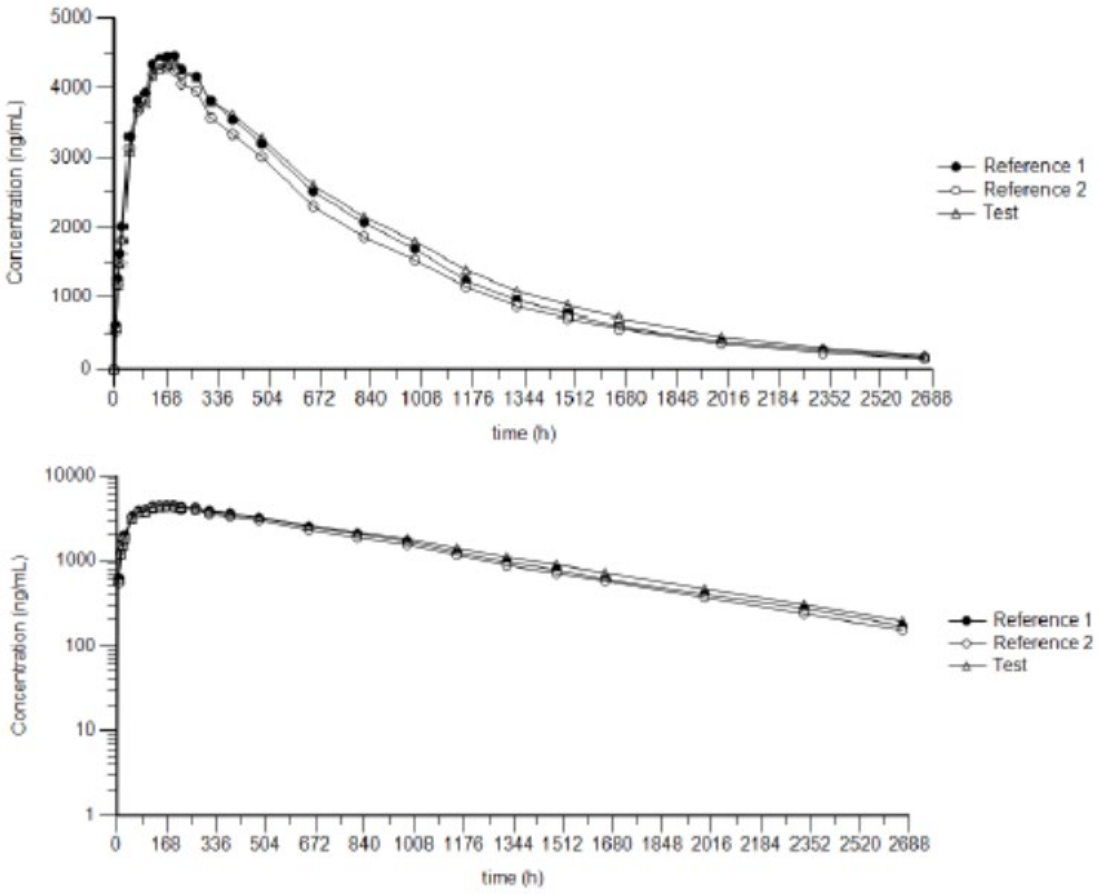
Serum concentration vs. time curves

In the FYB202 group, 1 subject had a pre-dose concentration of 48.3 ng/mL ustekinumab corresponding to ~1.2% of Cmax (=4150 ng/mL). Since the pre-dose concentration was less than 5% of the Cmax value in

that subject, the subject's data were included in all PK measurements and calculations without any adjustments.

For all other subjects, pre-dose concentrations were below LLOQ (i.e., <40 ng/mL).

Figure 4 Mean serum concentration vs. time curves after subcutaneous application of 45 mg (single dose 0.5 ml) of FYB202 (Test) [N=159] / EU-Stelara (Reference 1) [N=160] / US-Stelara (Reference 2) [N=159], upper panel: linear scale, lower panel: semilogarithmic scale (PKS)

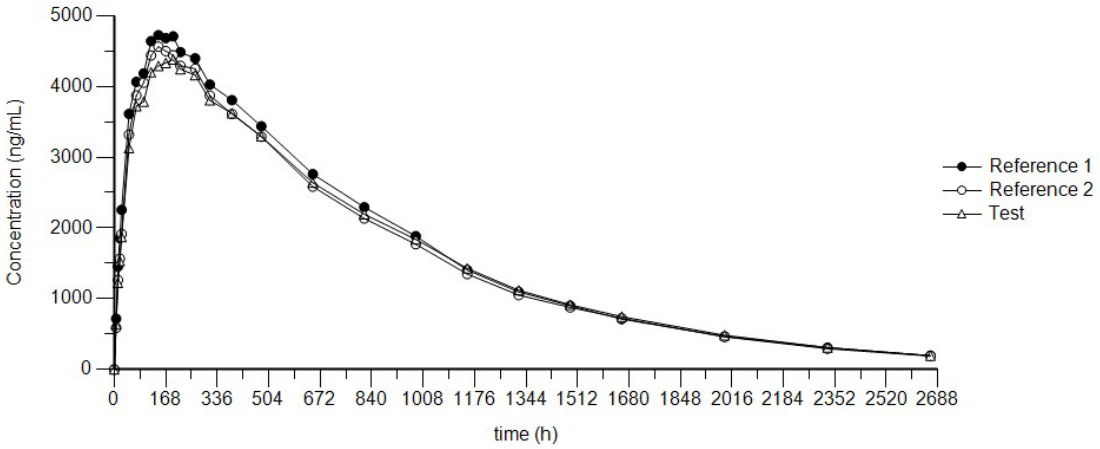


Subgroup analyses

ADA-negative subjects

Overall, 296 subjects of the PKS did not have or did not develop any ustekinumab ADAs during the whole course of the study, i.e., they were 'ADA-negative' (FYB202: N=127, EU- Stelara: N=91, US-Stelara: N=78). Arithmetic mean serum concentrations of ustekinumab increased after administration, peaking between 144 hours (=Day 6) and 192 hours (=Day 8) after dosing for all treatments

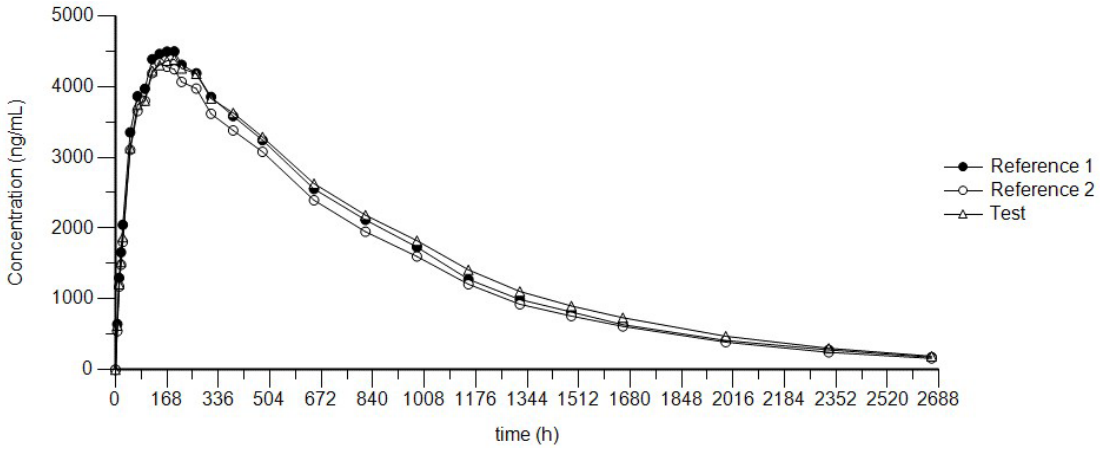
Figure 5 Mean serum concentration vs. time curves after subcutaneous application of 45 mg (single dose 0.5 ml) of FYB202 (Test) [N=127] / EU-Stelara (Reference 1) [N=91] / US-Stelara (Reference 2) [N=78] (PKS, ADA-negative subjects)



NAb-negative subjects.

Overall, 406 subjects of the PKS did not have or did not develop any ustekinumab NAbs during the whole course of the study, i.e., they were 'NAb-negative' (FYB202: N=141, EU- Stelara: N=135, US-Stelara: N=130). Arithmetic mean serum concentrations of ustekinumab increased after administration, peaking between 168 hours (=Day 7) and 192 hours (=Day 8) after dosing for all treatments.

Figure 6 Mean serum concentration vs. time curves after subcutaneous application of 45 mg (single dose 0.5 ml) of FYB202 (Test) [N=141] / EU-Stelara (Reference 1) [N=135] / US-Stelara (Reference 2) [N=130] (PKS, NAb-negative subjects)



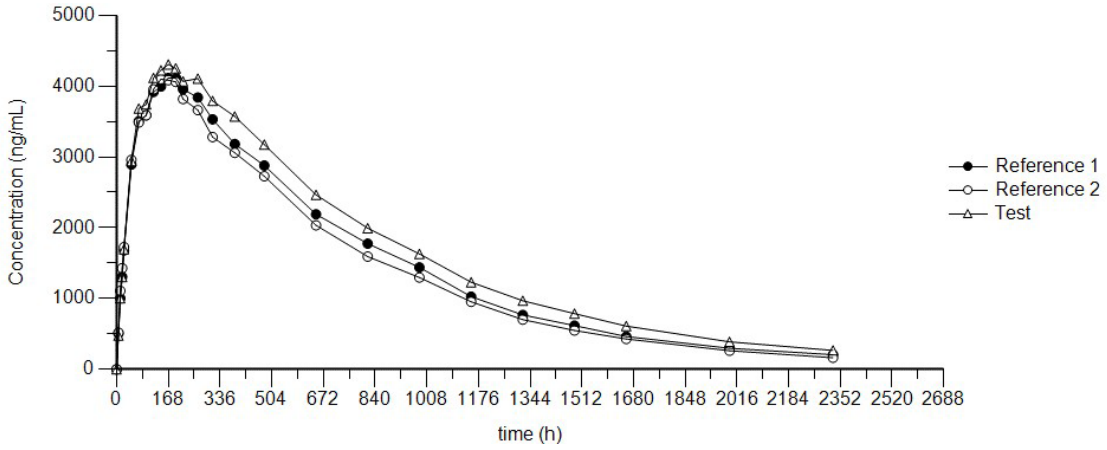
ADA-positive subjects

Overall, 182 subjects of the PKS had or developed any ustekinumab ADAs during the whole course of the study, i.e., they were 'ADA-positive' (FYB202: N=32, EU-Stelara: N=69, US- Stelara: N=81).

Arithmetic mean serum concentrations of ustekinumab increased after administration, peaking between 168 hours (=Day 7) and 192 hours (=Day 8) after dosing for all treatments. As depicted below, the arithmetic

mean serum concentrations of ustekinumab were comparable between the 3 treatment groups. However, in the elimination phase, FYB202 concentration showed a slightly slower decrease compared to the 2 reference products.

Figure 7 Mean serum concentration vs. time curves after subcutaneous application of 45 mg (single dose 0.5 ml) of FYB202 (Test) [N=32] / EU-Stelara (Reference 1) [N=69] / US-Stelara (Reference 2) [N=81] (PKS, ADA-positive subjects)

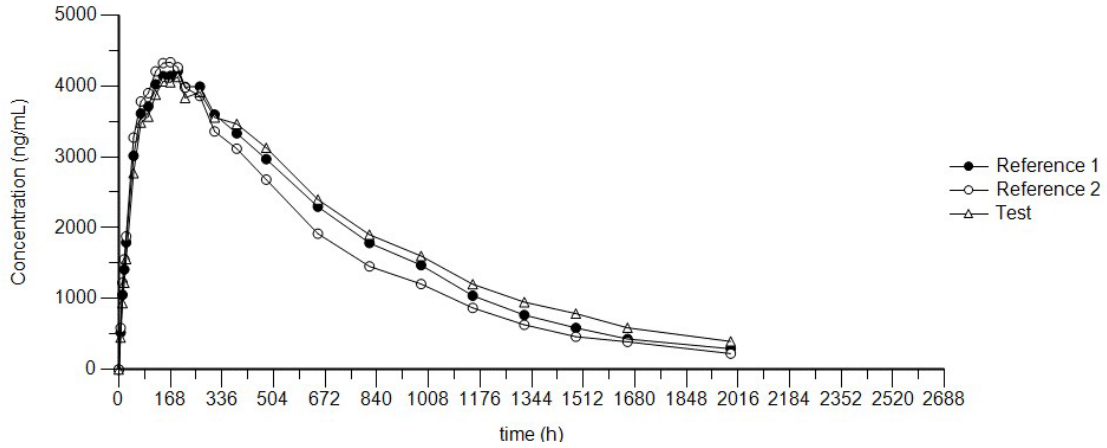


NAb-reactive subjects

Overall, 72 subjects of the PKS had or developed any ustekinumab NAbs during the whole course of the study, i.e., they were 'NAb-reactive' (FYB202: N=18, EU-Stelara: N=25, US- Stelara: N=29).

Arithmetic mean serum concentrations of ustekinumab increased after administration, peaking between 168 hours (=Day 7) and 192 hours (=Day 8) after dosing for all treatments. As depicted below, the arithmetic mean serum concentrations of ustekinumab were comparable between the 3 treatment groups. However, in the elimination phase, US-Stelara concentration showed a slightly faster decrease compared to FYB202 and EU-Stelara.

Figure 8 Mean serum concentration vs. time curves after subcutaneous application of 45 mg (single dose 0.5 ml) of FYB202 (Test) [N=18] / EU-Stelara (Reference 1) (N=25] / US-Stelara (Reference 2) [N=29] (PKS, NAb-reactive subjects)



Evaluation for all subjects

The main mean PK parameters of **FYB202** (Test) and **EU-Stelara** (Reference 1) are summarised in **Table 16** and **Table 17**.

Table 17 Mean pharmacokinetic parameters of ustekinumab after subcutaneous application of 45 mg (single dose 0.5 ml) of FYB202 (Test) (PKS, all subjects, N=159)

	$AUC_{0\text{-}Inf}$ (h*ng/mL)	$AUC_{0\text{-}tlast}$ (h*ng/mL)	C_{max} (ng/mL)	t_{max} (h)	CL (mL/h)	Vz (mL)	Lz (1/h)	$t_{1/2}$ (h)
N	159	159	159	159	159	159	159	159
Mean	4240000	4090000	4730	184	12.3	7680	0.00191	480
SD	1260000	1170000	1340	66.4	8.59	2420	0.00384	123
Min	446000	441000	1110	6.00	5.55	2110	0.000855	14.5
Median	4240000	4130000	4720	169	10.6	7340	0.00142	487
Max	8110000	7250000	10300	481	101	21400	0.0478	811
Geometric Mean	4010000	3880000	4520	171	11.2	7350	0.00153	454
CV% Geom. Mean	38.11	37.26	32.55	45.35	38.11	30.47	44.61	44.61

Table 18 Mean pharmacokinetic parameters of ustekinumab after subcutaneous application of 45 mg (single dose 0.5 ml) of EU-Stelara (Reference 1) (PKS, all subjects, N=160)

	$AUC_{0\text{-}Inf}$ (h*ng/mL)	$AUC_{0\text{-}tlast}$ (h*ng/mL)	C_{max} (ng/mL)	t_{max} (h)	CL (mL/h)	Vz (mL)	Lz (1/h)	$t_{1/2}$ (h)
N	159	160	160	160	159	159	159	159
Mean	4080000	3940000	4830	181	12.2	7530	0.00171	452
SD	1210000	1180000	1320	65.4	4.18	2350	0.000725	124
Min	1420000	376000	1630	48.0	5.65	2650	0.000913	141
Median	4030000	3920000	4870	169	11.2	7320	0.00149	465
Max	7970000	7610000	8740	480	31.7	19300	0.00491	759
Geometric Mean	3890000	3740000	4640	170	11.6	7180	0.00161	431
CV% Geom. Mean	31.82	36.46	30.45	37.24	31.82	32.04	34.06	34.06

ADA-negative subjects

The mean PK parameters calculated for ustekinumab in the population of ADA-negative subjects are in line with the mean serum concentration vs. time profiles.

The extent of bioavailability, represented by geometric mean $AUC_{0\text{-}inf}$, was slightly different between the 3 groups (FYB202: 4210000 h*ng/mL, EU-Stelara: 4350000 h*ng/mL, US-Stelara: 4140000 h*ng/mL). Comparable results were obtained for $AUC_{0\text{-}tlast}$.

Likewise, the maximum exposure, represented by geometric mean C_{max}, was slightly different between the 3 groups (FYB202: 4530 ng/mL, EU-Stelara: 4960 ng/mL, US-Stelara: 4650 ng/mL).

The time to maximum exposure, represented by median t_{max}, was comparable for FYB202 (170 h), EU-Stelara (169 h) and US-Stelara (168 h).

Mean apparent terminal elimination half-life (mean $t_{1/2}$ ± SD) was comparable for FYB202 (508 ± 92.1 h) and EU-Stelara (504 ± 92.4 h) and slightly shorter for US-Stelara (490 ± 89.5 h). Mean apparent total

clearance (CL) and mean apparent volume of distribution (Vz) were comparable between all 3 treatment groups.

NAb-negative subjects.

The mean PK parameters calculated for ustekinumab in the population of NAb-negative subjects are in line with the mean serum concentration vs. time profiles.

The extent of bioavailability, represented by geometric mean AUC0-inf, was slightly different between the 3 groups (FYB202: 4190000 h*ng/mL, EU-Stelara: 3980000 h*ng/mL, US-Stelara: 3740000 h*ng/mL). Comparable results were obtained for AUC0-tlast.

Likewise, the maximum exposure, represented by geometric mean Cmax, was slightly different between the 3 groups (FYB202: 4550 ng/mL, EU-Stelara: 4690 ng/mL, US-Stelara: 4420 ng/mL).

The time to maximum exposure, represented by median tmax values, was comparable for FYB202 (169 h), EU-Stelara (169 h) and US-Stelara (168 h).

The mean apparent terminal elimination half-life (mean t1/2 ± SD) was slightly longer for FYB202 (498 ± 98.0 h) compared to EU-Stelara (471 ± 112 h) and US-Stelara (455 ± 101 h).

Mean apparent total clearance (CL) and mean apparent volume of distribution (Vz) were comparable between all 3 treatment groups.

Statistical evaluation of pharmacokinetic parameters

Assessment of PK similarity was based on the subjects included in the PKS (N=478).

Table 19 Summary of statistical analysis for the primary pharmacokinetic parameters of ustekinumab PKS, all subjects, N=478)

Parameter	N Observations	Point estimate (%)	90% Confidence interval		CV_{ANCOVA} (%)
			Lower limit (%)	Upper limit (%)	
	Test (FYB 202) vs. Reference 1 (EU-Stelara)				
$AUC_{(0\text{-}inf)}$	318	102.85	96.84	109.23	33.41
C_{max}	319	97.22	92.05	102.67	30.20
	Test (FYB 202) vs. Reference 2 (US-Stelara)				
$AUC_{(0\text{-}inf)}$	318	112.05	105.24	119.3	34.86
C_{max}	318	101.65	96.19	107.42	30.52
	Reference 1 (EU-Stelara) vs. Reference 2 (US-Stelara)				
$AUC_{(0\text{-}inf)}$	318	109.00	102.84	115.53	32.22
C_{max}	319	104.59	99.06	110.44	30.09

Statistical analysis for subgroups

The statistical analyses performed for the subgroups were without formal testing for pharmacokinetic similarity.

Table 20 Summary of statistical analysis for the primary pharmacokinetic parameters of Ustekinumab PKS, ADA-negative subjects, N=296

Parameter	N Observations	Point estimate (%)	90% Confidence interval		CV_{ANCOVA} (%)
			Lower limit (%)	Upper limit (%)	
	Test (FYB 202) vs. Reference 1 (EU-Stelara)				
$AUC_{(0\text{-}inf)}$	218	98.24	92.57	104.26	26.59
C_{max}	218	92.68	86.87	98.89	29.07
	Test (FYB 202) vs. Reference 2 (US-Stelara)				
$AUC_{(0\text{-}inf)}$	205	101.66	95.54	108.17	26.58
C_{max}	205	97.54	91.05	104.51	29.62
	Reference 1 (EU-Stelara) vs. Reference 2 (US-Stelara)				
$AUC_{(0\text{-}inf)}$	169	103.64	96.95	110.79	26.54
C_{max}	169	105.27	98.20	112.86	27.69

ADA-negative subjects

The geometric mean ratios (90% CIs) of $AUC_{0\text{-}inf}$ were 98.24% (92.57–104.26%) for the comparison of FYB202 against EU-Stelara and 101.66% (95.54–108.17%) for the comparison of FYB202 against US-Stelara. The 90% CIs for both comparisons fell within the range of 80.00% to 125.00%.

Geometric mean ratios (90% CIs) of C_{max} were 92.68% (86.87–98.89%) for the comparison of FYB202 against EU-Stelara and 97.54% (91.05–104.51%) for the comparison of FYB202 against US-Stelara. The 90% CIs for both comparisons fell within the range of 80.00% to 125.00%. When comparing the reference study interventions EU-Stelara and US-Stelara, the geometric mean ratios of $AUC_{0\text{-}inf}$ and C_{max} were 103.64% and 105.27%, respectively. The corresponding 90% CIs were both fully contained within the range of 80.00% to 125.00% ($AUC_{0\text{-}inf}$: 96.95–110.79%, C_{max}: 98.20–112.86%). The inter-subject variability as reflected by CV_{ANCOVA} was between ~27% and ~30% for both co-primary endpoints. Differences in t_{max} between treatment groups based on the non-parametric comparison were not detected.

NAb-negative subjects:

Table 21 Summary of statistical analysis for the primary pharmacokinetic parameters of Ustekinumab (PKS, NAb-negative subjects, N=406)

Parameter	N Observations	Point estimate (%)	90% Confidence interval		CV_{ANCOVA} (%)
			Lower limit (%)	Upper limit (%)	
	Test (FYB 202) vs. Reference 1 (EU-Stelara)				
$AUC_{(0\text{-}inf)}$	276	105.81	100.03	111.92	28.82
C_{max}	276	97.54	91.95	103.46	30.34
	Test (FYB 202) vs. Reference 2 (US-Stelara)				
$AUC_{(0\text{-}inf)}$	271	111.59	105.68	117.83	27.62
C_{max}	271	102.79	96.85	109.11	30.37
	Reference 1 (EU-Stelara) vs. Reference 2 (US-Stelara)				
$AUC_{(0\text{-}inf)}$	265	105.56	99.37	112.13	30.43
C_{max}	265	105.55	99.28	112.22	30.89

Geometric mean ratios (90% CIs) of AUC_{0-inf} were 105.81% (100.03–111.92%) for the comparison of FYB202 against EU-Stelara and 111.59% (105.68–117.83%) for the comparison of FYB202 against US-Stelara. The 90% CIs for both comparisons fell within the range of 80.00% to 125.00%.

Geometric mean ratios (90% CIs) of C_{max} were 97.54% (91.95–103.46%) for the comparison of FYB202 against EU-Stelara and 102.79% (96.85–109.11%) for the comparison of FYB202 against US-Stelara. The 90% CIs for both comparisons fell within the range of 80.00% to 125.00%.

Immunogenicity Impact on Pharmacokinetics

Statistical analysis was also performed for the subgroups based on immunogenicity. This analysis was only explorative without formal testing for pharmacokinetic similarity.

The ADA-negative subgroup comprised 296 subjects (FYB202: N=127, EU-Stelara: N=91, US-Stelara: N=78) and the NAb-negative subgroup 406 subjects (FYB202: N=141, EU-Stelara: N=135, US-Stelara: N=130). Despite the lower sample size compared to the overall population, for these two subgroups, all 90% CIs of the geometric mean ratios were fully contained within the range of 80.00% to 125.00% for both primary endpoints, AUC0-inf and Cmax. The inter-subject variability as reflected by CV ANCOVA was slightly smaller than in the overall population with values between ~27% and ~31% for both endpoints. The ADA-positive subgroup comprised 182 subjects (FYB202: N=32, EU-Stelara: N=69, US Stelara: N=81). Despite the lower sample size compared to the overall population, all 90% CIs of the geometric mean ratios were fully contained within the range of 80.00% to 125.00% for both primary endpoints, AUC0-inf and Cmax. The inter-subject variability as reflected by CV ANCOVA was slightly larger than in the overall population with values between ~31% and ~41% for both endpoints. The NAb-reactive subgroup comprised 90 subjects (FYB202: N=18, EU-Stelara: N=25 (Cmax) / 24 (AUC0-inf), US-Stelara: N=29). All 90% CIs of the geometric mean ratios for AUC0-inf fell outside the range of 80.00% to 125.00%. Nevertheless, for Cmax, all 90% CIs of the geometric mean ratios were fully contained within the range of 80.00% to 125.00%. Notably, the intersubject variability for AUC0-inf was very large (CV ANCOVA ~51% and ~57%). Furthermore, the sample sizes of the treatment groups within this subgroup were very small. Therefore, any potential differences in exposure have to be interpreted with caution.

For Cmax, inter-subject variability was smaller (CVANCOVA ~30% and ~32%), since it occurred early enough to be not substantially affected by NAb reactivity, resulting in geometric mean ratios and corresponding 90% CIs within the range of 80.00% to 125.00% for all comparisons.

As expected, in the subgroups of ADA-positive/NAb-reactive subjects, the apparent terminal elimination half-life (t1/2) was shorter and the mean apparent clearance (CL) was faster than in the subgroups of ADA/NAb-negative subjects.

Ctrough in the target population

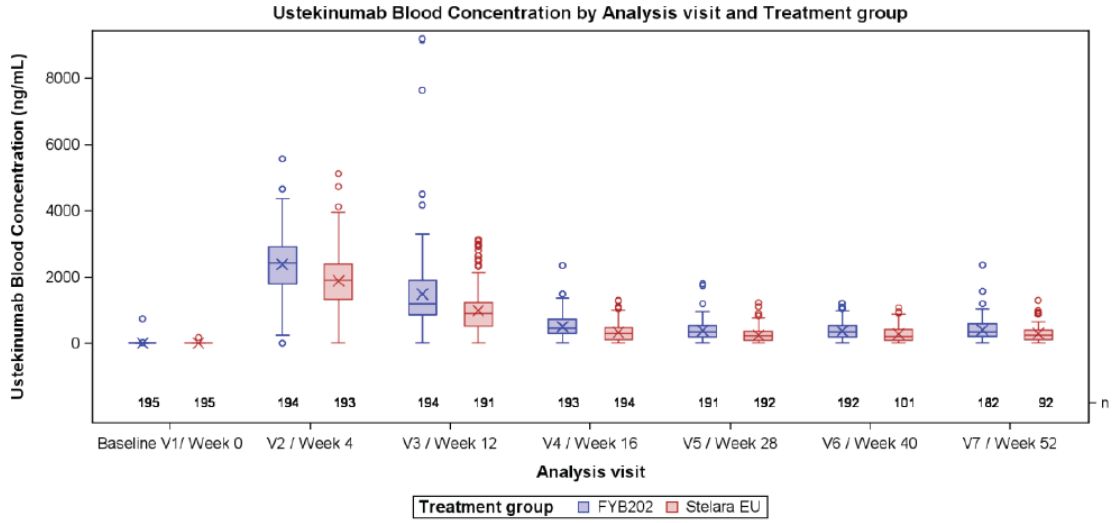
PK endpoints in study FYB202-03-01 comprised serum trough levels of ustekinumab (Ctrough) at Weeks 4, 12, 16, 28, 40, and 52 and change in ustekinumab Ctrough from Week 28 through Week 52 in patients following a single transition from Stelara to FYB202.

Serum Ctrough levels of ustekinumab showed a high inter-patient variability, particularly at Weeks 4 and 12 (coefficients of variation (CV) ranged between 56.93% - 126.40%). Smaller interpatient variability was observed during steady-state at Weeks 16, 28, 40 and 52 (**Figure 9**, **Table 22**). Ctrough levels were highest at Week 4, then decreased linearly and stabilized between Week 16 and Week 52. The geometric Ctrough

levels were between 300.02 and 411.68 ng/mL for FYB202 and between 176.69 and 227.12 ng/mL for Stelara EU. Some patients had measurable ustekinumab levels at baseline. In a secondary analysis based on the PKSAS, these patients were excluded from summary tables. The respective Figure for the PKSAS showed a similar plasma curve compared to **Figure 9**.

Numerically higher geometric mean Ctrough levels for patients treated with FYB202 compared to patients treated with Stelara EU were observed, particularly at Weeks 4 and 12 (**Figure 9**, **Figure 10**). There was no generally higher exposure with FYB202, but the measured difference in drug levels was likely related to the higher incidence of ADAs in the Stelara EU group. Ctrough levels were low and comparable at steady-state from Week 16 onwards. The figure for the PK SAS showed a similar plasma curve compared to **Figure 10**.

Figure 9 Ustekinumab Ctrough levels (ng/mL) at Weeks 0, 4, 12, 16, 28, 40, and 52 (SAF, N=392)



The graph shows ustekinumab C_{trough} levels in ng/mL during the study, note that the boxes for V6/ Week 40 and V7/ Week 52 include data of patients keeping to their initial randomised treatment after rerandomisation at Week 28 and exclude data of patients who had a single transition Stelara EU-FYB202.
Boxplot markers: x = Mean, line = Median, lower box boundary = 1st quartile, upper box boundary = 3rd quartile, o = Outlier (above/below 1.5*IQR); Upper whisker: maximum value below upper fence; Lower whisker: minimum value above lower fence; Upper fence: 1.5 times the IQR above the 3rd quartile; Lower fence: 1.5 times the IQR below the 1st quartile; IQR = inter quartile range: 3rd quartile - 1st quartile

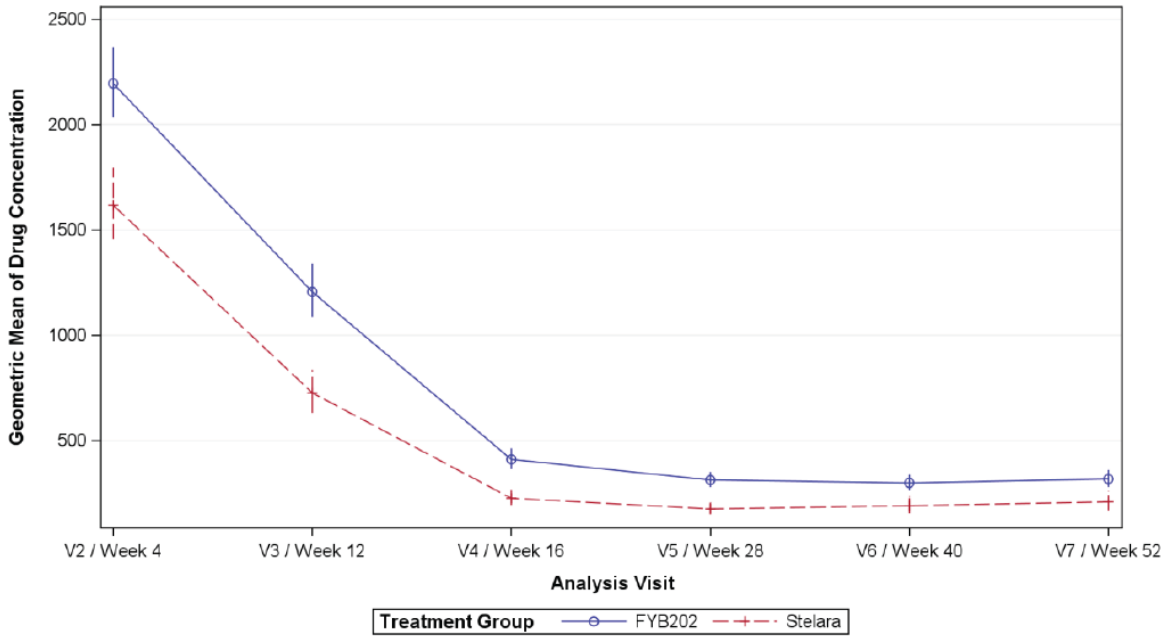
Table 22 Ctrough ustekinumab concentrations at Weeks 0, 4, 12, 16, 28, 40, and 52 (SAF, N=392)

Analysis Visit	FYB202 (N=197) Absolute value	Stelara EU (N=195) Absolute value
Baseline V1/ Week 0		
N	195	195
Mean (SD)	23.91 (53.01)	20.88 (12.25)
Geomean	20.45	20.23
95% CI	19.70-21.23	19.78-20.70
CV	27.02	16.27
V2 / Week 4		
N	194	193
Mean (SD)	2404.24 (863.61)	1905.96 (855.90)
Geomean	2195.01	1617.38
95% CI	2036.35-2366.03	1456.93-1795.51
CV	56.93	84.77
V3 / Week 12		
N	194	191
Mean (SD)	1497.53 (1063.44)	997.44 (674.49)
Geomean	1206.64	727.43
95% CI	1086.77-1339.73	632.74-836.28
CV	85.22	126.40
V4 / Week 16		
N	193	194
Mean (SD)	529.76 (328.23)	350.30 (277.10)
Geomean	411.68	227.12
95% CI	365.55-463.64	194.38-265.37
CV	100.77	153.22
V5 / Week 28		
N	191	192
Mean (SD)	403.98 (267.45)	272.02 (216.64)
Geomean	314.02	176.69
95% CI	279.72-352.52	151.35-206.28
CV	96.35	150.43
V6 / Week 40		
N	192	101
Mean (SD)	393.74 (244.39)	292.06 (233.35)
Geomean	300.02	191.68
95% CI	264.97-339.71	155.09-236.89
CV	106.85	147.02

V7 / Week 52		
N	182	92
Mean (SD)	423.39 (300.74)	312.16 (254.96)
Geomean	318.56	210.18
95% CI	280.83-361.36	169.84-260.11
CV	104.98	137.26

CI= confidence interval, CV = coefficient of variation, Geomean: geometric mean, N = number of patients per group, n = number of patients per category, SAS = safety analysis set, SD = standard deviation, V = visit
Note: Values for V6/ Week 40 and V7/ Week 52 include data of patients keeping to their initial randomised treatment after rerandomisation at Week 28 and exclude data of patients who had a single transition Stelara EU-FYB202

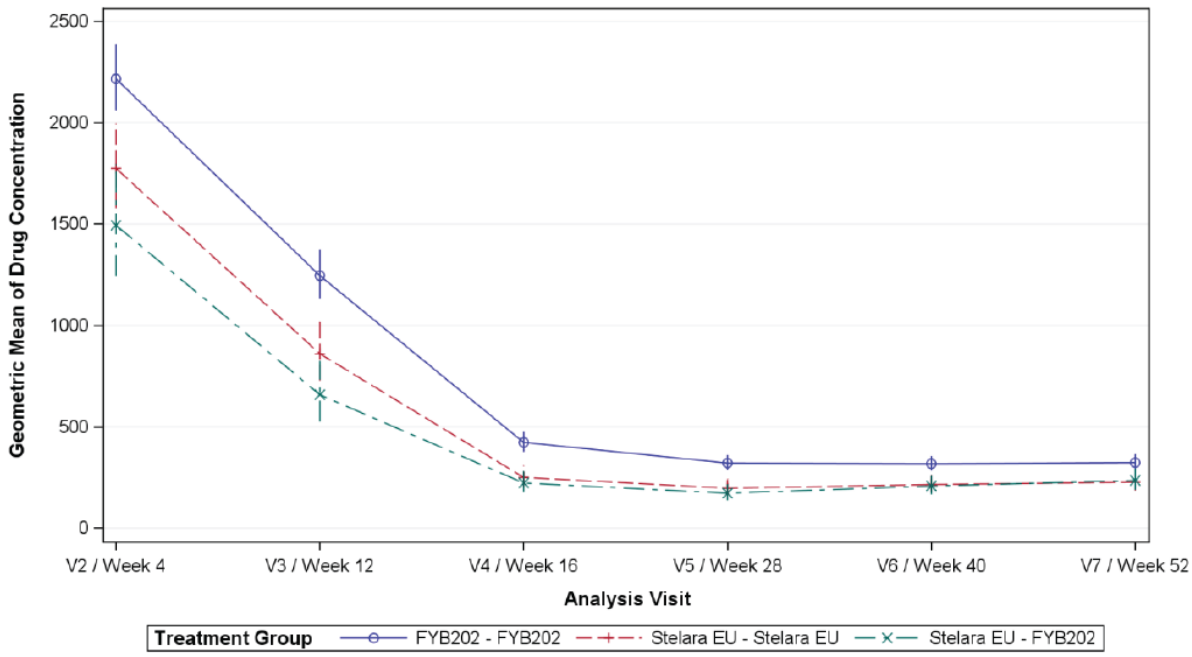
Figure 10 Ctrough levels (ng/mL) at Weeks 0, 4, 12, 16, 28, 40, and 52 (SAF, N=392)



The graph presents geometric mean with 95% CI ustekinumab C_{trough} concentrations (ng/mL) during the study, note that the values for V6/ Week 40 and V7/ Week 52 include data of patients keeping to their initial randomised treatment after rerandomisation at Week 28 and exclude data of patients who had a single transition Stelara EU-FYB202.

Stable Ctrough levels from Week 16 to Week 52 were also observed in all three re-randomised groups with similar Ctrough levels in the single transition Stelara EU-FYB202 group and the continuous groups using the RRAS. The geometric mean Ctrough levels after re-randomisation were between 317.82 and 323.63 ng/mL for FYB202-FYB202, between 197.63 and 227.53 ng/mL for Stelara EU-Stelara EU and between 172.43 and 235.68 ng/mLfor patients with the single transition Stelara EU-FYB202 (**Table 22**). For the PKRRAS, similar levels were observed.

Figure 11 Ustekinumab Ctrough levels (ng/mL) at Weeks 0, 4, 12, 16, 28, 40, and 52 (RRAS, N=375)



The graph presents geometric mean with 95% CI ustekinumab C_{trough} concentrations (ng/mL) during the study, note that values for V2/ Week 4, V3/ Week 12, and V4/ Week 16 retrospectively include data of respective patients before rerandomisation at Week 28.

Table 23 Ctrough ustekinumab concentrations at Weeks 28, 40, and 52 (RRAS, N=375)

Analysis Visit	FYB202 - FYB202 (N=189) Absolute value	Stelara EU - Stelara EU (N=97) Absolute value	Stelara EU - FYB202 (N=89) Absolute value
V5 / Week 28			
N	187	97	89
missing value	0	0	0
Mean (SD)	409.81 (266.97)	292.97 (233.05)	262.60 (197.37)
Geomean	321.43	197.63	172.43
95% CI	286.52-360.59	160.45-243.42	137.30-216.56
CV	94.18	138.32	149.08
V6 / Week 40			
N	188	96	89
missing value	0	0	0
Mean (SD)	401.69 (240.73)	306.23 (230.70)	305.81 (222.84)
Geomean	317.82	215.62	208.26
95% CI	283.84-355.86	177.38-262.12	167.07-259.60
CV	92.44	123.75	140.96

Analysis Visit	FYB202 - FYB202 (N=189) Absolute value	Stelara EU - Stelara EU (N=97) Absolute value	Stelara EU - FYB202 (N=89) Absolute value
V7 / Week 52			
N	178	89	84
missing value	0	0	0
Mean (SD)	415.62 (261.65)	322.01 (253.41)	348.19 (334.45)
Geomean	323.63	227.53	235.68
95% CI	287.33-364.53	186.31-277.87	189.41-293.25
CV	95.39	120.84	132.56

CI= confidence interval, CV = coefficient of variation, Geomean: geometric mean, N = number of patients per group, n = number of patients per category, RRAS = re-randomised analysis set, SD = standard deviation, Q1 – Q3 = interquartile range, Min = minimum, Max = maximum, V = visit
[a] Relative to Baseline V1/Week0

Impact of ADA on trough drug serum concentration in phase III study Baseline to Week 52 – Pharmacokinetic Safety Analysis Set Geometric mean trough drug serum concentration vs. time

The geometric mean trough drug serum concentration vs. time profiles from baseline to Week 52 for the Pharmacokinetic Safety Analysis Set are summarised in **Table 23** and **Figure 12** by ADA positive vs. ADA negative status in each treatment group.

Table 24 Geometric mean trough drug serum concentration vs. time by ADA status from baseline to Week 52 in Study FYB202-03-01 – Pharmacokinetic Safety Analysis Set

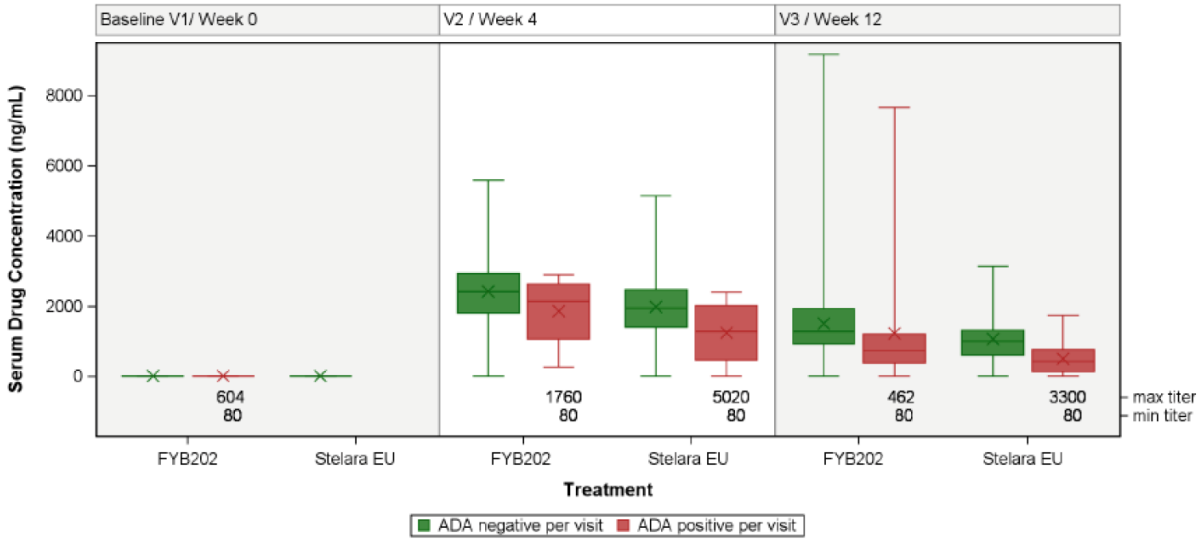
		FYB202		Stelara EU	
Week	**Statistic (ng/mL)**	**ADA Positive (N=23)**	**ADA Negative (N=169)**	**ADA Positive (N=56)**	**ADA Negative (N=138)**
0	n	23	169	56	138
	Geom. Mean	20.00	20.00	20.00	20.00
	95% CI	n.c.	n.c.	n.c.	n.c.
	Median	20	20	20	20
	Min/Max	20 - 20	20 - 20	20 - 20	20 - 20
4	n	21	169	56	136
	Geom. Mean	1873.95	2234.44	1223.96	1808.07
	95% CI	[1457.65; 2409.14]	[2062.21; 2421.07]	[969.44; 1545.30]	[1620.91; 2016.83]
	Median	2430	2430	1555	2025
	Min/Max	272 - 3250	20 - 5600	20 - 3020	20 - 5150
12	n	22	168	56	134
	Geom. Mean	789.35	1270.97	426.00	911.46
	95% CI	[485.73; 1282.74]	[1147.79; 1407.38]	[312.41; 580.90]	[795.27; 1044.63]
	Median	927	1240	589.5	1020
	Min/Max	20 - 3040	20 - 9180	20 - 1930	20 - 3160

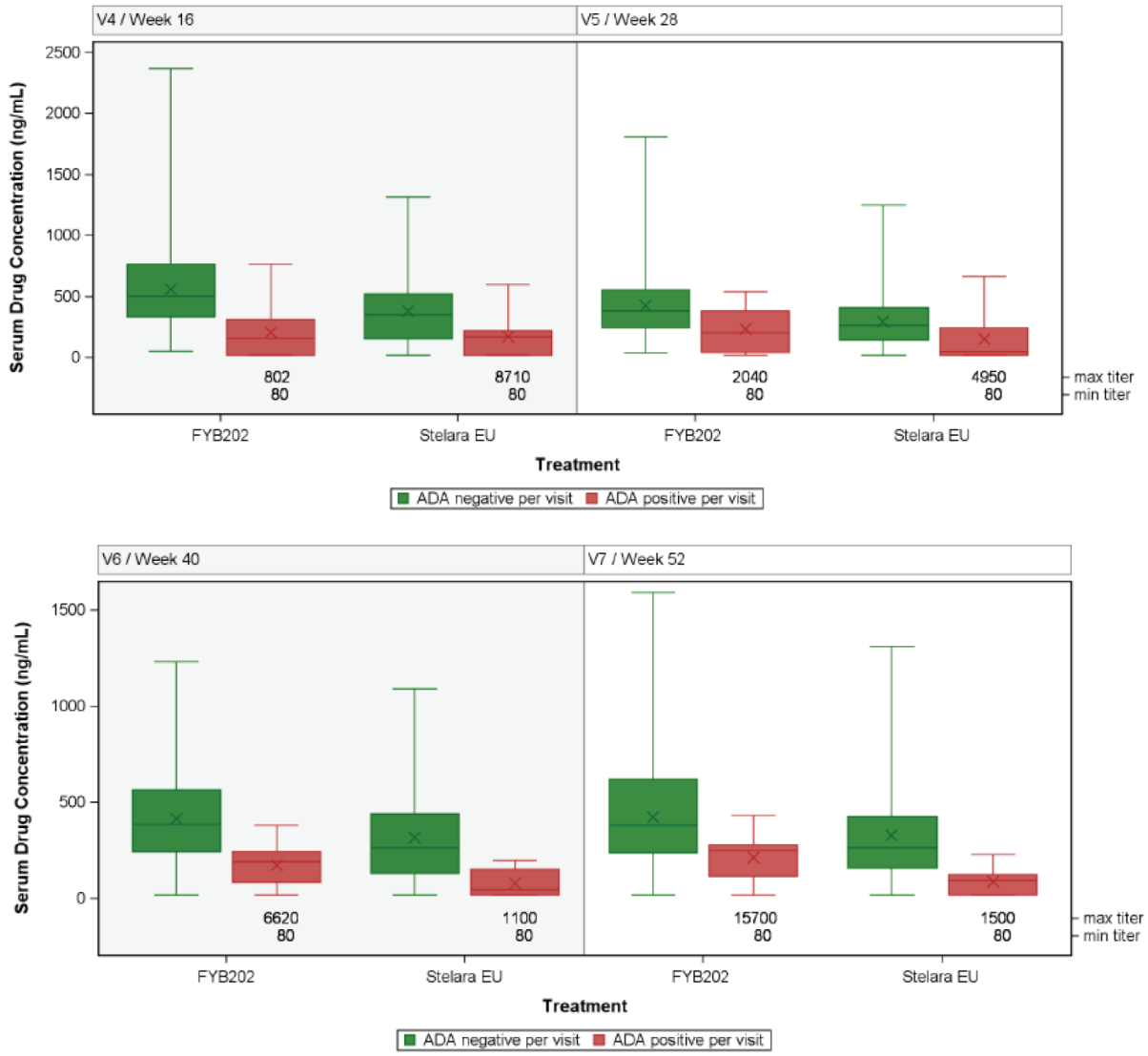
16	n Geom. Mean 95% CI Median Min/Max	22 198.68 [105.69; 373.48] 310 20 - 984	167 450.47 [406.01; 499.80] 476 54.1 - 2370	55 117.81 [83.94; 165.33] 176 20 - 790	138 292.54 [250.83; 341.19] 359 20 - 1320
28	n Geom. Mean 95% CI Median Min/Max	21 144.33 [85.10; 244.77] 195 20 - 630	167 346.19 [310.88; 385.50] 384 20 - 1810	56 88.08 [63.23; 122.71] 96.85 20 - 665	135 234.39 [201.90; 272.11] 278 20 - 1250
40	n Geom. Mean 95% CI Median Min/Max	22 154.66 [91.36; 261.82] 193 20 - 762	167 331.11 [294.64; 372.10] 379 20 - 1230	29 114.00 [75.53; 172.05] 152 20 - 508	72 236.31 [186.72; 299.07] 313 20 - 1090
52	n Geom. Mean 95% CI Median Min/Max	21 207.44 [125.07; 344.07] 265 20 - 782	159 331.10 [292.15; 375.25] 380 20 - 1590	28 137.13 [89.52; 210.07] 185 20 - 670	64 253.36 [200.04; 320.90] 292 20 - 1310

N = total number of patients in the corresponding treatment group and analysis set; n = number of patients with data; n.c.=not calculable; ADA=anti-drug antibody; SD=standard deviation; CV=Coefficient of variation; Min=minimum; Max=maximum; P10=10% percentile; Q25=lower quartile; Q75=upper quartile; P90=90% percentile; CL=confidence limit. Visit 1 is considered a Baseline visit. For visits V6 and V7, only patients who did NOT have a transition from Stelara EU to FYB202 are included in the Stelara EU summary.

Concentrations below the lower limit of quantification (40.0 ng/mL) were set to 20.0 ng/mL.

Figure 12 Boxplots of trough drug serum concentration by time and ADA status – Baseline to Week 52 – Pharmacokinetic Safety Analysis Set





Concentrations below the lower limit of quantification (40.0 ng/mL) were set to 20.0 ng/mL.
ADA = anti-drug antibody. The visit-based ADA positive subgroup is defined as any subject with a positive ADA results at the respective visit.

Titre min/max: minimal and maximal ADA titre measurement at the specific visit.

Boxplot: whiskers from minimal to maximal value, box from lower to upper quartile, x marker = mean, line marker = median

For visits V6 and V7, only patients who did NOT have a transition from Stelara EU to FYB202 are included in the Stelara EU figure.

Relationship of trough drug serum concentration to ADA status in each treatment group

Within each treatment group, the geometric mean trough drug serum concentration was lower at all time points for the ADA-positive subpopulation compared to the ADA-negative population.

The magnitude of difference between the ADA positive vs. ADA negative subpopulations varied with timepoint: the maximal relative decrease associated with ADA positive status was detected at Week 28. Nevertheless, the magnitude of the difference was similar for both treatment groups from Week 16 through

Week 52, indicating a similar scale of impact of ADA on trough drug serum concentration for FYB202 vs. Stelara EU.

Relationship of trough drug serum concentration to treatment group

For ADA-negative patients, geometric mean serum concentration was lower at all time points for the Stelara EU group compared to the FYB202 group. This outcome indicated an effect on PK that was independent of ADA status and also independent of timepoint.

Comparing the ADA-positive patients across the treatment groups, the geometric mean trough drug serum concentration was also lower at all time points for the Stelara EU group compared to the FYB202 group. Thus, neither ADA positive nor ADA status appeared to impact the apparent between-group difference in drug trough concentration.

Most importantly, the observed inter-group difference in drug serum concentration vs. time was without impact on clinical efficacy regardless of ADA status.

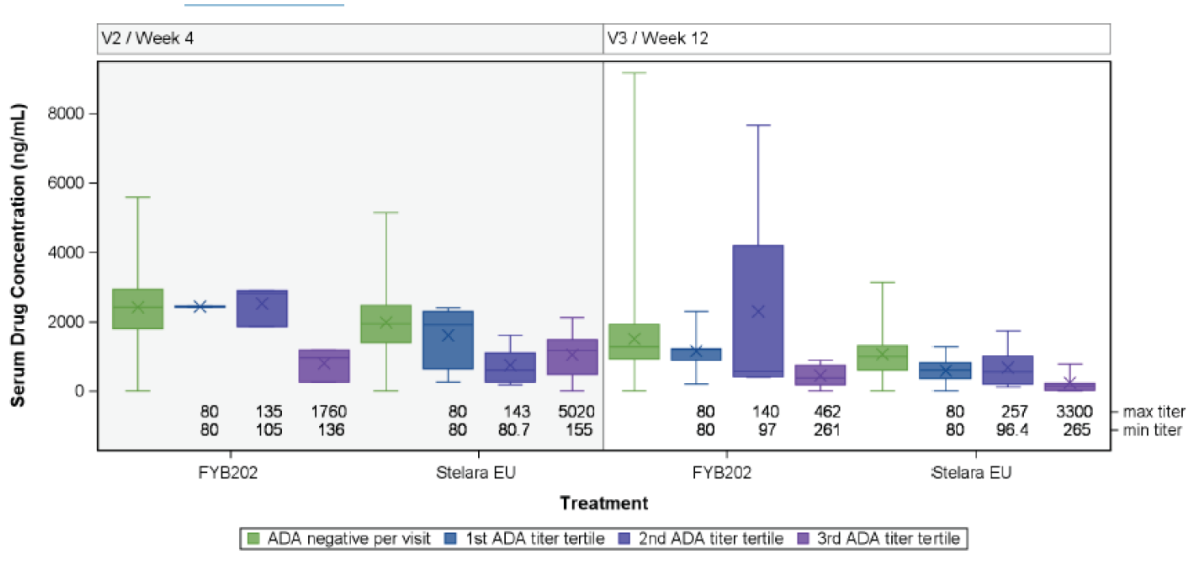
Influence of ADA titre on trough drug serum concentration

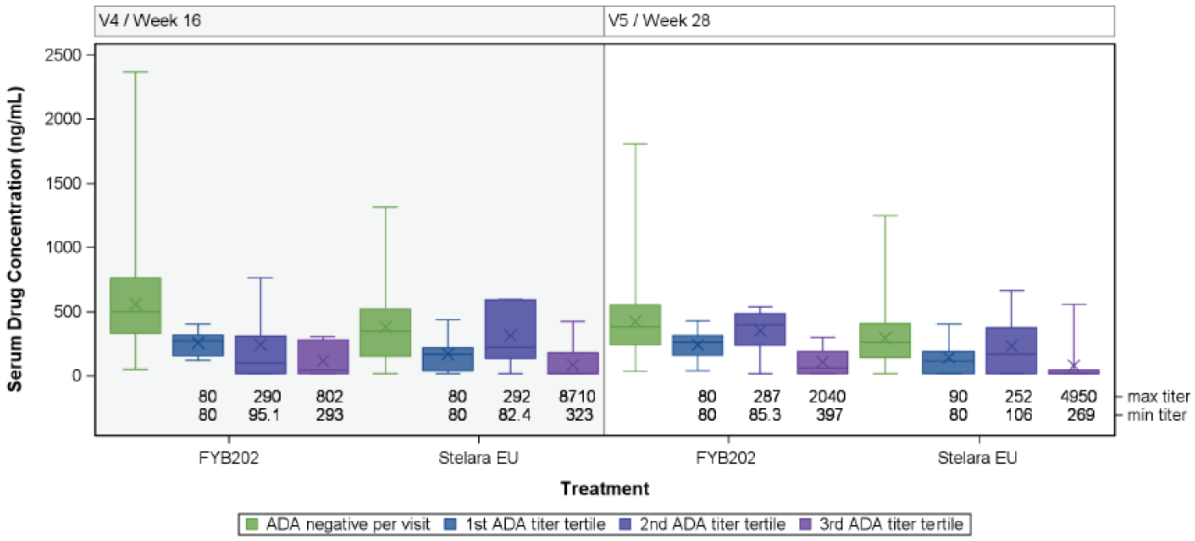
Although the number of ADA-positive data points was limited, **Figure 13** presents an additional analysis of the relationship of serum drug concentration to ADA titre.

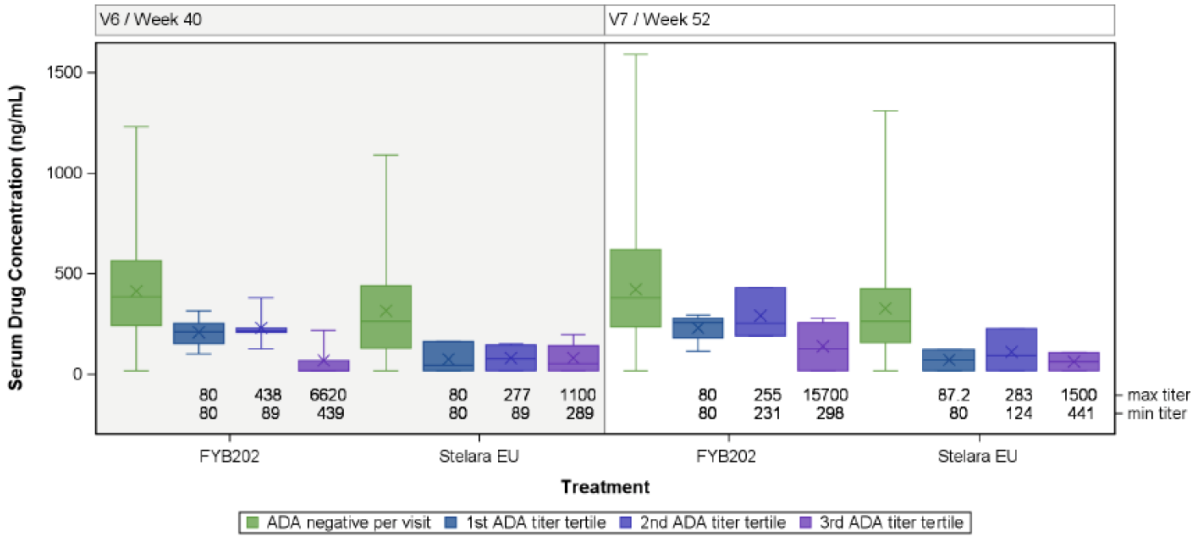
At Week 28, which was the time point associated with the highest ADA prevalence in each treatment group, ADA-positive patients with ADA titres in the highest quartile (397 to 2040 for FYB202; 269 to 4950 for Stelara EU) had the lowest serum drug concentration.

The geometric mean ADA titre at Week 28 was comparable across treatment groups (212.63 for FYB202 vs. 203.29 for Stelara EU). Thus, although there was a numerically higher ADA prevalence at Week 28 for Stelara EU (19.5%) compared to FYB202 (12.6%), the titre of the ADA positive signals was similar.

Figure 13 Boxplots of trough drug serum concentration by time and ADA titre tertile from baseline to Week 52 in Study FYB202-03-01 – Pharmacokinetic Safety Analysis Set







Concentrations below the lower limit of quantification (40.0 ng/mL) were set to 20.0 ng/mL.

ADA = anti-drug antibody. ADA titre tertiles are calculated on visit-based ADA titre for any subject with a positive ADA result at the respective visit.

Titre min/max: minimal and maximal ADA titre measurement at the specific visit.

Boxplot: whiskers from minimal to maximal value, box from lower to upper quartile, x marker = mean, line marker = median
For visits V6 and V7, only patients who did NOT have a transition from Stelara EU to FYB202 are included in the Stelara EU figure.

2.6.3. Discussion on clinical pharmacology

Bioanalytical methods

PK Assay

The assay has been appropriately validated in accordance with the EMA guideline on Bioanalytical method validation (EMEA/CHMP/EWP/192217/2009). In the method validation report, the reference standard and critical reagents have been listed, which provides details on the lot number, expiration date, source and storage condition. Certificates of analysis were provided for the FYB202 reference material, which is acceptable to the CHMP. Appropriate assay acceptance criteria were in place for routine assays. Appropriate method performance during routine sample analysis is confirmed in the bioanalytical method reports.

ADA Assay

The full validation has been performed and from the data available, a floating cut-point was used during the screening assay. The screening cut point factor was calculated from healthy subjects as 1.084 based on a 5% false positive rate, while the titre cut point factor was 1.174 based on a 0.1% false positive rate. The specificity (confirmatory) cut point was 10.7% based on a 1% false positive rate. New cut point factor rates were determined in the repeated Phase I PK study in healthy patients; this is acceptable to the CHMP.

Sensitivity for the assay was calculated by diluting a sample from 800 ng/mL and the lowest positive control (LPC) for the screening assay was found to be 13.6 ng/mL, while the confirmatory sensitivity was found to be 27.7 ng/mL (inhibitory LPC). The assay precision was performed to determine inter-assay precision using the positive controls. The intra-assay precision was determined to be less than 6.6% across all the concentrations tested for a single run with 6 replicates. Sensitivity and selectivity were tested in 10 healthy serum, 10 psoriatic serum, three lipemic and haemolysed samples. The results showed that samples met the acceptance and there was no effect from haemolysis or hyperlipidaemia on the assay. The drug tolerance of the method is demonstrated for 13.6 ng/ml positive control at a level of 25 µg/ml drug and 100 – 18000 ng positive control at a level of 100 µg/ml drug. Similar results were observed for FYB202 and Stelara. At a drug concentration of 10 µg/mL, one Stelara US batch failed to be reactive. As drug serum levels remained <11 µg/ml across all three studies and only a few values were that high, the CHMP concluded that drug tolerance issues are not expected to impact the detection of ADA. Appropriate assay validity criteria were in place during routine assay runs and acceptable assay performance was observed during sample analysis.

Nab assay

The full validation has been performed. The cut point value was calculated as 0.902 based on a 1% false positive rate, this was determined from 48 healthy individuals by two analysts across separate days. The approach for the determination of cut points is acceptable to the CHMP. The applicant used a floating cut point approach, although, as for the ADA assay this has not been stated. Accuracy and precision of the method were evaluated. The results for intra-assay precision met the acceptance criteria for % CV of $\leqslant$ 20%. For the results of the inter-assay precision study, the results failed to meet the acceptance criteria for % CV of $\leqslant$ 20% for all the controls. The applicant then applied a response ratio by dividing the positive controls by the negative controls and the inter-run precision was within 20.0% for % CV for all the positive controls. This approach is accepted. The sensitivity has been calculated as 0.856 µg/mL based on the 99% consistency level, using a one-sided probability of 1%. The method has also been appropriately validated for selectivity, recovery and hook effect. No interference was detected in healthy and psoriatic spiked samples with the LPC and highest positive control (HPC). As for the method development report, there were free-drug tolerance effects with the assay only able to tolerate 6 µg/mL FYB202 at LPC (0.873 µg/mL) and MPC (1.50 µg/mL) antibody concentration level, and 10 µg/mL FYB202 at HPC (5.00 µg/mL) antibody concentration level. Appropriate assay validity criteria were in place during routine assay runs and acceptable assay performance was observed

during sample analysis.

Bioequivalence

In accordance with the biosimilarity guidance of EMA, the clinical biosimilar comparability exercise was planned with a comparative PK trial (phase 1) in healthy subjects and a comparative clinical efficacy and safety trial (phase 3) in patients with moderate-to-severe plaque psoriasis, both against the reference medicinal product Stelara. The phase 3 efficacy and safety trial was a randomised, double-blind, parallel-group trial that included a secondary PK analysis of trough concentrations (Ctrough).

Overall, two phase 1 PK trials were conducted in healthy subjects.

Study FYB202-01-01

This first phase 1 PK trial was planned as a three-arm trial comparing FYB202 with EU-approved Stelara (Stelara EU), FYB202 with US-licensed Stelara (Stelara US) and Stelara EU with Stelara US. PK similarity of the two Stelara products should serve as a PK bridge for the phase 3 trial in which FYB202 was compared to Stelara EU only. This clinical trial was a multi-centre, randomised, double-blind, 3-arm, parallel-group, single-dose trial in healthy male and female adult subjects aged 18 to 55 years, weighing between 60 and 90 kg and a BMI within the range of 20.5 to 28.0 kg/m2. A total of 691 subjects were screened; 315 subjects (136 female, 179 male) were randomised and dosed, 306 subjects completed the trial and 9 subjects terminated prematurely (2 protocol non-compliance, 1 death, 1 lost to follow-up, 6 other reasons). Subjects were administered a single subcutaneous injection of either 45 mg FYB202, Stelara EU or Stelara US. The duration of the trial was 112 days per subject. Overall, 38 protocol deviations were classified as 'major/important'. Thirty-eight (38) subjects were re-screened, although the time between their informed consent form signature and rescreening examination had exceeded 30 days. Twenty-two (22) subjects thereof were randomized. The scientific integrity of the trial and the subjects' safety and well-being were not compromised. Thus, all affected subjects remained in the Safety Analysis Set (SAS) and the Pharmacokinetic Analysis Set (PKS). Overall, 315 subjects were included in the SAS, and 313 subjects were included in the PKS.

FYB202-01-01 failed to show PK similarity of FYB202 with Stelara EU and Stelara US, as the CIs for the geometric mean ratios for AUC0-inf exceeded slightly the upper limit of the acceptance range of 80.00–125.00 % (FYB202/Stelara: ratio EU 117.44 %, 90 % CI (108.32 %;127.32 %); FYB202/Stelara US: ratio 118.82 %, 90 % CI (109.65 %;128.77 %)). For Cmax, PK similarity was shown for both comparisons (FYB202/Stelara EU: ratio 108.52 %, 90 % CI (100.48 %;117.19 %); FYB202/Stelara US: ratio 111.82 %, 90 % CI (103.54 %;120.76 %).

Root cause analysis and impact on Study FYB202-01-02 design

An extensive root cause analysis was performed and confirmed that the study setup, study conduct and bioanalytical methods of study FYB202-01-01 are adequate. However, it was found that the single administered dose relative to FYB202 was approximately 4.9%-6.6% lower for Stelara EU and 3.5%-5.2% lower for Stelara US. Furthermore, the incidences of ADAs and NAbs were more than 2-fold higher in subjects of the two Stelara groups compared to the FYB202 group. In line with that, when only considering the subgroups of ADA-negative and NAb-negative subjects all geometric mean ratios and the corresponding 90 % CIs were fully contained within the range of 80.00–125.00 % for both primary endpoints, AUC0-inf and Cmax.

Analyses were performed *post hoc* to explore the reasons for the failure of PK similarity including ANCOVAs

with different covariates (body weight, BMI, age) and factors (gender) and ANCOVA based on arithmetic mean ratios and CIs according to Fieller. An additional ANCOVA with protein content adjustment (in mg/mL and mg) was performed to adjust the ratios and CIs for the difference between the protein contents. For simplicity, the applied correction assumed a 100 % impact of differences in content on serum concentrations. As outlined in the follow-up EMA SA, *the root cause analyses as presented by the applicant imply that the difference in the protein content between the products may explain part of the difference in pharmacokinetics, as the point estimates and confidence intervals were within the bioequivalence acceptance limits after correction for protein content/administered dose*. The point estimate and confidence intervals for Cmax ratios (FYB202/EU Stelara 95.80-111.73%) decreased by approximately 5% after the correction of dose for protein content. The results for Cmax suggest that the treatments have comparable absorption after correction for dose. However, the confidence interval for AUC0-inf ratios remains entirely above unity even after corrections for protein content. Demonstration of equivalence between EU- and US-Stelara provides support for the robustness of the study results.

The findings of the trial FYB202-01-01 and the design of a repeat phase 1 trial were discussed with regulatory authorities (EMA and US-FDA). The following adjustments were made for the repeat phase 1 PK trial FYB202-01-02: to assure that the ustekinumab dose was similar in all three groups, the setpoints for drug substance concentration and drug product filling volume were adjusted for FYB202 to be more aligned with the reference product Stelara. Furthermore, in accordance with the advice from the authorities, the sample size was planned more conservatively considering the results of the first phase 1 PK trial FYB202- 01-01. Based on this sample size estimation, it was planned to include a substantially larger number of subjects, i.e., 495 randomised subjects to ensure 468 evaluable subjects overall compared to the planned sample size of 350 randomised / 270 evaluable subjects for the first trial FYB202-01-01.

Rustic Study FYB202-01- 02

In general, the design of FYB202-01-02 was similar to that of the predecessor trial FYB202-01-01, except for the number of subjects enrolled. FYB202-01-02 was a multi-centre, randomised, double-blind, 3-arm, parallel-group, single-dose trial in healthy male and female adult subjects aged 18 to 55 years, weighing between 60 and 90 kg and a BMI within the range of 20.5 to 30.0 kg/m2 (in FYB202-01-01 the BMI within the range of 20.5 to 28.0 kg/m2.

A total of 853 subjects were screened; 491 subjects (243 female, 248 male) were randomized and dosed, 386 subjects completed the trial and 5 subjects terminated prematurely (withdrawal of consent). Subjects were administered a single subcutaneous injection of either 45 mg FYB202, Stelara EU or Stelara US. The duration of the trial was 112 days per subject. Overall, 13 protocol deviations were classified as 'major': for 2 subjects, 2 subsequent blood samples were missing and neighbouring blood samples were outside the allowed time window for sampling. For 9 subjects, more than 2 subsequent blood samples were missing. Two (2) subjects were prematurely withdrawn from the PK assessments in the trial due to a positive pregnancy test before the end of the trial. Thus, these 13 subjects were excluded from the PKS. Overall, 491 subjects were included in the SAS, and 478 subjects were included in the PKS.

In FYB202-01-02, the PK analysis was performed based on the PKS (N=478). For PK similarity analysis, an ANCOVA using body weight as a covariate was used. All 90% CIs of the geometric mean ratios were fully contained within the acceptance range of 80.00% to 125.00%. In terms of PK similarity, FYB202-01-02 showed that FYB202 is similar to Stelara EU and Stelara US with respect to both primary endpoints, AUC0-inf and

Cmax. Geometric mean ratios (90% CIs) of AUC0-inf were 102.85% (96.84–109.23%) for the comparison of FYB202 against EU-Stelara and 112.05% (105.24–119.3%) for the comparison of FYB202 against US-Stelara. For the comparison of FYB202 against US-Stelara, the CI did not cross 1, this was not pursued since biosimilarity needs to be shown against the EU-Stelara only. Geometric mean ratios (90% CIs) of Cmax were 97.22% (92.05–102.67%) for the comparison of FYB202 against EU-Stelara and 101.65% (96.19–107.42%) for the comparison of FYB202 against US-Stelara. The inter-subject variability as reflected by CV ANCOVA was between ~30% and ~35% for both primary endpoints, which is in accordance with the estimated variability at the time of study design. Differences in t_{max} between treatment groups based on the non-parametric comparison were not detected.

Notably, in FYB202-01-01, the statistical comparison of Stelara EU and Stelara US revealed nearly identical AUC0-inf with a point estimate of 101.18 %. In contrast, in FYB202-01-02, although PK similarity was demonstrated, AUC0-inf for Stelara EU was slightly larger compared to Stelara US with a point estimate of 109.00 %. Inter-subject variabilities as represented by CV ANCOVA were similar in both phase 1 trials with values between about 30 % and 35 %.

As in the earlier PK study, the analyses of subgroups based on immunogenicity status were merely descriptive for FYB202-01-02 for ADA-negative subjects the Geometric mean ratios (90% CIs) of AUC_{0-inf} were 98.24% (92.57–104.26%) for the comparison of FYB202 against EU-Stelara and 101.66% (95.54–108.17%) for the comparison of FYB202 against US-Stelara. Geometric mean ratios (90% CIs) of C_{max} were 92.68% (86.87–98.89%) for the comparison of FYB202 against EU-Stelara and 97.54% (91.05–104.51%) for the comparison of FYB202 against US-Stelara. The 90% CIs for both comparisons fell within the range of 80.00% to 125.00%. The CHMP noted that the CI falls slightly below unity but the upper bound is very close to 100% and the potential for lower cmax. The applicant was requested to discuss the clinical implications of this apparent difference. For NAb-negative subjects the geometric mean ratios (90% CIs) of AUC_{0-inf} were 105.81% (100.03–111.92%) for the comparison of FYB202 against EU-Stelara however, not crossing 1. The applicant was requested to discuss the clinical implications of this apparent difference. Geometric mean ratios (90% CIs) of C_{max} were 97.54% (91.95–103.46%) for the comparison of FYB202 against EU-Stelara. In their response, the applicant outlined that while the 90% CIs for Cmax in ADA negative subjects and for AUC0-inf for Nab negative subjects do not include unity, these results do not have any clinical impact. The CIs are well contained within the conventional 80 – 125% boundaries, which implies that no clinically meaningful differences are to be expected. Furthermore, the corresponding 95% CIs both cross 100%, thereby confirming that there are no indications of a significant difference. This is agreed upon by the CHMP.

The percentage of subjects with positive ADA and reactive NAb results at the study end was higher after the administration of EU-approved Stelara and US-licensed Stelara compared to FYB202. However, ADA titre levels were largely similar between all three groups.

For both, ADA-negative and NAB-negative subjects, the inter-subject variability for AUC_{0-inf} was about 30%, and therefore about 5 percentage points lower compared to the corresponding inter-subject variability in all subjects (30.39% in ADA-negative subjects and 30.59% in NAB-negative subjects versus 35.29% in all subjects). The inter-subject variabilities for Cmax were comparable (32.46% in ADA-negative subjects versus 34.24% in NAB-negative subjects versus 34.50% in all subjects). Compared to ADA-positive and NAB-reactive subjects, the inter-subject variability for AUC0-inf was markedly reduced (30.39% in ADA-negative subjects versus 44.72% in ADA-positive subjects; 30.59% in NAB-negative subjects versus 51.46% in NAB-reactive

subjects).

In terms of ADAs, the results of the two phase 1 PK trials were comparable: in both trials, the incidences of ADAs were more than 2-fold higher in subjects receiving Stelara EU or Stelara US compared to subjects receiving FYB202. Likewise, in FYB202-01-01, the incidences of NAbs were more than 2-fold higher in subjects receiving the RMPs compared to subjects receiving FYB202. In FYB202-01-02, however, the incidence of NAbs was only slightly higher after the application of the RMPs compared to FYB202. In both trials, the evaluation of different subgroups based on immunogenicity, i.e., ADA-negative, NAb-negative, ADA-positive and NAb-reactive, demonstrated that ADAs, in particular NAbs, seemed to affect the ustekinumab plasma concentrations, thereby increasing variability of PK, independent from the applied treatment. Thus, the relative impact of ADA-positivity/Nab reactivity on ustekinumab exposure was similar in all three treatment groups.

In study FYB202-01-01, differences in the partial AUCs on later time intervals suggest slightly higher clearance for the originator compared to FYB202. When comparing the partial AUCs between the products, the geometric means for partial AUCs in the second and third intervals (i.e. from Day 28 to Day 56 and from Day 56 to Day 84) were about 25% to 28% higher after administration of FYB202 compared to EU-approved Stelara or US-licensed Stelara, while the difference was less pronounced in the first interval until Day 28. No formal statistical analysis of the partial AUCs was conducted. Upon the CHMP's request, the applicant discussed the selection of partial AUCs time-points and lack of inclusion of the final part of the sampling period by providing an overview of results for AUCs (AUC0-t, AUC0-inf and partial AUCs), FYB202 vs. EU Stelara in both PK studies. The applicant submitted justifications regarding the selection of partial AUCs time-points, AUC0-d28, AUCd28-d56, AUCd56-d84 and AUCd56-d112. However, the first time point of 28 days was set far from Tmax (8.5 days) attained in the healthy subcutaneous trial of the reference ustekinumab, which would have been more appropriate to reflect the absorption phase of the proposed biosimilar. A timepoint set based on the average or median PK profiles for ustekinumab as observed in the PK studies would have also been informative for the absorption phase. For the elimination phase, the applicant selected the timepoint of 112 days to have a longer portion of the final elimination phase. Overall, the selection of the partial AUC time points was agreed by the CHMP. The applicant conducted descriptive statistics of pAUCs for all subjects and the ADA negative subjects, respectively, in the PK set for both PK studies. This is agreed as the partial AUC analyses should be handled as descriptive statistics rather than pivotal.

For ADA-negative subjects, all AUCs were comparable between the FYB202 and Stelara EU groups, which also reflects the impact of different ADA incidences between the groups on the PK and correlates with the impact of ADAs on clearance. For all subjects in the PK set in study FYB202-01-02, T1/2 of FYB202 was up to 5% higher (Kel up to 5% lower) compared to Stelara EU, which similarly to study FYB202-01-01 reflects the impact of different ADA incidences between the groups on the PK and correlates with the impact of ADAs on clearance. For ADA-negative subjects, t1/2 and Kel were similar between FYB202 and Stelara EU.

Regarding bridging data from SC to IV administration, if biosimilar comparability in both absorption and elimination is demonstrated for the subcutaneous route, it is acceptable to waive the evaluation of intravenous administration. Extrapolation of the SC data to the IV administration route is agreed based on the results of the study FYB202-01-02, including a demonstration of the comparability in the elimination phases.

The applicant did not apply for the 45 mg/0.5 mL vial presentation which is required for body weight-based dosing of patients with pPsO and a b.w. <60 kg. The absence of the presentation is adequately addressed in SmPC Section 4.2.

Discussion on Pharmacokinetic biosimilarity:
In Study FYB202-01-01, biosimilarity of FYB202 compared to EU-Stelara was not demonstrated for the co-primary endpoint AUC0-inf by the pre-defined primary analysis. During the follow-up SA procedure, the EMA highlighted the PKWP Q&A document 7.1 Biosimilars, "*the existence of a study which demonstrates biosimilarity does not mean that those which do not can be ignored. It should be thoroughly discussed and justified that the biosimilarity claim has been demonstrated overall, and that the evidence from the positive study or studies is sufficient to dominate the results from those that were not."* Based on the findings of the root cause analysis, the drug substance set point for protein concentration and drug product fill volume of FYB202 batches were amended for study FYB202-01-02. However, it remained unclear whether the difference in protein concentration dosed (FYB202 vs EU-Stelara) during FYB202-01-01 could have caused the failure to demonstrate PK comparability in order to accept that the failure of the first study is not indicative of a systematic difference between FYB202 and EU-Stelara, thus the applicant was asked to justify further the claim that protein concentration differences contributed to the failed PK study and discuss any other potential reasons for the study failure. The applicant was also asked to conduct a comparative analysis (FYB202 vs EU Stelara) of pooled data from Study FYB202-01-01 and Study FYB202-01-02.

In their response, the applicant discussed the impact of the protein concentration differences, the impact of differences in the incidences of ADAs and Nabs, the product quality attributes with a potential impact on PK, the investigation on analytical PK assay to measure free ustekinumab concentrations and the potential impact from study conduct and statistical analysis of the clinical trial.

Additional ANCOVA with protein content adjustment indicates that the CIs for the geometric mean ratio for $AUC_{0\text{-}inf}$ and C_{max} decreased approximately 3% and was for FYB202/Stelara EU: 113.50 %, 90% CI (104.69 %;123.04 %) for $AUC_{0\text{-}inf}$, and respectively, 104.87% (97.11%; 113.26%) for C_{max}. After dose adjustment, the CIs for the geometric mean ratio for $AUC_{0\text{-}inf}$ and C_{max} decreased by approximately 5% and was for FYB202/Stelara: 111.96%, 90% CI (103.27%, 121.38%) for $AUC_{0\text{-}inf}$, and respectively, 103.46% (95.80%; 111.73%) for C_{max}. It was also noted that after protein content correction, based on protein concentration as well as on calculated administered dose, whereas for C_{max}, the 90% confidence intervals cross the unity, for $AUC_{0\text{-}inf}$ remains entirely above unity. The results for C_{max} suggest that the treatments have comparable absorption after protein content adjustment. Moreover, the geometric LS mean of AUC0-inf (h*ng/mL) was approximately 15% still higher for FYB202 (4425980) compared to Stelara EU (3768729), even after protein correction. However, the 90% confidence intervals were fully contained within the acceptance range (80% to 125%), for both primary endpoints, $AUC_{0\text{-}inf}$ and C_{max}. Although this was a post-hoc analysis, the CHMP agreed that the differences in protein content may have contributed to the upper boundary of the confidence interval for $AUC_{0\text{-}inf}$ falling outside the 80 – 125% limits in study FYB202-01-01.

Also, a higher ADA incidence of Stelara EU had a possible influence on the differences in the PK between the products. Moreover, from a quality point of view, the claim of biosimilarity is supported by the analytical similarity exercise. Overall, the CHMP agreed that differences in protein content and incidences of ADA could explain the failure to demonstrate PK biosmilarity in study FYB202-01-01.

The applicant was also requested to perform a comparative analysis (FYB202 vs EU Stelara) of pooled data from Study FYB202-01-01, in which the PK biosimilarity was not demonstrated as the geometric mean ratios for AUC0-inf slightly exceeded the upper limit of the acceptance range of 80.00–125.00 %, and Study FYB202-01-02, in which the PK biosimilarity was demonstrated. According to the applicant, the appropriateness of the pooled analysis is based on the following: very similar design, populations (e.g., same inclusion/exclusion criteria), conducts, and methodologies (including the same bioanalytical method with the same sensitivity) of

the two PK studies. Based on the pooled data set, the profiles of the mean concentrations of FYB202 and Stelara EU appear similar. The point estimates and the 90%CI of the primary endpoints $AUC_{0\text{-}inf}$ and C_{max} pooled, i.e., 108.23% (103.13%; 113.59%) for $AUC_{0\text{-}inf}$ and 101.55% (97.05%; 106.27%) for C_{max} were fully contained in the acceptance range 80%-125%. The applicant provided also summary statistics for all PK parameters with exploratory 90% CIs for the respective geometric mean ratios using the same ANCOVA model for all parameters except for t_{max}, where the Hodges-Lehmann estimate for the median difference together with the corresponding 90% CI was provided. All 90% CIs for the geometric mean ratios were within the conventional range of 80 – 125%; however, there is no formal bioequivalence testing for these parameters. The estimate for the median difference in t_{max} showed that there is only a little difference in the t_{max} times between FYB202 and Stelara EU. The applicant outlined that the sample size of Study FYB202-01-02 was increased to increase the power of the study, thereby also reducing the risk of outliers which may negatively impact the analysis. Upon the CHMP's request, the applicant indicated that there was no formal outlier testing performed, but the data were visually inspected to assess whether the data are potentially not log-normally distributed, which may impact the robustness of the analysis on the log scale. The applicant's response suggests and supports the notion that the PK parameters were analysed on an untransformed scale for the parameters Cmax and AUC(inf), because potential outliers became more apparent after log transformation. The CHMP noted that the increase in the sample size whose objective was also to minimize the impact of potential outliers does not appear to have been successful because after log transformation, the applicant suggests skewness worsened. Moreover, the true population distribution may still be log-normal, even if the sampling distribution does not appear to be the case. Overall, the CHMP considers the additional untransformed analysis data-driven and not confirmatory. The issue was not further pursued.

The applicant was asked to elaborate further on the pooled analysis by providing a tipping point analysis, calculating the largest possible (nominal) coverage probability of the confidence interval that would (just) still be within the acceptance range. The EMA MWP was consulted, and a summary of the responses is provided hereafter. The results of the tipping point analysis are reassuring, in line with the Points to Consider on Application with 1. Meta-analyses; 2. One pivotal study.

Additional expert consultation

During the procedure, the Methodology Working Party (MWP) was consulted to address questions from the CHMP. A summary of the responses is provided below.

- **Role of the apparently/potentially conflicting results of Study FYB202-01-01 and Study FYB202-01-02, taking into consideration changes in the sample size and protein content, which have been made to the second study (Study FYB202-01-02)**

MWP considered that in case of apparent failure of a first study to meet the bioequivalence acceptance criteria, a root cause analysis should be done to identify factors explaining that the failure is not indicative of a clinically relevant difference between the test and reference products. If a compelling root cause can be identified, then it may be most appropriate to rely solely on the second 'successful' study. If no compelling root cause can be identified, it may be appropriate to also consider the results of a pooled analysis. In general, the weight that would need to be put on the pooled analysis would depend on the reasons for differences in the studies, noting that a positive second study would be required.

In Fymskina case, the findings of the root cause analysis were considered non compelling and pooled analysis needed to conclude on clinical bioequivalence.

It is a matter of clinical judgement to interpret whether the results of the pooled analysis are relevant, considering any differences between the two studies including any changes that were implemented in the second study to address the concerns identified in the root cause analysis.

In the event that the studies are pooled, as long as the combined analysis yields statistical evidence considerably stronger than $p<0.05$, MWP considered that it may be acceptable as evidence of PK comparability.

MWP commented also that an assessment of study-by-treatment interaction terms based on statistical significance tests cannot be the sole basis for the decision to pool the data. Any suspected interaction, statistically significant or not, should be judged on its clinical relevance.

- **Tipping point analysis (in terms of largest coverage probability of the confidence interval within the acceptance range) for the pooled data setting**

MWP commented that the proposed tipping point analysis would provide an estimate of what value the pooled data would provide and could be useful in helping to interpret the analyses. There is no acceptance criterion for tipping point analysis agreed across all products. Hence, it remains a case-by-case basis. MWP considered that the results of Fymskina are sufficiently compelling from a statistical perspective.

The decision on whether it is appropriate to consider pooling at all, and if so, how much weight to put on the pooled analysis, is also a case-by-case basis, and based on clinical judgement.

2.6.4. Conclusions on clinical pharmacology

Comparative PK studies designed to demonstrate equivalence between a similar biological medicinal product and the reference product with regard to key PK parameters are an essential part of the comparability exercise. In study FYB202-01-01, biosimilarity of FYB202 compared to EU-Stelara was not demonstrated for the co-primary endpoint AUC0-inf by the pre-defined primary analysis, since AUC0-inf exceeded slightly the upper limit of the acceptance range of 80.00–125.00 %. Based on the findings of the root cause analysis, the drug substance set point for protein concentration and drug product fill volume of FYB202 batches were amended for the PK study FYB202-01-02. The biosimilarity of FYB202 compared to EU-Stelara was demonstrated in the FYB202-01-02 study.

Regarding the reasons for the study FYB202-01-01's failure to demonstrate PK biosimilarity of FYB202 to the reference product Stelara EU, the CHMP agrees that the differences in protein content may have contributed to the upper boundary of the confidence interval for $AUC_{0\text{-inf}}$ falling outside the 80 – 125% limits in study FYB202-01-01. Also, the higher ADA incidence of Stelara EU had a possible influence on the differences in the PK between the products. Moreover, from a quality point of view, the claim of biosimilarity is supported by the analytical similarity exercise.

A comparative analysis (FYB202 vs EU Stelara) of pooled data from Study FYB202-01-01, and Study FYB202-01-02, both studies including comparable PK populations, provide supportive reassurance of the biosimilarity between FYB202 and Stelara. The applicant was asked to elaborate further on the pooled analysis by providing a tipping point analysis, calculating the largest possible (nominal) coverage probability of the confidence interval that would (just) still be within the acceptance range and the EMA MWP was consulted. The results of the tipping point analysis are reassuring, in line with the Points to Consider on Application with 1. Meta-analyses; 2. One pivotal study.

Comparability is established for the SC route of administration, for the extrapolation of the SC data to the IV administration route and for the consequential extrapolation to other indications.

The CHMP concludes that, from a clinical pharmacology perspective, FYB202 is biosimilar to EU Stelara.

2.6.5. Clinical efficacy

Table 25 Clinical study phase III

Study ID	**Enrolment status** **Start date** **Total enrolment/ enrolment goal**	**Design** **Control type**	**Study & control drugs** **Dose, route of administration and duration** **Regimen**
FYB202-03-01	Study has been completed. Start date: 23-Sep-2020 Completion date: Until and including Week 28: 14-Oct2021 Until the end of study: 21-Mar-2022 The study was conducted at 27 sites in 4 countries: Estonia (23 [5.9%] patients), Georgia (49 [12.5%] patients), Poland (212 [54.1%] patients) and Ukraine (108 [27.6%] patients).	Phase III A multicentre, double-blind, parallel-group, randomised Phase 3 study designed to demonstrate the clinical similarity of FYB202 compared with Stelara in patients with moderate-to-severe plaque psoriasis regarding efficacy, safety, and immunogenicity.	**Study & control drugs:** FYB202 (proposed biosimilar) Stelara **Dose and Route of administration:** 45mg via subcutaneous injection (SC) **Duration:** Week 0 -week 52 **Regimen:** Patients were randomised 1:1 to receive SC injections of either FYB202 or Stelara 45 mg at Weeks 0 and 4 and at 12-week intervals thereafter (Weeks 16, 28, and 40); the end-of-study visit took place at Week 52.

2.6.5.1. Dose-response study(ies)

Not applicable for biosimilars.

2.6.5.2. Main study(ies)

Study FYB202-03-01, A Randomised, Double-blind, Parallel-group, Phase 3 Study to Compare the Efficacy, Safety, and Immunogenicity of the Proposed Biosimilar Ustekinumab FYB202 to Stelara in Patients with Moderate-to-Severe Plaque Psoriasis

Methods

This was a multicentre, double-blind, parallel-group, randomised Phase 3 study designed to demonstrate the clinical similarity of FYB202 compared with Stelara in patients with moderate-to-severe plaque psoriasis with regard to efficacy, safety, and immunogenicity.

The study was planned to randomise approximately 392 patients with moderate-to-severe plaque psoriasis meeting the eligibility criteria at approximately 24 sites in Europe.

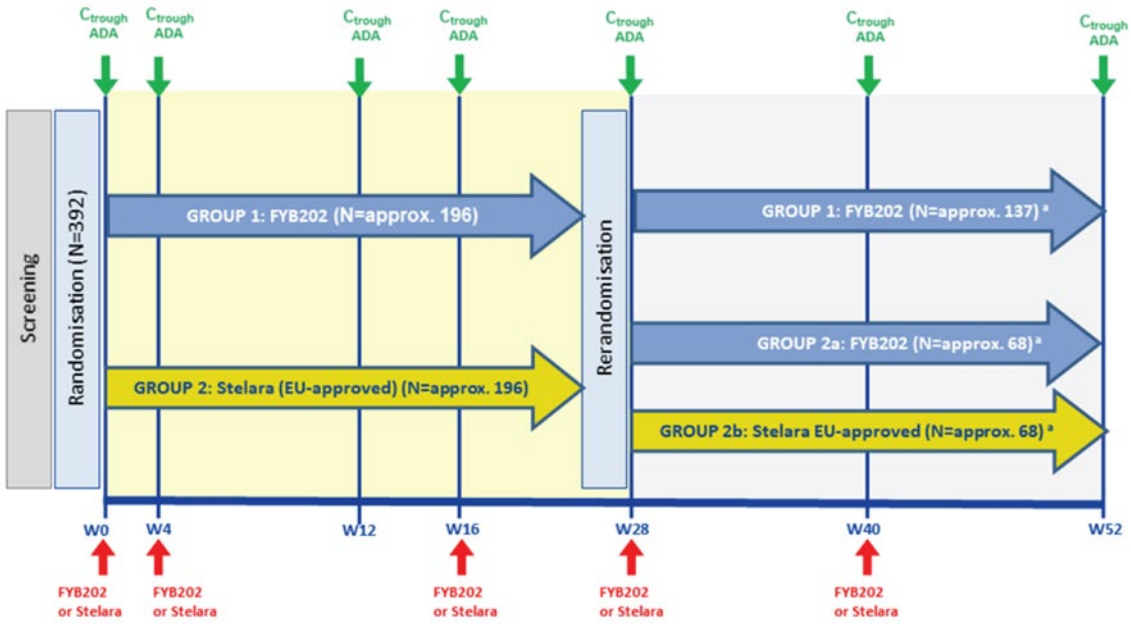
The patients were **randomised** 1:1 to receive SC injections of either FYB202 or EU-Stelara 45 mg at Weeks 0 and 4 and 12-week intervals thereafter (Weeks 16, 28, and 40). The end-of-study visit was at Week 52. Randomisation was stratified by prior inadequate response or intolerance to systemic biological treatment in the opinion of the investigator.

Patients who did not achieve a PASI 75 response at Week 28 (estimated at approximately 30% of patients) were considered non-responders. The non-responders were discontinued from study intervention but were to be followed until the end of the study at Week 52 and were to undergo all study-related assessments.

Patients who achieved PASI 75 response at Week 28 (i.e. responders), were **re-randomised** in a blinded fashion as follows: patients initially randomised to the Stelara treatment arm were re-randomised 1:1 so that 50% of patients in the original Stelara arm received FYB202 and 50% continued to receive Stelara at Weeks 28 and 40; patients originally randomised to FYB202 continued to receive FYB202 at Weeks 28 and 40.

The study duration was approximately 56 weeks for each patient. This included a screening period of up to 4 weeks, a treatment period of 40 weeks, and a final visit 12 weeks after the last dose of study intervention at Week 52.

Figure 14 Study schema



[a] Patients not achieving a PASI 75 response at Week 28 (approximately 30%) were considered non-responders and were discontinued from study intervention but were to be followed until study end and were to undergo all study-related assessments.
ADA = antidrug antibodies, Ctrough = trough ustekinumab concentration, N = number of patients, PASI 75 = 75% or greater reduction (improvement) in Psoriasis Area and Severity Index score, W = week.

- **Study Participants**

Adult male and female patients (⩾18 years of age) with moderate-to-severe plaque psoriasis were eligible for inclusion in this study.

The study was conducted between 23-Sep-2020 and 21-Mar-2022 at 27 sites in 4 countries: Estonia (23 [5.9%] patients), Georgia (49 [12.5%] patients), Poland (212 [54.1%] patients) and Ukraine (108 [27.6%] patients).

Inclusion Criteria

Adult male and female patients had to meet all of the following inclusion criteria:

1. Patients who provided written informed consent and could complete study procedures.

2. Patients who were at least 18 years of age at the time of screening.

3. Patients ≤100 kg body weight at screening and at baseline with stable moderate-to-severe plaque psoriasis for at least 6 months (e.g., no morphology changes or significant flares of disease activity in the opinion of the investigator).

4. Patients with PASI score of at least 12 at screening and at baseline.

5. Patients with involved body surface area (BSA) of at least 10% at screening and at baseline.

6. Patients with a PGA score of at least 3 at screening and at baseline by means of a 5-point scoring scale.

7. Patients who were candidates for systemic therapy or phototherapy.

8. Previous failure, inadequate response in the opinion of the investigator, intolerance, or contraindication to at least 1 conventional anti-psoriatic systemic therapy (including but not limited to ciclosporin, MTX, acitretin, fumaric acid esters, and PUVA).

9. Patients eligible for anti-psoriatic treatment.

10. For female patients (except those at least 2 years post-menopausal or surgically sterilised): a negative serum pregnancy test at screening and at baseline.

11. Female patients of childbearing potential (see definition in Appendix 1 of the protocol Appendix 16.1.1.2) with a fertile male sexual partner must use adequate contraception from screening until 4 months after the last dose of the study intervention. Adequate contraception was defined as using hormonal contraceptives or an intra-uterine device (IUD), combined with at least one of the following forms of contraception: a diaphragm, cervical cap, or a condom. Total abstinence from heterosexual activity, in accordance with the lifestyle of the patient, was acceptable. Female patients did not have to donate ova starting at screening and throughout the clinical study period and for 4 months after study intervention administration.

12. Male patients who are sexually active with women of childbearing potential had to agree that they would use adequate contraception if not surgically sterilised and would not donate sperm from the time of screening until 6 months after the last dose of the study intervention. Adequate contraception for the male patient and his female partner of childbearing potential was defined as using hormonal contraceptives or an IUD combined with at least one of the following forms of contraception: a diaphragm, a cervical cap, or a condom. Total abstinence from heterosexual activity, in accordance with the lifestyle of the patient, was acceptable.

13. Patients with a negative QuantiFERON-TB Gold Plus (QFT-Plus) test for tuberculosis (TB) during screening. Note: Patients with a positive or indeterminate QFT-Plus test were allowed if they had all of the following:

a. No evidence of active TB on chest radiograph within 3 months prior to randomisation

b. Documented history of adequate anti-TB treatment prior to receiving study intervention in accordance with the local recommendations at least 4 weeks prior to randomisation

c. No known exposure to active TB after most recent anti-TB treatment

d. Asymptomatic at screening and baseline

Investigators were asked to contact the medical monitor before enrolling patients receiving active treatment for TB.

Exclusion Criteria

Patients who met any of the following exclusion criteria were not to be randomised in the study:

1. Patients diagnosed with erythrodermic psoriasis, pustular psoriasis, guttate psoriasis, medication-induced psoriasis, any other skin disease, or other systemic inflammatory autoimmune disorder (Crohn’s disease, rheumatoid arthritis, systemic lupus erythematosus, scleroderma) at the time of the screening and baseline visits that would interfere with evaluations of the effect of study intervention on psoriasis.

2. Patients with concomitant psoriatic arthritis at screening or baseline.

3. Patients who had received any topical psoriasis treatment, including corticosteroids within 4 weeks prior to randomisation.

4. Patients who had received the following treatments for psoriasis within the time periods indicated below:

a. PUVA phototherapy and/or ultraviolet B (UVB) phototherapy and/or laser therapy within 4 weeks prior to randomisation

b. Non-biologic psoriasis systemic therapies (e.g., ciclosporin, MTX, and acitretin), tofacitinib, or apremilast within 4 weeks prior to randomisation

c. Adalimumab within 12 weeks prior to randomisation

d. Etanercept or secukinumab within 12 weeks prior to randomisation e. Infliximab, brodalumab, certolizumab pegol, ixekizumab, golimumab, or alefacept within 24 weeks of randomisation

5. Patients who were taking drugs that may cause new onset or exacerbation of psoriasis (including, but not limited to, beta-blockers, lithium, and calcium channel blockers) within 6 months prior to randomisation (week 0) and during the study unless the patient has been on a stable dose for at least 6 months prior to randomisation (week 0) without exacerbation of psoriasis.

6. Patients who had received ustekinumab or any biologics directly targeting IL-12 or IL-23

(e.g., guselkumab, tildrakizumab, or risankizumab).

7. Prior use of 2 or more biological medicinal products for psoriasis.

8. Patients who had received any biological or investigational medicinal product within 5 half-lives, or until the pharmacodynamic effects return to baseline, or 30 days, whichever was longer before starting the study intervention.

9. Ongoing use of prohibited treatments, including systemic corticosteroids. Washout periods detailed in the protocol must be adhered to.

10. Patients with a known history of hypersensitivity to any of the excipients of FYB202 or Stelara.

11. Patients with major surgical intervention planned during the duration of the study.

12. Patients with active infection or a history of infections as follows:

a. Any active infection for which systemic anti-infectives were used within 4 weeks prior to randomisation (see exception noted in inclusion criterion 13)

b. A serious infection, defined as requiring hospitalisation or intravenous antiinfectives, within 8 weeks prior to randomisation

c. Evidence of any clinically relevant bacterial, viral, fungal, or parasitic infection

d. Recurrent or chronic infections or other active infections, that in the opinion of the investigator, might cause this study to be detrimental to the patient

13. Patients who received bacille Calmette-Guerin (BCG) vaccine within 1 year prior to screening or who plan to receive the BCG vaccine during the study period or within 1 year following discontinuation of treatment.

14. Patients who had received or planned to receive live viral or live bacterial vaccination within 4 weeks prior to randomisation, during the study period, or within 15 weeks after treatment discontinuation.

15. Patients with a known history of or positive test for human immunodeficiency virus (HIV) infection.

16. Patients with hepatitis C antibody positivity at screening.

17. Patients with known active or chronic infection with hepatitis B virus at screening.

Patients with an uncontrolled, clinically significant disease such as diabetes mellitus,

cardiovascular disease, renal failure, liver disease, or hypertension.

19. Patients with a history of malignancy (EXCEPT basal cell carcinoma treated at least 5 years prior to screening and no evidence of recurrence in the past 12 weeks).

20. Patients with active neurological disease such as multiple sclerosis, Guillain-Barre syndrome, optic neuritis, transverse myelitis, or a history of neurologic symptoms suggestive of central nervous system demyelinating disease.

21. Patients with moderate to severe heart failure (New York Heart Association class III/IV).

22. Patients with any concurrent medical condition that, in the opinion of the investigator, could cause this study to be detrimental to the patient.

23. Pregnant or nursing (lactating) women.

24. History or evidence of current alcohol or drug abuse within the past 6 months prior to randomisation.

- **Treatments**

Patients were randomly assigned to treatment groups in accordance with the randomisation schedules generated using permuted block randomisation, taking into account the stratification for the first randomisation and the previous treatment group for the re-randomisation. The schedules were generated by an independent statistician. Access to the randomisation code was controlled; no blinded personnel had access to the list until the code was broken after the database lock.

At Week 0 (baseline), 392 patients were planned to be randomised 1:1 in a blinded fashion to either FYB202 or Stelara using an IRT. Patients were randomised sequentially (the lowest sequentially available randomisation number). Patients received a single 45-mg SC injection of either FYB202 or Stelara and were treated at Weeks 0, 4, and 16. Randomisation was stratified by prior inadequate response or intolerance to systemic biological treatment in the opinion of the investigator.

At Week 28, patients who achieved PASI 75 response were automatically re-randomised in a blinded fashion by the IRT. Patients who achieved PASI 75 response and were initially randomised to the Stelara treatment arm were re-randomised 1:1 so that 50% of patients in the original Stelara arm then received 45 mg FYB202 and 50% continued to receive 45 mg Stelara. Patients who achieved PASI 75 response and were originally randomised to FYB202 continued to receive FYB202. Following re-randomisation, patients were treated at Weeks 28 and 40. Patients not achieving PASI 75 response at Week 28 were not treated anymore with study intervention.

Treatments Administered

The study intervention included FYB202 and EU-approved Stelara:

	FYB202 (proposed biosimilar ustekinumab)	EU-approved Stelara (reference ustekinumab)
Trade name	Not applicable	Stelara
Dose	45 mg pre-filled syringe	45 mg pre-filled syringe
Route	SC	SC
Formulation	Solution for injection	Solution for injection
Strength	90 mg/mL	90 mg/mL

After the randomisation at the baseline visit, the patients received single 45-mg SC injections of either FYB202 or Stelara at Weeks 0, 4, and 16.

Re-randomised patients received single 45-mg SC injections of either FYB202 or Stelara at Weeks 28 and 40.

The dose, route of administration, dosage regimen, and treatment period of the proposed biosimilar FYB202 were consistent with those of EU-approved and US-licensed Stelara.

Patients received a single 45-mg SC injection of FYB202 or Stelara at Weeks 0 and 4, and then at 12-week intervals (Weeks 16, 28, and 40), in agreement with the Stelara SmPC.

Patients not achieving PASI 75 response at Week 28 were considered non-responders. Non-responders were discontinued from study intervention but were to be followed until the end of the study and were to undergo all study-related assessments.

The study intervention was administered to patients by an independent, unblinded study intervention administrator using the pre-filled syringe.

- **Objectives**

The primary objective of this study was to evaluate and compare percent improvement in PASI scores over 12 weeks.

The secondary objectives of this study were to:

• Evaluate and compare the efficacy, safety, and immunogenicity over time

• Evaluate and compare ustekinumab trough concentration (Ctrough) over time

• Evaluate and compare efficacy, safety, and immunogenicity in patients following a single transition from Stelara to FYB202

• Evaluate and compare ustekinumab Ctrough in patients following a single transition from Stelara to FYB202

- **Outcomes/endpoints**

Primary Efficacy Assessment – Psoriasis Area and Severity Index

The primary efficacy endpoint was based on the PASI score. It was recommended that the same evaluator (investigator or trained qualified designee) conduct the assessment throughout the study whenever possible. A single score combines the extent of body surface involvement of 4 areas (head, arms, legs, and trunk) with

lesion severity (erythema, desquamation, and infiltration) in each body area (EMA Guideline Psoriasis 2004, Feldman and Krueger 2005, Fredriksson and Pettersson 1978). The scores range from 0 (no disease) to 72 (maximal disease). Clinical studies defined a PASI score >20 (or 10 to 20) for severe psoriasis, and below that for moderate psoriasis (Feldman and Krueger 2005).

Secondary Efficacy Assessments:

Psoriasis Area and Severity Index
Four secondary efficacy endpoints were based on the PASI score.

Physician's Global Assessment
One secondary efficacy endpoint was based on the PGA assessed by the investigator. The PGA assesses the overall psoriasis lesions. The EMA recommended the use of PGA in conjunction with PASI for treatment efficacy assessment in clinical studies of psoriasis (EMA Guideline Psoriasis 2004, CHMP/EWP/2454/02 corr).

There are various forms of PGA that use different descriptions and scoring systems. In this study, a 5-point scale (0 = clear, 1 = almost clear, 2 = mild, 3 = moderate, and 4 = severe) was used according to Langley et al 2015.

Dermatology Life Quality Index
One secondary efficacy endpoint was based on the DLQI, a patient-reported outcome measure. The DLQI is a 10-item, patient-completed, validated questionnaire asking the patients to describe the impact of psoriasis on their lives over the past week (Finlay and Khan 1994).

The questionnaire was filled out on paper and patients were asked to check the box that applied to their situation for each question. The total DLQI score was entered directly in the eCRF. The measure contains questions relating to symptoms and feelings, daily activities, leisure, work and school, personal relationships, and treatment. The possible responses are "very much," "a lot," "a little," "not at all," and "not relevant." Each question was scored 0 ("not at all," "not relevant") to 3 ("very much").

The maximum possible score was 30. The scores indicate effects on the patient's life as follows: scores 0 to 1 = No effect on the patient's life, 2 to 5 = Small effect, 6 to 10 = Moderate effect, 11 to 20 = Very large effect, and 21 to 30 = Extremely large effect (Hongbo et al 2005).

A 5-point change in score from baseline was considered clinically relevant (Basra et al 2008[2]).

Itching Visual Analogue Scale
One of the secondary efficacy endpoints was based on the I-VAS, a patient-reported outcome measure. The I-VAS is a simple, subjective patient-completed measure to document how the patient perceives his or her itch in the past 24 hours.

The I-VAS was composed of 2 horizontal lines drawn on paper. The upper line represented the average itch experienced by the patient over the past 24 hours and the lower line represented the worst itch experienced by the patient over the past 24 hours. The beginning of each line was labelled 0 (no itch) and the end of the line was labelled 10 (worst imaginable itch).

[2] Basra, M. K. A., Fenech, R., Gatt, R. M., Salek, M. S., & Finlay, A. Y. (2008). The Dermatology Life Quality Index 1994–2007: a comprehensive review of validation data and clinical results. British Journal of Dermatology, 159(5), 997-1035.

Patients were asked to indicate the level of their average and worst itch by placing a single mark on the top line and a single mark on the bottom line, respectively. The results were measured and directly recorded in the eCRF. Scoring was evaluated by the investigator as follows: 0 = no pruritus; <3 = mild pruritus; ≥3 to 7 = moderate pruritus; ≥7 to <9 = severe pruritus; 9 = very severe pruritus.

Body Surface Area

The BSA involved in psoriasis was not used for a secondary efficacy endpoint but represented a variable used for inclusion criterion 5. The patients had to have an involved BSA of at least 10% at screening and baseline. As such, any change in the percentage of affected BSA compared to screening and baseline during later visits could be seen as a benefit (in case of a reduction) or of disease worsening (in case of a rise) the patients have from ustekinumab treatment.

The Investigator evaluated the percentage of a patient's BSA that was affected by psoriasis using a continuous scale of 0% (no involvement) to 100% (complete involvement). A 1% involvement corresponds to the size of the patient's entire hand (Van Voorhees et al 2009[3]).

- **Sample size**

A sample size of 392 patients in total, randomised in a 1:1 ratio to both treatment groups, was planned for this study. Assuming a screen failure rate of about 20%, approximately 490 patients were foreseen to be screened.

Approximately 196 patients in each treatment group were required to reach 90% power, using the 2 one-sided test procedures as equivalence tests, and thereby assuming a normal distribution of the primary efficacy variable and no difference between both treatment groups. 196 patients in each treatment group were thus planned to be enrolled, randomised, and treated with study intervention.

Randomisation and Blinding (masking)

Patients were randomly assigned to treatment groups in accordance with the randomisation schedules generated using permuted block randomisation, taking into account the stratification for the first randomisation and the previous treatment group for the re-randomisation. The schedules were generated by an independent statistician. Access to the randomisation code was controlled; no blinded personnel had access to the list until the code was broken after the database lock.

- **Statistical methods**

The primary estimand was planned as a treatment policy strategy:

- Treatment condition: FYB202 or EU-approved Stelara administered according to planned schedule
- Population: patients with moderate-to-severe plaque psoriasis fulfilling the in- and exclusion criteria in the FAS
- Endpoint: Percent improvement in PASI score from baseline to week 12
- Intercurrent event and strategies:

[3] Van Voorhees A, Feldman SR, Koo JYM, Lebwohl MG, Menter A. The psoriasis and psoriatic arthritis pocket guide. Portland: National Psoriasis Foundation; 2009.

All intercurrent events were to be handled according to a treatment policy strategy, i.e. all values of interest will be analysed whether or not the intercurrent event occurred.

The following intercurrent events were considered for this estimand:

- Use of prohibited medication as rescue medication was classified depending on whether it was used as rescue medication prior to the assessment of the primary efficacy endpoint. All medications until and including week 28 were to be reviewed since all PASI assessments until and including week 28 are included in the primary MMRM.
- No assessment of PASI until analysis visit week 12.
- Poor compliance to study intervention prior to week 12: less than two study interventions were applied prior to Visit 3 / Week 12.
- Questionable/spurious data, i.e. any efficacy data that was not assessed according to protocol e.g. procedure-wise, by time window. If the reasons for assessments not performed according to the protocol are related to ADRs, the intercurrent event will be flagged accordingly. All PASI assessments before week 28 will be reviewed since all PASI assessments until and including week 28 were included in the primary MMRM.
- The patient received study intervention from a treatment group the patient was not randomised to. All administrations before week 28 were reviewed since all PASI assessments until and including week 28 were included in the primary MMRM.

• Population level summary: Mean difference between treatment groups (FYB202 and EU-approved Stelara)

The SAP did not state any estimand approaches for the secondary efficacy endpoints:

"If not mentioned otherwise, the analyses of secondary efficacy endpoints described below will be repeated for the FAS and the PPS. Results after re-randomisation at week 28 will be analysed based on the RRAS only. All analyses by visit will be evaluated for the analysis visits defined above.

Primary endpoint

For the primary endpoint, a mixed model repeated measures (MMRM) was planned to be used to analyse the percent improvement in PASI score from baseline to week 12 including the baseline assessment of the PASI score, the baseline assessment of weight and the duration of psoriasis at baseline as covariates, and prior inadequate response or intolerance to systemic biological treatment, the treatment group (FYB202 or EU-approved Stelara), and visit as fixed effects.

Additionally, an interaction term between the treatment group and visit as well as an interaction term between baseline PASI scores and visit was included. The MMRM used all available percent improvements in PASI score from baseline until week 28 for all patients in the FAS for model estimation. Within patients' correlations were modelled using an unstructured variance-covariance matrix with a Kenward-Roger degree of freedom approximation will be used.

Missing data with respect to the percent improvement of PASI score from baseline to week 12 were not imputed explicitly. If a patient had a missing percent improvement in PASI score from baseline to week 12, the model assumed that the patient's missing percent improvement was comparable to the observed percent

improvement in PASI score from baseline of other patients having similar baseline characteristics and a comparable course of percent improvements in PASI score from baseline in the same treatment group.

Additional sensitivity and supplementary analyses were included involving varying assumptions around data handling, assumptions of correlations between responses at multiple visits, and ANCOVA analyses at week 12 using observed cases. The applicant also added that: "The primary efficacy analysis model cannot include patients without any post-treatment assessment of the PASI score. To compensate, a sensitivity analysis will be performed where missing percent improvement in PASI score assessments at week 12 will be imputed using MI; and an ANCOVA model will be used on the imputed dataset to analyse the primary efficacy endpoint."

Results

- Participant flow

The study was conducted between 23-Sep-2020 and 21-Mar-2022 at 27 sites in 4 countries: Estonia (23 [5.9%] patients), Georgia (49 [12.5%] patients), Poland (212 [54.1%] patients) and Ukraine (108 [27.6%] patients).

The study duration was 12.7 months from the first patient's first visit until and including Week 28 (between 23-Sep-2020 and 14-Oct-2021) and 7.3 months after re-randomisation (between 11- Aug-2021 and 21-Mar-2022).

A total of 507 patients were screened (including 30 rescreening visits), and 115 patients were screen failures (including 30 rescreened patients). The resulting 392 patients were randomised to receive study treatment; 197 patients were randomised to receive FYB202 and 195 patients Stelara EU.

There were 387 patients who completed V5 (Week 28) and 5 patients who discontinued the study prematurely before V5 (Week 28). At V5 (Week 28), 9 patients were non-responders and a further 3 patients had other reasons for not being re-randomised.

These other reasons were discontinuation of the study due to AEs or non-attendance of V5 due to patient incompliance.

As such, 375 patients were re-randomised at V5 (Week 28); 189 patients on FYB202 stayed on FYB202 as per study design, 97 patients on Stelara EU were re-randomised to Stelara EU (Stelara EU-Stelara EU), and 89 patients on Stelara EU were re-randomised to FYB202 (Stelara EU-FYB202).

Following initial randomisation, 380 patients completed the study until V7 (Week 52); 191 patients from the FYB202 group and 189 patients from the Stelara EU group.

Following re-randomisation of 375 patients, 372 patients completed the study until V7 (Week 52); 187 patients on FYB202-FYB202, 97 patients on Stelara EU approved Stelara EU, and 88 patients on Stelara EU-FYB202.

Screen failures

Screen failures were defined as all patients who signed the informed consent form (ICF) but discontinued prior to randomisation.

Information collected for screen failures included screening visit date, demographics, date of informed consent, and reason for screening failure. Discontinuation of each screen failure patient should be registered in the Interactive Response Technology (IRT) system.

Rescreening of a patient was allowed in the study and could be performed under certain circumstances. The Investigator should contact the medical monitor before rescreening a patient. Rescreening could only be performed once per screened patient and one of the following criteria had to apply:

- The patient had already consented and fulfilled all eligibility criteria but the enrolment was delayed due to an unexpected change in the patient's personal situation (e.g., an issue with the family).
- The patient did not fulfil all eligibility criteria previously due to an event (e.g., laboratory test result, planned surgery) or any other technical/logistical reason (e.g., laboratory samples lost by courier, malfunction of a device) that had been resolved.
- The patient did not fulfil all eligibility criteria previously but became eligible due to a protocol amendment and change of inclusion and exclusion criteria.

In cases where previous screening procedures were discontinued, and the patient was not randomised, the following procedures had to be undertaken:

- The patient had to sign and date a new ICF prior to being rescreened.
- A new unique patient identification number was assigned to the patient.

Discontinuations
Overall, 5 (1.3%) patients discontinued the study prematurely before V5 (Week 28); 4 patients in the FYB202 group and 1 patient in the Stelara EU group.

One patient in the FYB202 group discontinued the study and study intervention after 1 injection with primary reason protocol deviation. This patient violated the inclusion criterion 13 by being randomised although the QuantiFERON-TB Gold Plus test was positive. The sponsor asked the investigator to discontinue the patient from treatment due to safety reasons before the second dose of study intervention at Week 4.

Another patient in the FYB202 group discontinued the study and study intervention after 1 injection with primary reason AE (Covid-19 pneumonia, Pulmonary embolism).

One patient discontinued the study and treatment (after 1 injection), and another patient discontinued the study and treatment after 3 injections in the FYB202 group, with the primary reason being withdrawal by the subject.

One patient in the Stelara EU group discontinued the study and study intervention after 2 injections with the primary reason being AE (Headache, Dizziness).

There was 1 patient treated with Stelara EU who discontinued the study prematurely at V5 (Week 28) due to the AE Renal cancer metastatic after having received 3 injections of study medication.

There were 3 (0.8%) patients who discontinued the study prematurely after re-randomisation; 2 patients on FYB202 re-randomised to FYB202 and 1 patient on EU-approved Stelara re-randomised to FYB202. These patients received all scheduled study interventions.

One patient in the FYB202-FYB202 group discontinued with the primary reason being withdrawal by the the subject.

One patient in the FYB202-FYB202 group discontinued with primary reason other (the patient was unable to attend the V7 visit within the time limit set by the sponsor).

One patient in the Stelara EU-FYB202 group discontinued with primary reason AE (pregnancy with congenital anomaly).

Note that there were 11 (2.8%) patients who discontinued study intervention (but not the study) before or at V5 (Week 28). 4 patients in the FYB202 group and 5 patients in the Stelara EU group received no further study intervention after V5 because they had not responded to treatment. One of these non-responders discontinued the follow-up phase due to withdrawal by the subject.

The other 2 patients who discontinued study intervention at V5 (but not the study) were in the Stelara EU group: one patient had not attended V5 despite several attempts to contact the patient and could therefore not be re-randomised. The other patient had an unscheduled visit on Day 183, which was counted as an analysis visit V5. The patient continued the study until Day 197 (eCRF visit V5) and discontinued only then because of the AEs Cholestasis and Hepatitis toxic.

None of the re-randomised patients discontinued study intervention (but not the study) after V5 (Week 28).

Removal of Patients from Therapy or Assessment

A patient was considered to have completed the study when he or she completed the final assessment at Week 52 (visit 7). If a patient was discontinued at any time after randomisation into the study, the investigator was to make every effort to follow the patient and complete the early termination assessments. Patients who discontinued the study prematurely were not replaced.

Patients who did not achieve a PASI 75 response at Week 28, were considered to be non-responders and were discontinued from the study intervention. These patients could take other psoriasis-related treatments at the investigator's discretion. Investigators were to make every effort to follow non-responders for the remainder of the study visits (Weeks 40 and 52); non-responders were to undergo all study-related assessments, and their data was to be reported in associated source documents and the eCRF. Collected data included AEs, psoriasis-related treatments and concomitant medication.

Protocol deviations

A total of 17 major protocol deviations (**Table 25**) led to the exclusion of 13 patients from the per protocol analysis set (PPS). Both groups had similar numbers of patients with major protocol deviations (6 patients in the FYB202 and 7 patients in the Stelara EU group).

The more common deviations were measurable blood concentration prior to the first study intervention, study intervention non-compliance and visit window deviations.

Table 26 Major protocol deviations (FAS, N=392)

Deviation	FYB202 (N=197)		Stelara EU (N=195)		Total (N=392)	
	N	(%)	n	(%)	n	(%)
Major protocol deviations						
Any major protocol deviation	6	(3.0)	7	(3.6)	13	(3.3)
Measurable blood concentration at Baseline	3	(1.5)	1	(0.5)	4	(1.0)
Other reason	0	(0.0)	1	(0.5)	1	(0.3)
Study intervention incompliance	3	(1.5)	1	(0.5)	4	(1.0)
Violation of exclusion criterion 7	0	(0.0)	1	(0.5)	1	(0.3)
Visit window deviation at visit 2 - Week 4	1	(0.5)	1	(0.5)	2	(0.5)
Visit window deviation at visit 3 - Week 12	1	(0.5)	4	(2.1)	5	(1.3)

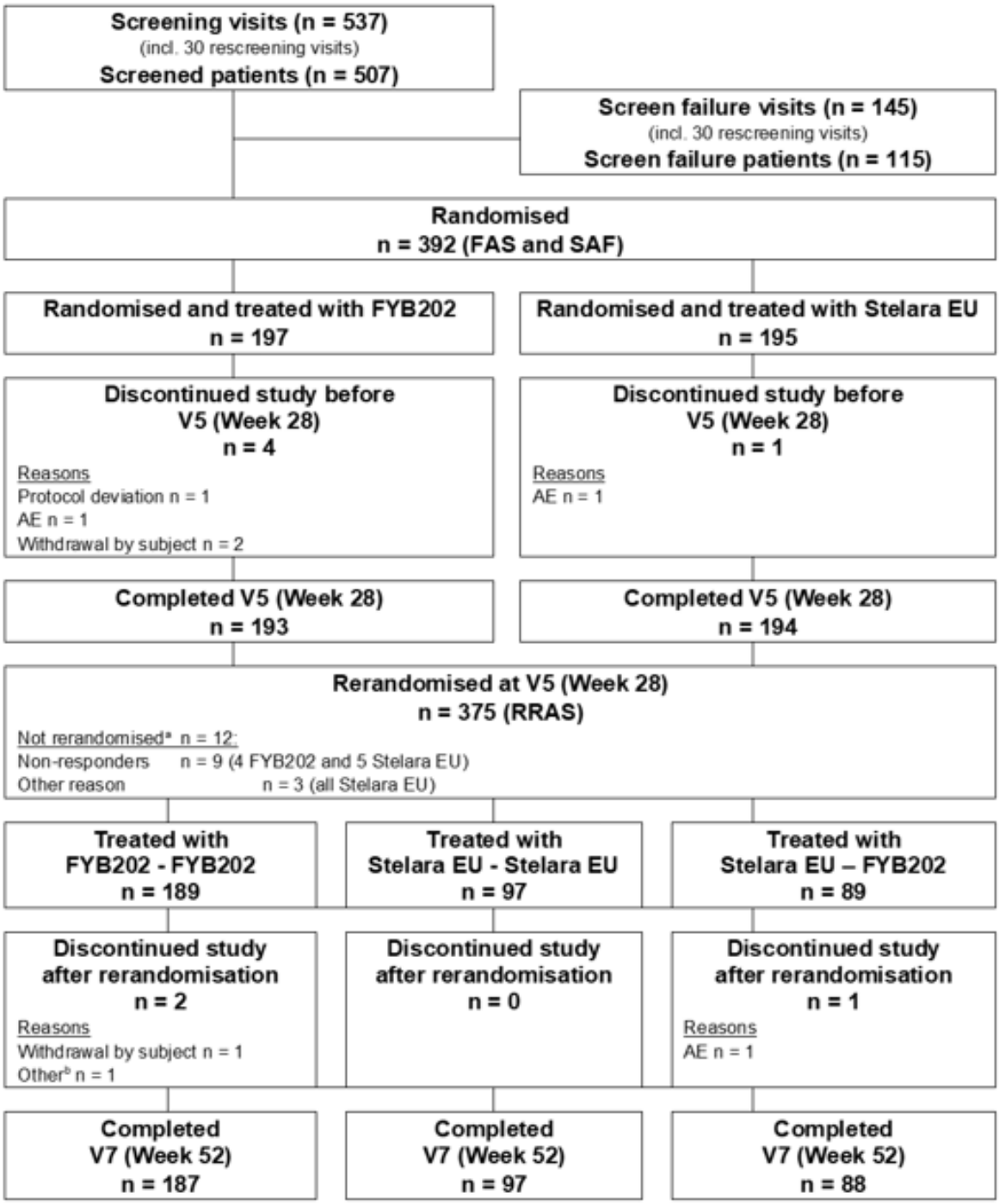
N = number of patients per group, n = number of patients per category, FAS = full analysis set
Other reason for major protocol deviation was "Subject stopped initial contraceptive Lindynette and started using emergency contraceptive instead. Site staff was not informed. Subject became pregnant and gave birth to premature twins with congenital anomaly." (Listing 16.2.2.1)

Minor protocol deviations did not lead to exclusion from any analysis set.

Up to and including V5 (Week 28), 121 minor protocol deviations were reported appearing similar in proportion and type for both treatment groups. Visit window deviations were generally more frequent than other deviations: 48 with FYB202 and 42 with Stelara EU. Other deviations included deviations of study procedures: 6 with FYB202 and also 6 with Stelara EU; violation of inclusion criteria: 8 with FYB202 and 4 with Stelara EU; study intervention incompliance: 3 with FYB202 and 1 with Stelara EU; use of prohibited medication 1 with FYB202 and 2 with Stelara EU.

After re-randomisation, 121 minor protocol deviations were reported, and the proportion and type appeared similar in the 3 treatment groups. Visit window deviations were frequent: 38 (20.1%) with FYB202-FYB202, 28 (28.8%) with Stelara EU-Stelara EU, and 17 (19.1%) with Stelara EU-FYB202. Also, deviations in study procedures-lab issues were frequent: 15 (7.9%) with FYB202-FYB202, 11 (11.3%) with Stelara EU-Stelara EU, and 8 (9.0%) with Stelara EU-FYB202.

Table 27 Patient disposition



AE = adverse event, n = number of patients per category, Stelara EU = EU-approved Stelara, V = visit, FAS = full analysis set, SAF = safety analysis set, RRAS = rerandomised analysis set

[a] including 4 patients who discontinued the study prematurely; one patient withdrew at Week 28 as non-responder, the other reasons for not being rerandomised for a patient was lost to follow-up, for one patient it was AE (Renal cancer metastatic), and for one patient it was AE (Cholestasis, Hepatitis toxic)

[b] Other : "The Patient Was Unable To Attend The V7 Visit Within The Time Limit Set By The Sponsor"

Source: Table 14.1.2.1.1, 14.1.2.1.2, Listing 16.2.1.4

- Recruitment

The study was conducted between 23-Sep-2020 and 21-Mar-2022 at 27 sites in 4 countries: Estonia (23 [5.9%] patients), Georgia (49 [12.5%] patients), Poland (212 [54.1%] patients) and Ukraine (108 [27.6%] patients).

The study duration was 12.7 months from the first patient's first visit until and including Week 28 (between 23-Sep-2020 and 14-Oct-2021) and 7.3 months after re-randomisation (between 11- Aug-2021 and 21-Mar-2022).

- Conduct of the study

There were no important changes to the planned analysis that are considered to impact conclusions. There were several ad hoc analyses performed.

The applicant claimed that the phase III study was conducted in accordance with GCP.

Protocol Amendments

The study protocol was amended once; the original protocol and the amended protocol are provided within the dossier.

Amendment leading to Protocol Version Final 2.0 introduced the following relevant changes:

- Signature page and administrative structure were updated to reflect a change in personnel.
- The number of sites where the study was conducted was changed from "approximately 24" to "27".
- The analysis strategy of having one main analysis based on all data until and including Week 28 and one final analysis including all data until Week 52 was amended to have only one single statistical analysis including all data until Week 52.
- All unblinding procedures that would have been needed for the main analysis were removed.
- The database lock related to the main analysis was removed.
- The main analysis was removed from all statistical analysis sections.
- In the primary analysis using MMRM the interaction term between PASI score and visit was added.

These changes were not considered to have affected the interpretation of study results as they were minor and occurred prior to study unblinding.

There were no changes in the conduct of the study.

Monitoring

This study was monitored for quality assurance at all stages of its development by the clinical research personnel employed by the sponsor or its representative. Monitoring included personal visits and telephone communication to ensure that the investigation was conducted according to the protocol, CRO`s SOPs, Guidelines of Good Clinical Practice, and applicable regulatory requirements. Quality control procedures were applied to each stage of data handling to ensure that all data were reliable and had been processed correctly.

On-site review of eCRFs included a review of forms for completeness and clarity, and consistency with source documents available for each patient.

Data Management and Quality Control

Data management was performed in accordance with the study-specific Data Management Plan, ICH guidelines and the CRO`s data management SOPs and procedures.

Site staff were not granted access to enter patient data in the eCRF system until adequately trained and training documentation was available at the CRO

Study data was entered manually into the eCRF by each site. Edit checks regarding completeness, plausibility, and consistency were performed.

The audit trail in the eCRF system documented all data changes.

Laboratory data were received externally and reconciliation of Laboratory data was performed in accordance with the CRO`s data management SOPs.

Audit and Inspection

Audits by qualified auditors were performed for vendors and clinical sites following the quality assurance audit plan for the study.

Baseline data

Table 28 Demographics (FAS, N=392)

Parameter Category	FYB202 (N=197)	Stelara EU (N=195)	Total (N=392)
Gender [n (%)]			
Male	117 (59.4%)	117 (60.0%)	234 (59.7%)
Female	80 (40.6%)	78 (40.0%)	158 (40.3%)
Childbearing potential	56 (28.4%)	53 (27.2%)	109 (27.8%)
Post-Menopausal	22 (11.2%)	23 (11.8%)	45 (11.5%)
Surgically Sterile	2 (1.0%)	2 (1.0%)	4 (1.0%)
Race [n (%)]			
White	197 (100.0%)	195 (100.0%)	392 (100.0%)

Parameter Category	FYB202 (N=197)	Stelara EU (N=195)	Total (N=392)
Ethnicity [n (%)]			
Not Hispanic or Latino	197 (100.0%)	195 (100.0%)	392 (100.0%)
Age at Screening [years]			
N	197	195	392
missing values	0	0	0
Mean (SD)	41.3 (12.87)	42.1 (13.20)	41.7 (13.02)
Median	39.0	42.0	41.0
Min - Max	19 - 74	18 - 77	18 - 77
Q1 - Q3	31.0 - 50.0	32.0 - 52.0	32.0 - 50.0
BMI at Screening [kg/m^2]			
N	197	195	392
missing values	0	0	0
Mean (SD)	26.60 (4.214)	27.42 (4.355)	27.01 (4.299)
Median	26.56	27.15	26.79
Min - Max	18.2 - 38.9	16.9 - 39.3	16.9 - 39.3
Q1 - Q3	23.63 - 29.01	24.44 - 30.22	24.10 - 29.76

N = number of patients per group, n = number of patients per category, FAS = full analysis set, SD = standard deviation, Q1 – Q3 = interquartile range, Min = minimum, Max = maximum

- **Baseline data**

Table 29 Baseline Disease Characteristics

Parameter Category	FYB202 (N=197) n (%)	Stelara EU (N=195) n (%)	Total (N=392) n (%)
Time since onset of psoriasis [years]			
N	197	195	392
missing values	0	0	0
Mean (SD)	16.46 (10.872)	15.88 (10.126)	16.17 (10.498)
Median	15.10	13.10	14.10
Min - Max	1.1 - 47.1	1.3 - 51.1	1.1 - 51.1
Q1 - Q3	7.20 - 23.10	8.10 - 21.10	8.10 - 22.10
Time since onset of psoriasis [years] in female patients			
N	80	78	158
missing values	0	0	0
Mean (SD)	18.39 (11.383)	18.52 (11.502)	18.46 (11.406)
Median	17.60	16.65	17.15
Min - Max	1.1 - 47.1	1.9 - 51.1	1.1 - 51.1
Q1 - Q3	9.45 - 24.90	9.20 - 27.00	9.20 - 25.90

Time since onset of psoriasis [years] in male patients			
N	117	117	234
missing values	0	0	0
Mean (SD)	15.13 (10.350)	14.12 (8.709)	14.62 (9.558)
Median	12.50	12.70	12.60
Min - Max	1.3 - 44.3	1.3 - 38.1	1.3 - 44.3
Q1 - Q3	7.00 - 20.10	8.00 - 18.10	7.10 - 19.10
Time since onset of psoriasis (categorized) [n (%)]			
<= 10 years	64 (32.5%)	58 (29.7%)	122 (31.1%)
> 10 years and <= 20 years	68 (34.5%)	81 (41.5%)	149 (38.0%)
> 20 years	65 (33.0%)	56 (28.7%)	121 (30.9%)
Any prior treatment for psoriasis [n (%)]			
No	2 (1.0%)	2 (1.0%)	4 (1.0%)
Yes	195 (99.0%)	193 (99.0%)	388 (99.0%)
Any prior systemic biological treatment for psoriasis [n (%)]			
No	157 (79.7%)	159 (81.5%)	316 (80.6%)
Yes	40 (20.3%)	36 (18.5%)	76 (19.4%)
Inadequate response or intolerance to biological treatments [n (%)]			
Yes	2 (5%)	5 (13.9%)	7 (9.2%)
No	38 (95%)	31 (86.1%)	69 (90.8%)

N = number of patients per group, n = number of patients per category, FAS = full analysis set, SD = standard deviation, Q1 – Q3 = interquartile range, Min = minimum, Max = maximum

Table 30 Efficacy parameters at baseline (FAS, N=392)

Parameter Category or statistic	FYB202 (N=197) n (%)	Stelara EU (N=195) n (%)	Total (N=392) n (%)
PASI Score at Baseline			
N	197	195	392
missing value	0	0	0
Mean (SD)	24.07 (8.484)	24.75 (9.999)	24.41 (9.263)
Median	21.60	21.80	21.70
Min - Max	12.3 - 52.8	12.0 - 63.3	12.0 - 63.3
Q1 - Q3	18.80 - 28.20	17.70 - 30.60	18.00 - 28.85
PGA at Baseline [n (%)]			
N	197	195	392
3 = moderate	133 (67.5%)	139 (71.3%)	272 (69.4%)
4 = severe	64 (32.5%)	56 (28.7%)	120 (30.6%)
DLQI at Baseline			
N	197	194	391
missing value	0	1	1
Mean (SD)	13.1 (6.37)	13.6 (6.53)	13.4 (6.45)
Median	13.0	13.0	13.0
Min - Max	2 - 30	1 - 30	1 - 30

- **Numbers analysed**

Table 31 Analysis sets and reasons for exclusion from PPS or RRAS sets (Randomised patients, N=392)

alysis set ason for exclusion from PPS or RRAS	FYB202 (N=197)		Stelara EU (N=195)		Total (N=392)	
	n	(%)	n	(%)	n	(%)
S	197	(100.0)	195	(100.0)	392	(100.0)
F	197	(100.0)	195	(100.0)	392	(100.0)
S	191	(97.0)	188	(96.4)	379	(96.7)
son for exclusion from PPS						
Major Protocol Deviation	6	(3.0)	7	(3.6)	13	(3.3)
AS	189	(95.9)	186	(95.4)	375	(95.7)
son for exclusion from RRAS						
Non-Responder	4	(2.0)	5	(2.6)	9	(2.3)
Discontinued study before V5 (Week 28)	4	(2.0)	1	(0.5)	5	(1.3)
Not rerandomised for other reason	0	(0.0)	3	(1.5)	3	(0.8)

N = number of patients per group, n = number of patients per category, FAS = full analysis set, PPS = per protocol set, SAF = safety analysis set, RRAS = rerandomised analysis set, Not rerandomized for other reason included a patient who did not appear at the site at Visit 5 for re-randomisation), and two other patients (early termination at Visit 5 due to AEs)

Outcomes and estimation

- **Outcomes and estimation**

Primary efficacy endpoint

The primary efficacy endpoint, the percent improvement in PASI score from baseline (Week 0) to Week 12, was calculated to evaluate and compare both treatment groups as stated in the primary objective. The PASI score was calculated and analysed using an MMRM as specified. The MMRM included the baseline PASI score, baseline weight, time since onset of psoriasis and prior inadequate response or intolerance to systemic biological treatment as independent variables; estimates were thus adjusted for these parameters.

The null hypothesis of non-equivalence was tested using the estimated difference between FYB202 and Stelara EU in the % improvement from baseline to Week 13 of the PASI score.

Analysis of equivalence

The summary statistics and the MMRM model statistics showed that:

- The estimated PASI score improvement from baseline (Week 0) to Week 12 was 79.51% (95% CI: 74.64%; 84.38%) in patients treated with FYB202 and 76.24% (95% CI: 71.45%; 81.02%) in patients treated with Stelara EU.
- The estimated difference between both treatments was 3.27% with a two-sided 95% CI of [-0.90%; 7.44%].
- The two-sided 95% CI of [-0.90%; 7.44%] for the difference was completely contained in the pre-defined equivalence margin of the EU analysis of [-11% to 11%].

Additional sensitivity analyses were conducted as outlined below:

Table 32 Summary of sensitivity analyses displaying LS mean difference between FYB202 and Stelara EU in %improvement in PASI score from baseline to Week 12 (EU and US analysis)

Method, Set, Data	LS mean difference FYB202 – Stelara EU	SE	2-sided 90% CI	2-sided 90% CI within [-10% to +10%]	2-sided 95% CI	2-sided 95% CI within [-11% to +11%]	Table US EU
MMRM, FAS, Data up to and including Week 12							
	3.11	2.15	[-0.43; 6.66]	Yes	[-1.11; 7.34]	yes	14.2.2.1.1 14.2.2.1.2
ANCOVA, FAS							
	3.15	2.15	[-0.39; 6.68]	Yes	[-1.08; 7.37]	yes	14.2.2.2.1 14.2.2.2.2
ANCOVA, FAS - Multiple imputation							
	3.15	2.14	[-0.38; 6.68]	Yes	[-1.05; 7.35]	yes	14.2.2.3.1 14.2.2.3.2
MMRM, FAS Data up to and including Week 28, including patient discontinuation of study status prior to visit V4/Week 16 (Yes/No) as additional fixed effect							
	3.33	2.12	[-0.17; 6.83]	Yes	[-0.84; 7.50]	yes	14.2.2.4.1 14.2.2.4.2
MMRM, FAS Data up to and including Week 28, including patient discontinuation of study status prior to visit V3/Week 12 (Yes/No) as additional fixed effect							
	3.33	2.12	[-0.17; 6.83]	Yes	[-0.84; 7.50]	yes	14.2.2.5.1 14.2.2.5.2
MMRM, FAS Data up to and including Week 28, including patient any major protocol deviation status (Yes/No) as additional fixed effect							
	3.20	2.13	[-0.30; 6.71]	Yes	[-0.98; 7.38]	yes	14.2.2.7.1 14.2.2.7.2
MMRM, FAS Data up to and including Week 28, including major protocol deviation category as additional fixed effect							
	3.27	2.13	[-0.24; 6.78]	Yes	[-0.91; 7.46]	yes	14.2.2.8.1 14.2.2.8.2

ANCOVA = Analysis of Covariance, CI = confidence interval (based on normal approximation), FAS = full analysis set, LS = least squares, MMRM = Mixed Model Repeated Measures, SE = standard error, V = Visit
Sources: directly in table

A tipping point analysis for the primary efficacy endpoint to assess possible deviations from the MAR assumption underlying the MMRM analyses was performed additionally. The analyses used multiple imputation under a MNAR assumption and added various constant shifts of θ in various directions to the imputed values in each treatment group. The shift was broadened with each analysis performed until the equivalence criterion was no longer achieved (Table 14.2.2.9.2). A summary of the results is presented in Table 11-3 (EU analysis) and Table 11-4 (US analysis).

The two-sided 90% CI of [-0.22%; 6.77%] was completely contained in the predefined equivalence margin of the US analysis of [-10% to 10%].

- The null hypothesis of non-equivalence was rejected for the EU and US analyses, and equivalence of both treatments could be concluded.
- The descriptive analysis of the % improvement of the PASI yielded similar results compared to the LS means resulting from the MMRM: The arithmetic mean (SD) PASI score improvement from baseline (Week 0) to Week 12 was 83.00% (18.882%) in patients treated with FYB202 and 79.29% (23.037%) in patients treated with Stelara EU (see also **Table 32**).

Table 33 Comparison of % improvement in PASI score from baseline to Week 12 (FAS, N=392, EU and US analysis)

		MMRM Least Squares estimation					
Visit / Week Treatment group **Difference** Analysis	**N**	**n[a]**	**nmiss**	**LS mean[b]**	**SE**	**2-sided 95% CI**	**2-sided 90% CI**
V3 / Week 12							
FYB202	197	195	2	79.51	2.48	[74.64; 84.38]	
Stelara EU	195	195	0	76.24	2.44	[71.45; 81.02]	
Difference: FYB202 - Stelara EU				**3.27**	**2.12**	[-0.90; 7.44]	[-0.22; 6.77]
EU analysis		2-sided **95%** CI contained in [-11%; 11%][c] : yes					
US analysis		2-sided **90%** CI contained in [-10%; 10%][d] : yes					

CI = confidence interval (based on normal approximation), FAS = full analysis set, LS = least squares, N = total number of patients in the treatment group and analysis set, n / nmiss = number of non-missing / missing assessments, MMRM = Mixed Model Repeated Measures, PASI = Psoriasis Area and Severity Index, SE= standard error, V = Visit

[a] For the calculation of LS means based on the MMRM, patients with missing assessments at all post-baseline visits until Week 28 were not considered. Data up to and including Week 28.

[b] Estimates were adjusted for baseline PASI score, baseline weight, time since onset of psoriasis and prior inadequate response or intolerance to a systemic biological treatment.

[c] If the confidence interval for difference in LS means was completely contained in the interval [-11%; 11%], FYB202 and EU-approved Stelara were considered equivalent.

[d] If the confidence interval for difference in LS means was completely contained in the interval [-10%; 10%], FYB202 and EU-approved Stelara were considered equivalent.

Sensitivity analyses

The sensitivity analyses for the primary endpoint at V3 (Week 12) were performed using different MMRMs and ANCOVA for multiple imputations.

All sensitivity analyses and the primary efficacy analysis for the primary endpoint showed a similar difference for the % improvement in PASI score between FYB202 and Stelara EU treatment groups, the 95% CIs and the 90% CIs were completely contained within the respective equivalence margin for the EU and US analyses.

All sensitivity analyses supported the results of the primary analysis: the clinical equivalence of the two treatments with respect to the primary efficacy endpoint.

Secondary Efficacy Endpoints

Percent improvement of PASI score

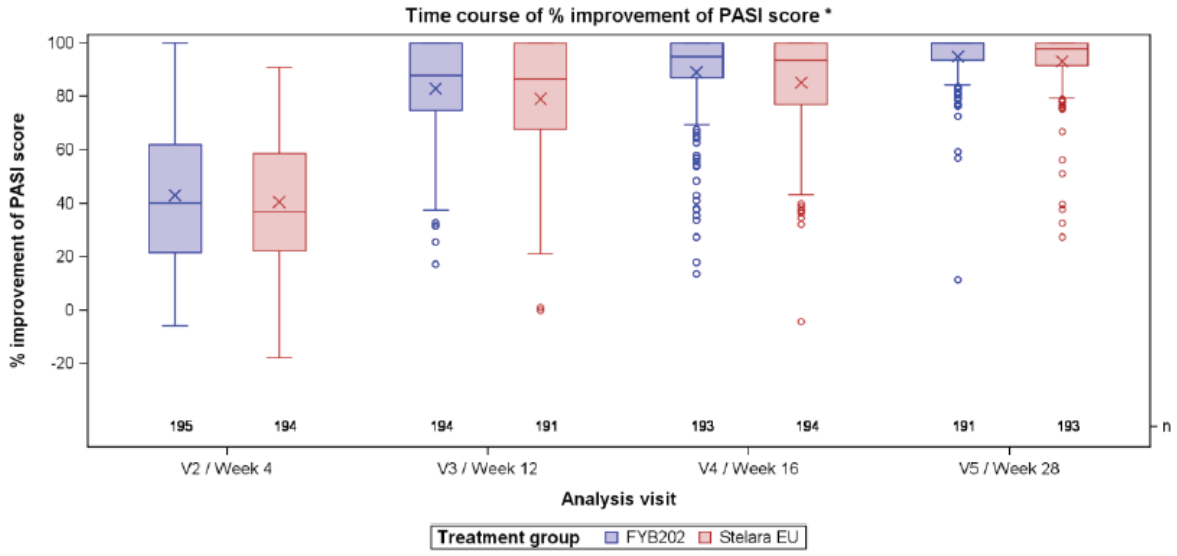
The secondary efficacy endpoint percent improvement in PASI score from baseline (Week 0) to Weeks 4, 16, 28, 40, and 52 were analysed. Analyses were based on the FAS, the PPS and the RRAS.

The median PASI score in the FYB202 and Stelara EU groups improved in a similar way from baseline to Week 4 by approximately 40%. As early as Week 12, the median improvement was more than 85% in both treatment groups, and full improvement was observed at Week 28, with a lower 75% quartile of more than 90% improvement. A sustained full improvement was visible from re-randomisation at Week 28 onwards in the group with a single transition from Stelara EU to FYB202 and very similarly in the groups keeping to their initial randomised treatment.

The MMRM statistics showed the following results:

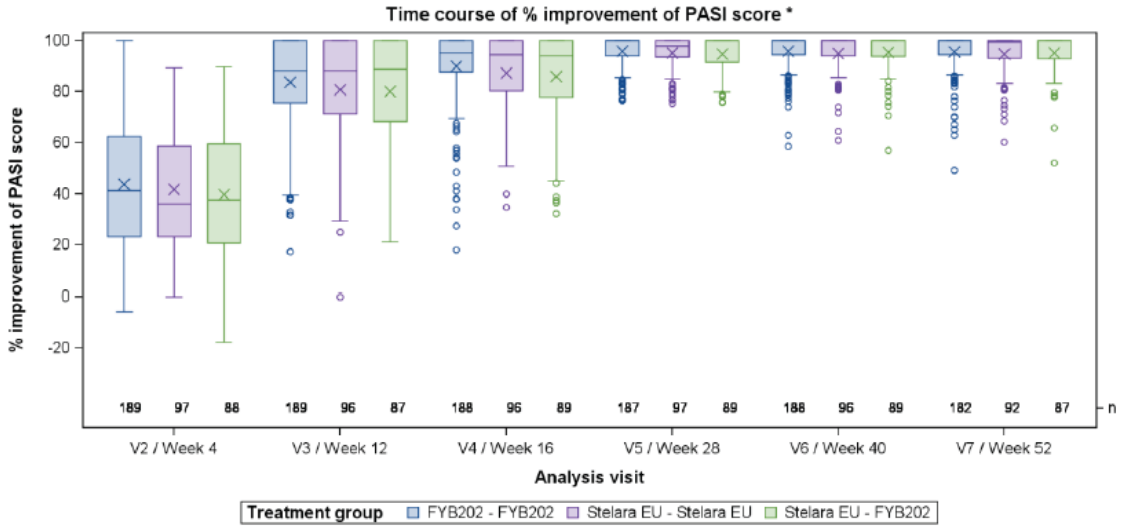
- The estimated (LS) mean PASI score improved similarly from baseline to Weeks 4, 16, and 28 in patients treated with FYB202 and Stelara EU.
- The estimated (LS) mean differences between both treatments were between 1.40% and 3.50%. The two-sided 95% CIs for the differences at Weeks 4, 16, and 28 were well comparable to the 95% CI for the difference seen for the primary efficacy endpoint at Week 12.

Figure 15 Percent improvement in PASI score from baseline (Week 0) to Weeks 4, 16, and 28 (before re-randomisation, FAS, N=392)



Legend below next figure.

Figure 16 Percent improvement in PASI score from baseline (Week 0) to Weeks 4, 16, 28, 40, and 52 (RRAS, N=375)



Boxplot markers: x = Mean, line = Median, lower box boundary = 1st quartile, upper box boundary = 3rd quartile, o = Outlier (below 1.5*IQR); Upper whisker: maximum value below upper fence; Lower whisker: minimum value above lower fence; Upper fence: 1.5 times the IQR above the 3rd quartile; Lower fence: 1.5 times the IQR below the 1st quartile; IQR = inter quartile range: 3rd quartile - 1st quartile, FAS = full analysis set, PASI = Psoriasis Area and Severity Index , RRAS = rerandomised analysis set, V = visit,

Table 34 Raw PASI score and % improvement of PASI score from baseline (Week 0) to each subsequent visit until V5/ Week 28 (FAS, N=392)

Analysis Visit	Raw PASI score FYB202 (N=197)	Raw PASI score Stelara EU (N=195)	% Improvement of PASI score[a] FYB202 (N=197)	% Improvement of PASI score[a] Stelara EU (N=195)
Baseline V1/ Week 0				
n	197	195		
missing value	0	0		
Mean (SD)	24.07 (8.484)	24.75 (9.999)		
Median	21.60	21.80		
Min - Max	12.3 - 52.8	12.0 - 63.3		
Q1 - Q3	18.80 - 28.20	17.70 - 30.60		
V2 / Week 4				
n	195	194	195	194
missing value	2	1	2	1
Mean (SD)	13.66 (8.273)	14.42 (8.437)	42.98 (24.988)	40.50 (23.992)
Median	12.00	12.45	40.14	36.95
Min - Max	0.0 - 53.4	1.6 - 49.0	-5.7 - 100.0	-17.8 - 91.0
Q1 - Q3	8.10 - 17.20	8.70 - 17.20	21.67 - 62.12	22.22 - 58.73

Analysis Visit	Raw PASI score FYB202 (N=197)	Stelara EU (N=195)	% Improvement of PASI score[a] FYB202 (N=197)	Stelara EU (N=195)
V3 / Week 12				
n	194	191	194	191
missing value	3	4	3	4
Mean (SD)	4.13 (5.684)	5.04 (6.435)	83.00 (18.882)	79.29 (23.037)
Median	2.40	2.40	88.11	86.67
Min - Max	0.0 - 39.2	0.0 - 38.2	17.4 - 100.0	0.0 - 100.0
Q1 - Q3	0.00 - 5.40	0.00 - 7.60	74.82 - 100.00	67.87 - 100.00
V4 / Week 16				
n	193	194	193	194
missing value	4	1	4	1
Mean (SD)	2.72 (5.436)	3.59 (5.607)	89.23 (16.768)	85.31 (19.136)
Median	1.00	1.25	95.10	93.67
Min - Max	0.0 - 45.6	0.0 - 40.2	13.6 - 100.0	-4.1 - 100.0
Q1 - Q3	0.00 - 2.40	0.00 - 5.00	87.18 - 100.00	77.24 - 100.00
V5 / Week 28				
n	191	193	191	193
missing value	6	2	6	2
Mean (SD)	1.34 (4.017)	1.79 (3.947)	95.06 (9.528)	93.15 (11.989)
Median	0.00	0.40	100.00	98.00
Min - Max	0.0 - 46.8	0.0 - 29.5	11.4 - 100.0	27.5 - 100.0
Q1 - Q3	0.00 - 1.20	0.00 - 2.00	93.62 - 100.00	91.67 - 100.00

PASI = Psoriasis Area and Severity Index, N = number of patients per group, n = number of patients per category, FAS = full analysis set, SD = standard deviation, Q1 – Q3 = interquartile range, Min = minimum, Max = maximum, V = visit

[a] Relative to Baseline V1/ Week0

Table 35 Raw PASI score and % improvement of PASI score from baseline (Week 0) to V5/ Week 28, V6/ Week 40, and V7 (Week 52) (RRAS, N=375)

Analysis Visit	Raw PASI score			% Improvement of PASI score[a]		
	FYB202 - FYB202 (N=189)	Stelara EU - Stelara EU (N=97)	Stelara EU - FYB202 (N=89)	FYB202 - FYB202 (N=189)	Stelara EU - Stelara EU (N=97)	Stelara EU - FYB202 (N=89)
Baseline V1/ Week 0						
n	189	97	89			
missing value	0	0	0			
Mean (SD)	23.90 (8.138)	24.21 (9.839)	24.96 (9.777)			
Median	21.60	21.60	21.60			
Min - Max	12.3 - 52.8	12.0 - 63.3	12.3 - 57.6			
Q1 - Q3	18.80 - 28.20	17.70 - 27.90	18.00 - 31.30			
V5 / Week 28						
n	187	97	89	187	97	89
missing value	2	0	0	2	0	0
Mean (SD)	0.91 (1.602)	1.11 (1.608)	1.30 (2.045)	96.02 (6.068)	95.21 (6.645)	94.73 (7.587)
Median	0.00	0.40	0.00	100.00	98.00	100.00
Min - Max	0.0 - 10.5	0.0 - 6.8	0.0 - 8.6	76.6 - 100.0	75.4 - 100.0	75.9 - 100.0
Q1 - Q3	0.00 - 1.20	0.00 - 1.50	0.00 - 2.10	94.17 - 100.00	93.71 - 100.00	91.67 - 100.00
V6 / Week 40						
n	188	96	89	188	96	89
missing value	1	1	0	1	1	0
Mean (SD)	0.95 (1.902)	1.11 (1.779)	1.11 (2.112)	95.90 (7.065)	95.04 (8.144)	95.39 (7.873)
Median	0.00	0.00	0.00	100.00	100.00	100.00
Min - Max	0.0 - 15.2	0.0 - 7.1	0.0 - 13.4	58.7 - 100.0	60.8 - 100.0	57.2 - 100.0
Q1 - Q3	0.00 - 1.20	0.00 - 1.30	0.00 - 1.80	94.64 - 100.00	94.09 - 100.00	93.88 - 100.00
V7 / Week 52						
n	182	92	87	182	92	87
missing value	7	5	2	7	5	2
Mean (SD)	0.98 (2.026)	1.12 (1.724)	1.18 (2.331)	95.71 (8.020)	94.68 (8.350)	95.20 (8.096)
Median	0.00	0.05	0.00	100.00	99.62	100.00
Min - Max	0.0 - 14.2	0.0 - 7.0	0.0 - 15.0	49.1 - 100.0	60.2 - 100.0	52.1 - 100.0
Q1 - Q3	0.00 - 1.20	0.00 - 1.50	0.00 - 1.90	94.57 - 100.00	93.24 - 100.00	92.88 - 100.00

PASI = Psoriasis Area and Severity Index, N = number of patients per group, n = number of patients per category, FAS = full analysis set, SD = standard deviation, Q1 – Q3 = interquartile range, Min = minimum, Max = maximum, V = visit

[a] Relative to Baseline V1/ Week0

Table 36 Comparison of % improvement in PASI score from baseline to Week 4, 16, and 28 (MMRM, FAS, N=392)

Visit / Week Treatment group Difference	N	MMRM Least Squares estimation n[a]	nmiss[a]	LS mean[b]	SE	2-sided 95% CI
V2 / Week 4						
FYB202	197	195	2	39.63	2.64	[34.45; 44.81]
Stelara EU	195	195	0	37.30	2.60	[32.20; 42.40]
Difference: FYB202 - Stelara EU				**2.33**	**2.47**	**[-2.54; 7.20]**
V4 / Week 16						
FYB202	197	195	2	85.72	2.35	[81.10; 90.34]
Stelara EU	195	195	0	82.23	2.31	[77.70; 86.76]
Difference: FYB202 - Stelara EU				**3.50**	**1.81**	**[-0.06; 7.05]**
V5 / Week 28						
FYB202	197	195	2	91.50	2.12	[87.34; 95.67]
Stelara EU	195	195	0	90.10	2.07	[86.04; 94.16]
Difference: FYB202 - Stelara EU				**1.40**	**1.09**	**[-0.74; 3.54]**

CI = confidence interval (based on normal approximation), FAS = full analysis set, LS = least squares, N = total number of patients in the treatment group and analysis set, n / nmiss = number of non-missing / missing assessments, MMRM = Mixed Model Repeated Measures, PASI = Psoriasis Area and Severity Index, SE = standard error, V = Visit

[a] For the calculation of LS means based on the MMRM, patients with missing assessments at all post-baseline visits until Week 28 were not considered. Data up to Week 28 was included in the MMRM.

[b] Estimates were adjusted for baseline PASI score, baseline weight, time since onset of psoriasis and prior inadequate response or intolerance to a systemic biological treatment.

Psoriasis Area and Severity Index Raw Scores

The secondary efficacy endpoint raw PASI scores at baseline and Weeks 4 and 12 were analysed. For completeness, the whole course of raw PASI scores is visualised for FAS, PPS and RRAS.

The raw PASI scores at Week 4 and Week 12 together with the % improvement from baseline V1 (Week 0) are presented in Table below.

The median PASI score in the FYB202 and Stelara EU improved from 21.60 points (FYB202) and 21.80 points (Stelara EU) at baseline to 12.00 points (FYB202) and 12.45 points (Stelara EU) at Week 4.

At later visits (Weeks 12, 16, and 28) the median PASI score further improved to <3 points. A sustained full improvement with median PASI scores <1 point was observed from re-randomisation at Week 28 onwards in the single transition Stelara EU – FYB202 group and the groups keeping to their initial randomised treatment.

Figure 17 Raw PASI score at screening, baseline (Week 0), Weeks 4, 16, and 28 (before re-randomisation, FAS, 392)

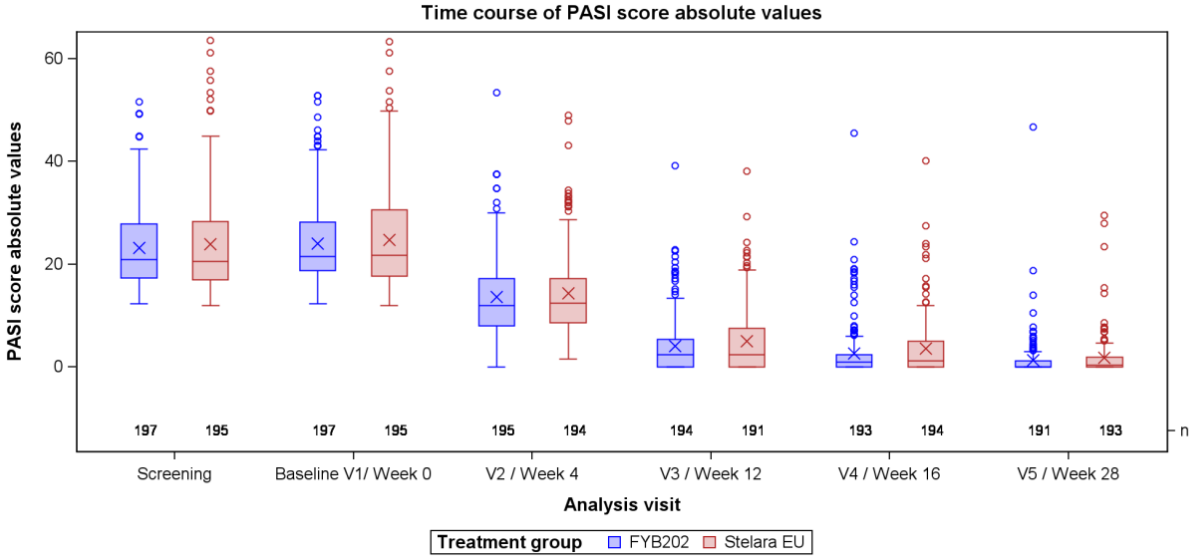
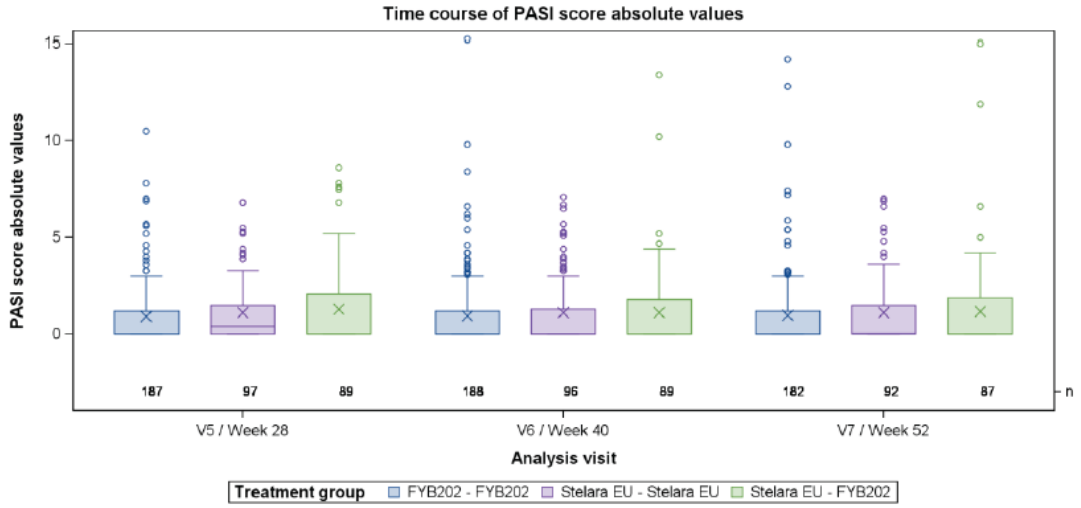


Figure 18 Raw PASI score at Weeks 28, 40, and 52 (After rerandomisation, RRAS, N=375)



Boxplot markers: x = Mean, line = Median, lower box boundary = 1st quartile, upper box boundary = 3rd quartile, o = Outlier (above 1.5*IQR); Upper whisker: maximum value below upper fence; Lower whisker: minimum value above lower fence; Upper fence: 1.5 times the IQR above the 3rd quartile; Lower fence: 1.5 times the IQR below the 1st quartile; IQR = inter quartile range: 3rd quartile - 1st quartile
FAS = full analysis set, N = total number of patients in the treatment group and analysis set, PASI = Psoriasis Area and Severity Index, RRAS = rerandomised analysis set, V = visit,

Psoriasis Area and Severity Index 75 and 90

The secondary efficacy endpoint proportions of patients with PASI 75 and PASI 90 responses at Weeks 4, 12, 16, 28, 40, and 52 were analysed.

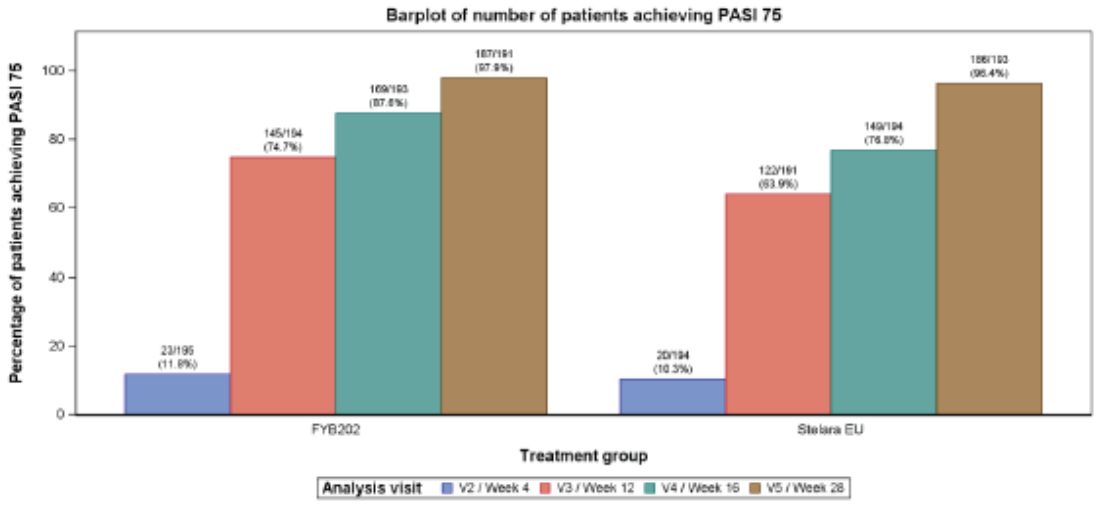
Additionally, the secondary endpoint, changes in PASI 75 and PASI 90 response from Week 28 through Week 52 in patients following a single transition from Stelara EU to FYB202, were analysed.

Psoriasis Area and Severity Index 75

The number and percentage of patients who reached an improvement in PASI score of at least 75% (PASI 75) were summarised by visit in the table below for the PPS, the RRAS and FAS.

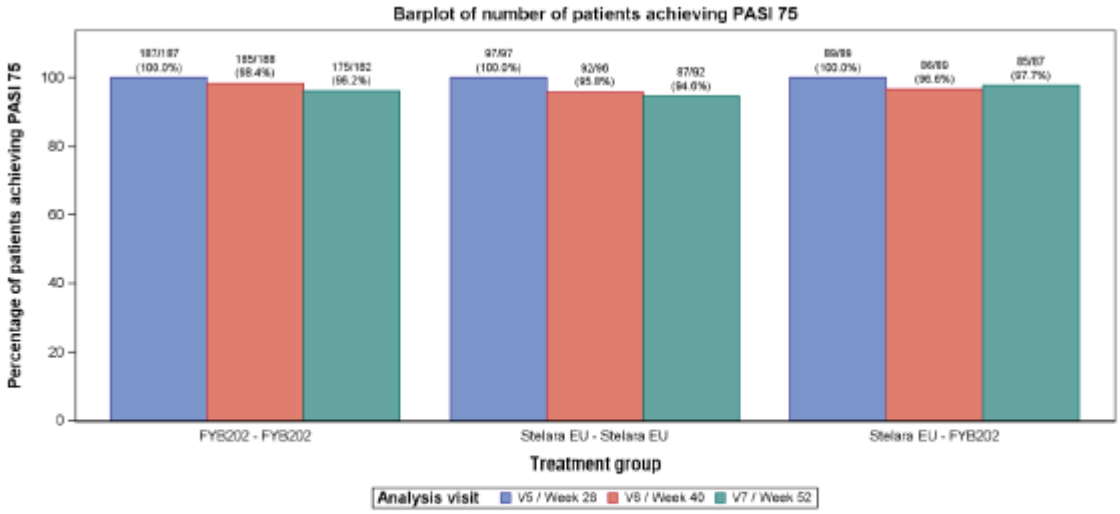
The dynamics in the PASI 75 response rates were similar for both groups with the largest increase between Weeks 4 and 12 and almost all patients achieved a PASI 75 response at Week 28. After re-randomisation from Week 28 onwards, a sustained response was visible in all three arms, showing that the single transition had no impact on a sustained response.

Figure 19 Number and percentage of patients reaching PASI 75 at Weeks 4, 12, 16, and 28 (before re-randomisation, FAS, N=392)



Legend below next figure.

Figure 20 Number and percentage of patients reaching PASI 75 at Weeks 28, 40, and 52 (after re-randomisation, RRAS, N=375)



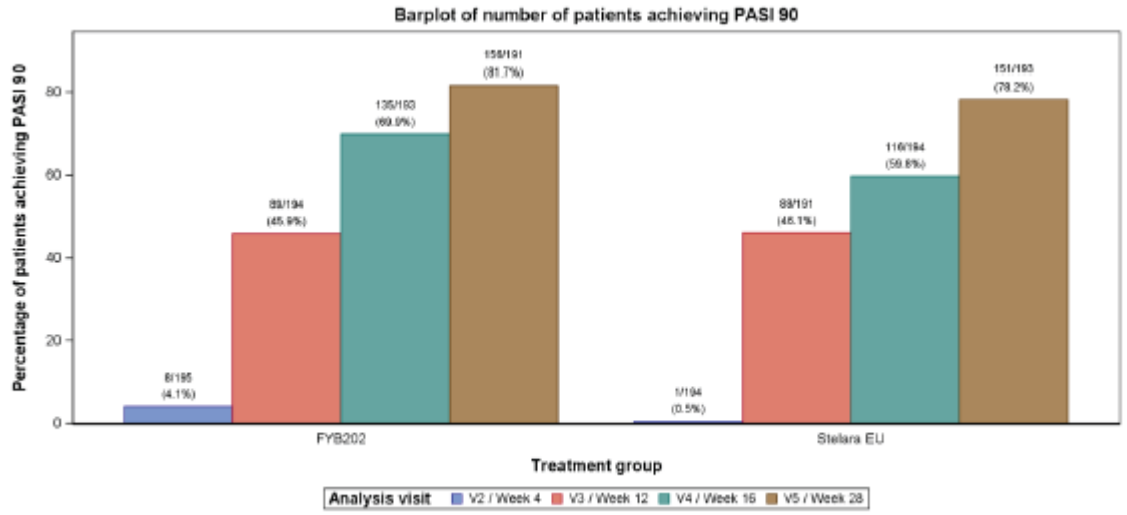
The bars represent the percentage of patients who reached ≥ 75% improvement in PASI score per visit (see colour code), numbers above the bars present n patients with PASI 75 / n patients with non-missing values, and the percentage of patients reaching PASI 75 is presented in brackets.

Psoriasis Area and Severity Index 90

The number and percentage of patients who reached an improvement in PASI score of at least 90% (PASI 90) improvement in PASI score was summarised below by visit for FAS, PPS and RRAS.

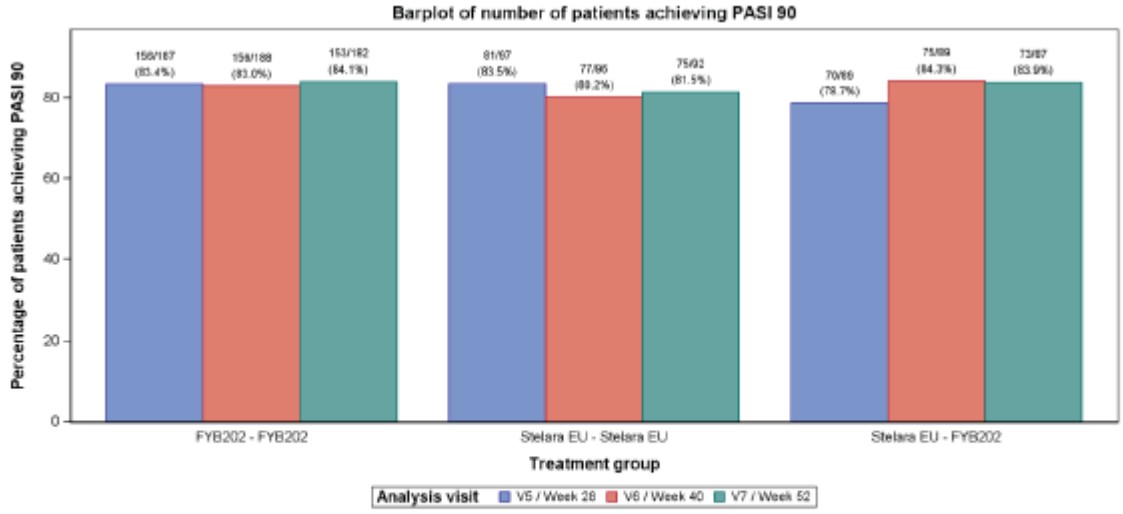
As for PASI 75, the PASI 90 response showed a similar development over the treatment course for both FYB202 and Stelara EU, with approximately 80% of patients achieving a PASI 90 response at Week 28. After re-randomisation from Week 28 onwards, PASI 90 response rates remained above 80% in the single transition Stelara EU – FYB202 group as well as in the groups keeping to their initial randomised treatment (**Figure 21**).

Figure 21 Number and percentage of patients reaching PASI 90 at Weeks 4, 12, 16, and 28 (before re-randomisation, FAS, N=392)



Legend below next figure.

Figure 22 Number and percentage of patients reaching PASI 90 at Weeks 28, 40, and 52 (after re-randomisation, RRAS, N=375)



The bars represent the percentage of patients who reached ≥ 90% improvement in PASI score per visit (see colour code), numbers above the bars present n patients with PASI 90 / n patients with non-missing values, and the percentage of patients reaching PASI 90 is presented in brackets.
FAS = full analysis set, PASI = Psoriasis Area and Severity Index, RRAS = re-randomised analysis set, V = visit, N = total number of patients in the treatment group and analysis set

Changes in PASI 75 and PASI 90 from Week 28 through Week 52 following a Single Transition from Stelara to FYB202

The changes in PASI 75 from Week 28 through Week 52 following a single transition from Stelara to FYB202 are visualized in the treatment group Stelara EU – FYB202 in Figure below, together with the two other treatment groups after re-randomisation.

The proportions of patients reaching PASI 75 were similar following the single transition compared to the treatment group keeping to FYB202 and to Stelara EU after re-randomisation.

The shifts showed for the single transition Stelara EU – FYB202:

- At Week 28, all 89 (100.0%) patients had reached PASI 75, otherwise they would have been excluded from rerandomisation.
- At Week 40, 86 (96.6%) patients kept their PASI 75 response and 3 (3.4%) did not.
- At Week 52, 85 (97.7%) patients kept their PASI 75 response and 2 (2.3%) did not; 2 patients had missing values.

In the FYB202-FYB202 treatment group, results were similar:

At Week 40, 183 patients kept their PASI 75 response and 3 (1.6%) did not.

At Week 52, 173 (96.2%) patients kept their PASI 75 response and 7 (3.8%) did not. 2 patients in the FYB202 group had no PASI assessment at analysis Week 28 but were rerandomised. These patients are not included in the Table below.

In the Stelara EU-Stelara EU treatment group, results were also similar:

At Week 40, 92 (95.8%) patients kept their PASI 75 response and 4 (4.2%) did not.

At Week 52, 87 (94.6%) patients kept their PASI 75 response and 5 (5.4%) did not.

	Analysis Visit and Treatment group			
V5/ Week 28	V6/ Week 40		V7/ Week 52	
	FYB202 – FYB202 (N=189)			
	Reached PASI 75	Did not reach PASI 75	Reached PASI 75	Did not reach PASI 75
Reached PASI 75	183	3	173	7
Did not reach PASI 75	0	0	0	0
	Stelara EU – Stelara EU (N=97)			
	Reached PASI 75	Did not reach PASI 75	Reached PASI 75	Did not reach PASI 75
Reached PASI 75	92	4	87	5
Did not reach PASI 75	0	0	0	0
	Stelara EU – FYB202 (N=89)			
	Reached PASI 75	Did not reach PASI 75	Reached PASI 75	Did not reach PASI 75
Reached PASI 75	86	3	85	2
Did not reach PASI 75	0	0	0	0

RRAS = re-randomised analysis set, N = total number of patients in the corresponding treatment group and analysis set, PASI 75 = ≥75% improvement (reduction) in Psoriasis Area and Severity Index score

Similar findings were observed for changes in PASI 90 from Week 28 through Week 52 following a single transition from Stelara to FYB202 together with the two other treatment groups after re-randomisation.

The proportions of patients reaching PASI 90 were similar following the single transition compared to the treatment groups keeping to FYB202 and to Stelara EU after re-randomisation.

For the single transition Stelara EU – FYB202:

- At Week 28, 70 (78.7%) patients reached PASI 90 and 19 (21.3%) did not.
- Of the 70 patients with PASI 90 response at Week 28, 69 patients still had PASI 90 response at Week 40 and 65 at Week 52.

In the FYB202-FYB202 treatment group, results were similar: At Week 28, 156 (83.4%) patients reached PASI 90 and 31 (16.6%) did not and 2 patients had no PASI assessment at analysis visit Week 28 (Table 14.2.4.3.1.3). Of the 156 patients with PASI 90 response, 144 patients still had PASI 90 response at Week 40 and 137 at Week 52.

In the Stelara EU – Stelara EU treatment group, results were also similar: At Week 28, 81 (83.5%) patients reached PASI 90 and 16 (16.5%) did not. Of the 81 with PASI 90 response, 75 patients still had PASI 90 response at Week 40 and 74 at Week 52.

Physician's Global Assessment

The absolute PGA scores and their absolute changes from baseline are presented for the FAS, the PPS and the RRAS. Additionally, categorised PGA scores are also summarised.

The median (Q1 - Q3) baseline PGA of 3.00 (3.00 – 4.00) points, categorised as a moderate disease intensity improved for both, the FYB202 and Stelara EU treatment groups, by showing lower scores in the median and mean throughout Weeks 4, 12, 16, and 28. The baseline PGA was reduced by 1.00 point in median for both groups at Week 4, by 2.00 points in both groups at Week 12, by 3.00 points for FYB202 and by 2.00 points for Stelara EU at Week 16, and by 3.00 points for both groups at Week 28.

After re-randomisation from Week 28 onwards, the median PGA score was 0.00 categorised as clear of disease showing sustained full improvement in the single transition Stelara EU – FYB202 group and in the groups keeping to their initial randomised treatment.

The tables for shifts from baseline PGA to Weeks 4, 12, 16, and 28 showed similar numbers of patients with the same shifts in PGA scores for the FYB202 and Stelara EU treatment groups in both the FAS and the PPS. They also show that very few patients deteriorated at all, by showing negative shifts from baseline to worst post-baseline assessment (2 patients in the FYB202 group and 1 patient in the Stelara EU group).

Table 37 PGA score and change from baseline (Week 0) to each subsequent visit until V5/ Week 28 (FAS, N=392)

Analysis Visit	FYB202 (N=197) Absolute PGA score	Absolute change from baseline	Stelara EU (N=195) Absolute PGA score	Absolute change from baseline
Baseline V1 / Week 0				
N	197		195	
missing value	0		0	
Mean (SD)	3.32 (0.470)		3.29 (0.454)	
Median	3.00		3.00	
Min - Max	3.0 - 4.0		3.0 - 4.0	
Q1 - Q3	3.00 - 4.00		3.00 - 4.00	
V2 / Week 4				
N	195	195	194	194
missing value	2	2	1	1
Mean (SD)	2.38 (0.740)	-0.94 (0.788)	2.46 (0.691)	-0.82 (0.675)
Median	2.00	-1.00	2.00	-1.00
Min - Max	1.0 - 4.0	-3.0 - 1.0	1.0 - 4.0	-3.0 - 1.0
Q1 - Q3	2.00 - 3.00	-1.00 - 0.00	2.00 - 3.00	-1.00 - 0.00
V3 / Week 12				
N	194	194	191	191
missing value	3	3	4	4
Mean (SD)	1.13 (0.906)	-2.20 (0.983)	1.24 (0.970)	-2.05 (1.065)
Median	1.00	-2.00	1.00	-2.00
Min - Max	0.0 - 3.0	-4.0 - 0.0	0.0 - 3.0	-4.0 - 0.0
Q1 - Q3	0.00 - 2.00	-3.00 – (-1.00)	0.00 - 2.00	-3.00 – (-1.00)
V4 / Week 16				
N	193	193	194	194
missing value	4	4	1	1
Mean (SD)	0.89 (0.871)	-2.44 (0.967)	1.10 (0.919)	-2.19 (1.011)
Median	1.00	-3.00	1.00	-2.00
Min - Max	0.0 - 4.0	-4.0 - 0.0	0.0 - 3.0	-4.0 - 0.0
Q1 - Q3	0.00 - 1.00	-3.00 – (-2.00)	0.00 - 2.00	-3.00 – (-1.00)
V5 / Week 28				
N	191	191	193	193
missing value	6	6	2	2
Mean (SD)	0.54 (0.694)	-2.79 (0.826)	0.70 (0.799)	-2.59 (0.909)
Median	0.00	-3.00	1.00	-3.00
Min - Max	0.0 - 4.0	-4.0 - 0.0	0.0 - 4.0	-4.0 - 0.0
Q1 - Q3	0.00 - 1.00	-3.00 – (-2.00)	0.00 - 1.00	-3.00 – (-2.00)

PGA = Physician's Global Assessment, N = number of patients per group, n = number of patients per category, FAS = full analysis set, SD = standard deviation, Q1 – Q3 = interquartile range, Min = minimum, Max = maximum, V = visit

[a] Relative to Baseline V1/ Week0

Table 38 PGA score and change from V5/ Week 28 to V6/ Week 40, and V7/ Week 52 (RRAS, N=375)

Analysis Visit	FYB202 - FYB202 (N=189) Absolute value	Absolute change from Week 28	Stelara EU - Stelara EU (N=97) Absolute value	Absolute change from Week 28	Stelara EU - FYB202 (N=89) Absolute value	Absolute change from Week 28
V5 / Week 28						
N	187		97		89	
missing value	2		0		0	
Mean (SD)	0.50 (0.634)		0.65 (0.678)		0.58 (0.688)	
Median	0.00		1.00		0.00	
Min - Max	0.0 - 2.0		0.0 - 3.0		0.0 - 2.0	
Q1 - Q3	0.00 - 1.00		0.00 - 1.00		0.00 - 1.00	
V6 / Week 40						
N	188	186	96	96	89	89
missing value	1	3	1	1	0	0
Mean (SD)	0.54 (0.719)	0.03 (0.535)	0.59 (0.705)	-0.05 (0.605)	0.54 (0.724)	-0.04 (0.620)
Median	0.00	0.00	0.00	0.00	0.00	0.00
Min - Max	0.0 - 3.0	-2.0 - 2.0	0.0 - 3.0	-2.0 - 2.0	0.0 - 2.0	-2.0 - 2.0
Q1 - Q3	0.00 - 1.00	0.00 - 0.00	0.00 - 1.00	0.00 - 0.00	0.00 - 1.00	0.00 - 0.00
V7 / Week 52						
N	182	180	92	92	87	87
missing value	7	9	5	5	2	2
Mean (SD)	0.58 (0.744)	0.08 (0.638)	0.64 (0.764)	0.00 (0.798)	0.57 (0.757)	-0.01 (0.77)
Median	0.00	0.00	0.00	0.00	0.00	0.00
Min - Max	0.0 - 3.0	-2.0 - 2.0	0.0 - 2.0	-2.0 - 2.0	0.0 - 2.0	-2.0 - 2.0
Q1 - Q3	0.00 - 1.00	0.00 - 0.00	0.00 - 1.00	0.00 - 0.00	0.00 - 1.00	0.00 - 0.00

PGA = Physician's Global Assessment, N = number of patients per group, n = number of patients per category, RRAS = rerandomised analysis set, SD = standard deviation, Q1 – Q3 = interquartile range, Min = minimum,

Dermatology Life Quality Index

The absolute DLQI scores and the absolute changes from the baseline DLQI score are presented for the FAS, the PPS and the RRAS.

Additionally, categorised DLQI scores are also summarised.

The median (Q1 - Q3) baseline DLQI of 13.00 (FYB202: 8.00 – 18.00, Stelara EU: 9.00 – 18.00) points, categorised as a very large effect [of psoriasis ed.] on patient's life improved for both the FYB202 and Stelara EU treatment groups, by showing lower median and mean scores throughout at Weeks 4, 12, 16, and 28.

The DLQI decreased from baseline by 5.00 points in median for both groups at Week 4, by 9.00 points for FYB202 and 10.00 points for Stelara EU at Week 12, by 10.00 points for both groups at Week 16, and by 11.00 points for both groups at Week 28.

After re-randomisation from Week 28 onwards, the median DLQI score was 0.00 categorised as no effect [of psoriasis ed.] on the patient's life, showing a sustained full improvement in the single transition Stelara EU – FYB202 group and in the groups keeping to their initial randomised treatment at Weeks 40 and 52.

The tables for shifts from baseline DLQI to DLQI at Weeks 4, 12, 16, and 28 showed similar numbers of patients with the same shifts in DLQI in the FYB202 and Stelara EU treatment groups in both, the FAS and the PPS.

After re-randomisation from Week 28 onwards, similar numbers of patients (relative to the treatment group size) with the same shifts from Week 28 were observed in the single transition Stelara EU – FYB202 group and in the groups keeping to their initial randomised treatment.

Scatterplots to assess the relationship between PASI and DLQI scores showed that at baseline, a direct correlation between PASI and DLQI could not be established. However, they showed that low PASI scores (below 20) were associated with DLQI scores mostly to values lower than 10. No differences between the treatment groups were observed.

After re-randomisation this relationship was less clearly visible because of the low dynamic ranges of both parameters.

Table 39 DLQI score and change from baseline (Week 0) to each subsequent visit until V5/ Week 28 (FAS, N=392)

Analysis Visit	FYB202 (N=197) Absolute DLQI score	Absolute change from baseline	Stelara EU (N=195) Absolute DLQI score	Absolute change from baseline
Baseline V1 / Week 0				
N	197		194	
missing value	0		1	
Mean (SD)	13.10 (6.372)		13.63 (6.531)	
Median	13.00		13.00	
Min - Max	2.0 - 30.0		1.0 - 30.0	
Q1 - Q3	8.00 - 18.00		9.00 - 18.00	
V2 / Week 4				
N	195	195	194	193
missing value	2	2	1	2
Mean (SD)	7.65 (5.612)	-5.48 (4.904)	7.86 (5.494)	-5.76 (5.675)
Median	7.00	-5.00	7.00	-5.00
Min - Max	0.0 - 27.0	-27.0 - 6.0	0.0 - 27.0	-25.0 - 22.0
Q1 - Q3	3.00 - 11.00	-8.00 – (-2.00)	4.00 - 11.00	-9.00 – (-2.00)
V3 / Week 12				
N	194	194	191	190
missing value	3	3	4	5
Mean (SD)	3.28 (4.340)	-9.81 (6.489)	3.38 (4.661)	-10.34 (6.707)
Median	2.00	-9.00	2.00	-10.00
Min - Max	0.0 - 25.0	-27.0 - 10.0	0.0 - 26.0	-27.0 - 12.0
Q1 - Q3	0.00 - 5.00	-14.00 – (-5.00)	0.00 - 5.00	-14.00 – (-5.00)
V4 / Week 16				
N	193	193	194	193
missing value	4	4	1	2
Mean (SD)	2.66 (4.133)	-10.47 (6.760)	3.23 (4.787)	-10.35 (7.135)
Median	1.00	-10.00	1.00	-10.00
Min - Max	0.0 - 30.0	-30.0 - 13.0	0.0 - 28.0	-27.0 - 16.0
Q1 - Q3	0.00 - 3.00	-15.00 – (-6.00)	0.00 - 5.00	-15.00 – (-5.00)
V5 / Week 28				
N	191	191	193	192
missing value	6	6	2	3
Mean (SD)	1.43 (3.614)	-11.69 (6.854)	2.06 (3.872)	-11.65 (7.175)
Median	0.00	-11.00	0.00	-11.00
Min - Max	0.0 - 30.0	-30.0 - 13.0	0.0 - 28.0	-30.0 - 13.0
Q1 - Q3	0.00 - 1.00	-17.00 – (-7.00)	0.00 - 2.00	-16.50 – (-6.00)

DLQI = Dermatology Life Quality Index, N = number of patients per group, n = number of patients per category, FAS = full analysis set, SD = standard deviation, Q1 – Q3 = interquartile range, Min = minimum, Max = maximum, V = visit

[a] Relative to Baseline V1/ Week0

Table 40 DLQI score and change from V5/ Week 28 to V6/ Week 40 and V7/ Week 52 (RRAS, N=375)

	FYB202 - FYB202 (N=189)		Stelara EU - Stelara EU (N=97)		Stelara EU - FYB202 (N=89)	
Analysis Visit	Absolute value	Absolute change from Week 28	Absolute value	Absolute change from Week 28	Absolute value	Absolute change from Week 28
V5 / Week 28						
N	187		97		89	
missing value	2		0		0	
Mean (SD)	1.23 (2.910)		2.30 (3.492)		1.12 (2.517)	
Median	0.00		0.00		0.00	
Min - Max	0.0 - 24.0		0.0 - 13.0		0.0 - 18.0	
Q1 - Q3	0.00 - 1.00		0.00 - 4.00		0.00 - 1.00	
V6 / Week 40						
N	188	186	96	96	89	89
missing value	1	3	1	1	0	0
Mean (SD)	1.40 (3.248)	0.13 (2.031)	2.23 (3.709)	-0.08 (2.024)	1.30 (2.626)	0.18 (1.998)
Median	0.00	0.00	0.00	0.00	0.00	0.00
Min - Max	0.0 - 20.0	-6.0 - 19.0	0.0 - 16.0	-9.0 - 6.0	0.0 - 13.0	-5.0 - 8.0
Q1 - Q3	0.00 - 1.00	0.00 - 0.00	0.00 - 3.50	0.00 - 0.00	0.00 - 2.00	-1.00 - 0.00
V7 / Week 52						
N	182	180	92	92	87	87
missing value	7	9	5	5	2	2
Mean (SD)	1.15 (2.422)	-0.08 (2.848)	1.72 (3.153)	-0.50 (2.732)	1.20 (2.430)	0.06 (1.882)
Median	0.00	0.00	0.00	0.00	0.00	0.00
Min - Max	0.0 - 18.0	-16.0 - 18.0	0.0 - 16.0	-10.0 - 9.0	0.0 - 12.0	-6.0 - 8.0
Q1 - Q3	0.00 - 1.00	0.00 - 0.00	0.00 - 2.00	-1.00 - 0.00	0.00 - 1.00	-1.00 - 0.00

DLQI = Dermatology Life Quality Index, N = number of patients per group, n = number of patients per category, FAS = full analysis set, SD = standard deviation, Q1 – Q3 = interquartile range, Min = minimum, Max = maximum, V = visit

Itching Visual Analogue Scale

Worst Itching Visual Analogue Scale

The absolute worst I-VAS scores (during the past 24 hours) and their absolute changes from baseline are presented for the FAS, the PPS, and the RRAS. Additionally, the categorised worst I-VAS scores are presented.

The median (Q1 - Q3) baseline worst I-VAS score points were 6.90 (4.80 – 8.20) for the FYB202 group (categorised as moderate) and 7.00 (4.50 – 8.20) for Stelara EU (categorised as severe) and the worst I-VAS improved for both FYB202 and Stelara EU treated patients showing lower scores at Weeks 4, 12, 16, and 28 (Table 10-20). The worst I-VAS was reduced from baseline by 3.10 (FYB202) and 3.00 (Stelara EU) scale points in median at Week 4, by 5.10 (FYB202) and 5.00 (Stelara EU) scale points at Week 12, by 5.30 (FYB202) and 4.90 (Stelara EU) scale points at Week 16, and by 6.00 (FYB202) and 5.45 (Stelara EU) scale points at Week 28.

After re-randomisation from Week 28 onwards, the median worst I-VAS score was 0.00 (categorised as no pruritus), showing sustained full improvement in all three treatment groups.

The tables for shifts from worst I-VAS at baseline to worst I-VAS at Weeks 4, 12, 16, and 28 showed similar numbers of patients with the same shifts in I-VAS scores for the FYB202 and Stelara treatment groups in both, the FAS and the PPS. They also show that only a few patients deteriorated by showing few negative shifts from baseline to worst post-baseline assessment (22 patients in the FYB202 group and 16 patients in the Stelara EU group).

After re-randomisation from Week 28 onwards, similar numbers of patients (relative to the treatment group size) with the same shifts from Week 28 to Weeks 40 and 52 were observed in the single transition Stelara EU – FYB202 group and in the groups keeping to their initial randomised treatment. Scatterplots to assess the relationship between PASI and I-VAS for worst itch showed that at baseline, a direct correlation between PASI and worst I-VAS could not be established. However, they showed that low PASI scores (below 20) were associated mostly with worst I-VAS scores lower than 2. No differences between the treatment groups were observed.

- **Ancillary analyses**

ADA and NAb effect on efficacy in plaque psoriasis patients: FYB202-03-01

Impact of ADA / NAb on efficacy endpoints

The Statistical Analysis Plan for the Integrated Summary of Immunogenicity pre-specified a number of descriptive analyses of the relationship of ADA and Nab status (positive vs. negative) to the primary and key secondary endpoints. In addition, a Mixed Model Repeated Measures Least Squares estimation was applied to test the statistical significance of treatment group differences by ADA / NAb status.

Percent improvement in PASI score from baseline to Week 12 (primary efficacy endpoint).

In both the FYB202 and Stelara EU treatment groups, the mean % improvement in PASI score from baseline to Week 12 was modestly lower for ADA-positive subjects compared to ADA-negative subjects (**Table 49**). Nevertheless, across the treatment groups, the 2-sided confidence intervals for the MMRM Least Squares estimation showed substantial overlap and were not statistically different for both the ADA negative or ADA positive sub-populations. Therefore, it was concluded that the lower ADA prevalence detected at Week 12 for FYB202 (7.2%) compared to Stelara EU (14.4%) had no impact on the primary efficacy endpoint in Study FYB202-03-01.

For Nab-positive patients, the mean improvement in PASI score from baseline to Week 12 was 73.4% for FYB202 compared to 73.1% for Stelara EU, consistent with a conclusion of absence of clinical impact of a higher NAb prevalence detected at Week 12 in the Stelara EU treatment group 6.7%) compared to the FYB202 group (3.6%).

Percent improvement in PASI score from baseline to Week 28 (secondary efficacy endpoint).

The 2-sided confidence intervals for the MMRM Least Squares estimation also showed substantial overlap at Week 28 across the treatment groups for both the ADA negative or ADA positive subpopulations from baseline to Week 28 (**Table 51** and **Figure 24**). This was also the case for NAb-positive and Nab-negative patients from baseline to Week 28 (**Table 52**). Thus, the observed differences in ADA and NAb incidence for FYB202 compared to Stelara EU did not impact either the primary or secondary efficacy endpoints.

Proportion of patients with PASI 75 responses at Weeks 12, 28, and 52.

In the FYB202 treatment group, the proportion of ADA-positive patients reaching PASI 75 was 52.4% at Week 12, 95.0% at Week 28 and 90.0% at Week 52. In the Stelara EU treatment group, the proportion of ADA-positive patients reaching PASI 75 was 53.7% at Week 12, 94.4% at Week 28 and 88.5% at Week 52. Similar proportions of PASI 75 responders were observed at the corresponding time points for Nab-positive patients in the two treatment groups.

These very similar proportions corroborate the conclusion that a lower detected incidence of ADA and Nab-positive patients in the FYB202 treatment group did not influence efficacy as measured by attainment of PASI 75 at Week 12, Week 28 and Week 52.

Within each treatment group, the proportion of patients achieving PASI 75 at Week 12 was lower for the ADA positive subpopulation compared to the ADA negative subpopulation: 52.4 % vs. 77.3% for FYB202; 53.7% vs. 67.9% for Stelara EU. Thus, ADA-positive status appeared to be associated with a modest reduction in efficacy at Week 12, with a similar scale of reduction across the two treatment groups.

The absence of a differential impact on efficacy associated with the observed difference in ADA and NAb incidence may be explained by the relatively low and similar ADA titres: at Week 28, the geometric mean ADA titre was 212.63 for FYB202 (n=24 ADA positive subjects) compared to 203.29 for Stelara EU (n=37 ADA positive subjects). Thus, although there was a numerical difference in ADA and NAb prevalence, levels of ADA or NAb did not reach a threshold for a negative impact on efficacy, an outcome that is consistent with the published experience for Stelara.

Impact of treatment transition at Week 28 on efficacy

Comparison of absolute improvement in PASI score from Week 28 to Week 52 indicated extremely small differences between the 3 treatment groups that were well contained within the 95% confidence intervals. This confirmed that efficacy was unaffected by transition of treatment at Week 28, consistent with the absence of impact on ADA/NAb or measured drug levels.

- **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 biosimilarity assessment (see later sections).

Table 41 Summary of Efficacy for trial FYB202-03-01

Title: A Randomised, Double-blind, Parallel-group, Phase 3 Study to Compare the Efficacy, Safety, and Immunogenicity of the Proposed Biosimilar Ustekinumab FYB202 to Stelara® in Patients with Moderate-to-Severe Plaque Psoriasis		
Study identifier	FYB202-03-01 EudraCT number: 2019-004364-21 US IND number: 141478	
Design	A multicentre, double-blind, parallel-group, randomised Phase 3 study designed to demonstrate the clinical similarity of FYB202 compared with Stelara in patients with moderate-to-severe plaque psoriasis regarding efficacy, safety, and immunogenicity.	
	Duration of main phase: Duration of Run-in phase: Duration of Extension phase:	First patient, first visit: 23-Sep-2020 Last patient, last visit: 21-Mar-2022

		not applicable
Hypothesis	Equivalence	
Treatments groups		There were 4 analysis sets; the full analysis set (FAS) and the safety set (SAF) were identical and included the same patients since all randomised patients received the study intervention at least once. FAS and SAF: 197 patients treated with FYB202 and 195 patients treated with Stelara EU (Total 392 patients) PPS: 191 patients treated with FYB202 and 188 patients treated with Stelara EU (Total 379 patients) Rerandomised Set (RRAS): 189 patients treated with FYB202 and 186 patients treated with Stelara EU (Total 375 patients) Subjects were randomised in a 1:1 ratio to receive either FYB202 or Stelara via subcutaneous injection. Investigative products (IPs; FYB202 or Stelara) were administered at Week 0, 4, and then every 12 weeks up to Week 40, and the end study visit was done at Week 52. The final CSR was submitted with the initial MAA.

	group descriptor		At Week 28, after receiving treatment at Week 0, 4 and 16, the patients were assessed for PASI response. Patients not achieving a ≥ 75% improvement from baseline in PASI score (PASI 75) at Week 28 were considered non-responders. Before the Week 28 administration of study intervention, the responding patients were rerandomised in a blinded fashion. Patients, initially randomised to the Stelara treatment arm were rerandomised 1:1, so that 50% of the patients in the original Stelara arm received FYB202 and 50% continued with Stelara. Patients originally randomised to FYB202 continued with FYB202.
Endpoints and definitions	Primary endpoint	Percent improvement in PASI score from baseline to Week 12.	Percent improvement in Psoriasis Area and Severity Index (PASI) score from Baseline to Week 12 in adult subjects with moderate to severe plaque psoriasis. Clinical equivalence was demonstrated if the 95% CI for the adjusted mean difference in percentage PASI improvement between test and reference groups was contained within the equivalence margin range of [-11%, 11%]

	Secondary Endpoints	PASI	• Percent improvement in PASI score from baseline (Week 0) to Weeks 4, 16, 28, 40, and 52 • Raw PASI scores at baseline and Weeks 4 and 12 • Proportion of patients with PASI 75 and PASI 90 responses at Weeks 4, 12, 16, 28, 40, and 52 • Changes in PASI 75 and PASI 90 responses from Week 28 through Week 52 in patients following a single transition from Stelara to FYB202
		PGA responses	• Change per Physician's Global Assessment (PGA) over time
		Change in DLQI scores	• Improvement of Dermatology Life Quality Index (DLQI) total score from baseline (Week 0) and at Weeks 4, 12, 16, 28, 40, and 52
		IVAS	• Itching Visual Analogue Scale (I-VAS) at baseline and Weeks 4, 12, 16, 28, 40, and 52
Database lock	The clinical study report presents the results of the final statistical analysis (database lock: 03-Aug-2022).		
Results and Analysis			
Analysis description	**Primary Analysis**		
Analysis population and time point description	PPS Week 12		
Descriptive statistics and estimate variability	Treatment group	FYB202	Stelara
	Number of subject	197	195
	LS mean in percent improvement in PASI from BL to Week12 [2-sided 95% CI]	79.51 [74.64; 84.38]	76.24 [71.45; 81.02]

Effect estimate per comparison	Primary endpoint Percent improvement in PASI from Baseline to Week 12	Comparison groups	FYB202 VS Stelara
		LSMean difference (SE)	3.27
		95% confidence interval for difference	[-0.90%; 7.44%]
		The two-sided 95% CI was completely contained in the pre-defined equivalence margin for the EU analysis of [-11%; 11%].	
Analysis description	**Secondary analysis**		
	At Week 12, PASI75 response rate was 74.7% for FYB202 and 63.9% for Stelara; PASI90, 45.9% for FYB202 and 46.1%% for Stelara; The change per **PGA** over time showed that the median (Q1 - Q3) baseline PGA of 3.00 (3.00 – 4.00) points, categorised as a moderate disease intensity, improved for both, the FYB202 and Stelara EU treatment groups, by showing lower median scores throughout Weeks 4, 12, 16, and 28. The baseline PGA was reduced by 1.00 point in the median for both groups at Week 4, by 2.00 points in both groups at Week 12, by 3.00 points for FYB202 and by 2.00 points for Stelara EU at Week 16, and by 3.00 points for both groups at Week 28. After re-randomisation from Week 28 onwards, the median PGA score did not change compared to Week 28 and was 0.00 categorised as clear of disease showing sustained full improvement in the single transition Stelara EU – FYB202 group and in the groups keeping to their initial randomised treatment. The MMRM statistics for the difference in change from baseline PGA score showed that the (LS) mean PGA score improved by showing similar reductions from baseline to Weeks 4, 12, 16, and 28 in patients treated with FYB202 and with Stelara EU. The (LS) mean differences between both treatments were between -0.10 and -0.20. The 95% CIs at Weeks 4, 12, 16, and 28 supported the similarity of the two treatments with respect to change in the PGA score. The secondary endpoint improvement of DLQI total score from baseline (Week 0) to Weeks 4, 12, 16, 28, 40, and 52 showed that the median (Q1 - Q3) baseline DLQI of 13.00 (FYB202: 8.00 – 18.00, Stelara EU: 9.00 – 18.00) points, categorised as a very large effect [of psoriasis ed.] on patient's life, improved for both the FYB202 and Stelara EU treatment groups, by showing lower median and mean scores throughout at Weeks 4, 12, 16, and 28.		

2.6.5.3. Clinical studies in special populations

Not applicable for biosimilars.

2.6.5.4. In vitro biomarker test for patient selection for efficacy

Not applicable.

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

Not applicable.

2.6.5.6. Supportive study(ies)

Not applicable.

2.6.6. Discussion on clinical efficacy

Design and conduct of clinical studies

A confirmatory Phase III study (FYB202-03-01) was conducted by the applicant to demonstrate the similarity in clinical efficacy between FYB202 and Stelara in accordance with the EMA guidelines [EMEA/CHMP/BMWP/42832/2005 Rev. 1; EMA/CHMP/BMWP/403543/2010]. The study was not aimed at establishing efficacy since the efficacy of Stelara in the respective therapeutic indications has already been established in pivotal clinical trials and published literature reports.

The EU reference product Stelara used in the phase III study FYB202-03-01 is acceptable to the CHMP. Study FYB202-03-01 was a randomised, double-blind, parallel-group, Phase III Study to compare the Efficacy, Safety, tolerability, PK, and Immunogenicity of the proposed biosimilar Ustekinumab FYB202 to Stelara in adult patients with moderate-to-severe plaque psoriasis. Patients were randomised 1:1 to receive FYB202 or Stelara (45 mg ustekinumab) at week 0 and week 4 and subsequently every 12 weeks up to week 40 (i.e. injections at week 0, 4, 16, 28 and 40). At week 28, patients in the Stelara arm with a response were re-randomised to either continue on with treatment with Stelara or transition into FYB202 up to week 40 (i.e. injections administered at week 28 and week 40). The primary efficacy endpoint was a percent improvement in PASI score from baseline (Week 0) to Week 12. The final phase III clinical study report for FYB202-03-01 including the clinical assessment performed at week 52 was provided.

In the context of this biosimilar application, the overall design and conduct of the phase III clinical study is acceptable to the CHMP and generally in line with EMA SA recommendations. The patient population was adequately selected and relevant to the target population. Overall, the eligibility criteria are acceptable to the CHMP. The choice of the target population (adult patients with psoriasis) for the confirmatory phase III study is acceptable to the CHMP as this population is considered a sensitive population to observe differences in terms of efficacy between FYB202 and Stelara. The primary and secondary efficacy objectives of the clinical study FYB202-03-01 are acceptable to the CHMP and in line with the "Guideline on similar biological medicinal products containing monoclonal antibodies – non-clinical and clinical issues" (EMA/CHMP/BMWP/403543/2010)".

Some uncertainties were raised during the assessment in relation to 4 unintended pregnancy cases which occurred during the phase III trials. Upon the CHMP's request, the applicant discussed the pregnancy cases reported and clarified that adequate measures in line with the recommendation of the Clinical Trial

Coordination Group guidance were followed to prevent pregnancy during the clinical studies conducted for FYB202. This is agreed by the CHMP.

A sample size of 392 patients in total, randomised in a 1:1 ratio to both treatment groups, was planned for this study. Assuming a screen failure rate of about 20%, approximately 490 patients were foreseen to be screened. The sample size is acceptable to the CHMP.

The statistical justification for the equivalence margins is based on a retention of the lower confidence interval of the Stelara treatment effect, reported as 67%. Upon the CHMP's request, the applicant further explained that the combined difference net of placebo showed a lower 95% bound of 67%. This is acceptable to the CHMP. The applicant further justified also the equivalence margins (-11%-+11%), which refer to the randomised controlled studies of ustekinumab and which is considered to be clinically meaningful to reflect equivalence in efficacy in terms of percent change from baseline in PASI at Week 12 between FYB202 and Stelara.

For the primary endpoint, a mixed model repeated measures (MMRM) was planned to be used to analyse the percent improvement in PASI score from baseline to week 12, including the baseline assessment of the PASI score, the baseline assessment of weight and the duration of psoriasis at baseline as covariates, and prior inadequate response or intolerance to systemic biological treatment, the treatment group (FYB202 or EU-approved Stelara), and visit as fixed effects. Additionally, an interaction term between the treatment group and visit as well as an interaction term between baseline PASI score and visit was included. The MMRM used all available percent improvements in PASI score from baseline until week 28 for all patients in the FAS for model estimation. The general approach of the analyses is supported by the CHMP.

The CHMP considered that the use of interaction terms in the model is likely to underestimate the final residual error and potentially narrow the confidence intervals. The applicant provided a relevant ANCOVA analysis at week 12 under a PP analysis and used a suitable estimand framework. The estimated difference between the two treatment groups was 3.27% with a 2-sided 95% confidence interval of [-1.00; 7.53], which is very similar to the primary analysis using the MMRM model as well as to the ANCOVA analysis based on the FAS and the other sensitivity analyses for the primary efficacy endpoint.

The study was conducted between 23-Sep-2020 and 21-Mar-2022 at 27 sites in 4 countries: Estonia (23 [5.9%] patients), Georgia (49 [12.5%] patients), Poland (212 [54.1%] patients) and Ukraine (108 [27.6%] patients).

The study duration was 12.7 months from the first patient's first visit until and including Week 28 (between 23-Sep-2020 and 14-Oct-2021) and 7.3 months after re-randomisation (between 11- Aug-2021 and 21-Mar-2022).

There were no changes in the study conduct.

The patient demographics indicate that there were more men than women participating in the study. About two-thirds of the women were of childbearing potential. The race of all patients was white and their ethnicity was not Hispanic or Latino. The age of the patients ranged between 18 and 77 years; the median (Q1 to Q3) age was 41.0 (32.0 to 50.0) years. The BMI ranged between 16.9 to 39.3 kg/m2; the median (Q1 to Q3) BMI was 26.79 (24.10 to 29.76) kg/m2. The patient demographics were balanced across both treatment groups. A review of the baseline disease characteristics indicates that the patient population was representative of a population with moderate-to-severe plaque psoriasis. The baseline psoriasis characteristics were well-balanced between both treatment groups. During the study, 27 (13.7%) patients treated with FYB202 and 34

(17.4%) patients treated with Stelara EU reported concomitant medications for psoriasis. Most patients used emollients and protectives: 25 (12.7%) patients in the FYB202 group and 29 (14.9%) in the Stelara EU group.

A substantial number of patients had a weight >90kg and numbers were generally balanced between FYB202 and Stelara treatment groups. The applicant was asked to clarify whether any patients had increased body weight to >100kg during the study. According to the inclusion criteria, patients were eligible to be enrolled in the study if they had ≤100 kg body weight at screening and at baseline. For plaque psoriasis patients included in the study FYB202-03-01, the recommended posology of ustekinumab was an initial dose of 45 mg administered subcutaneously, followed by a 45 mg dose 4 weeks later, and then every 12 weeks thereafter. According to the protocol, if patient body weight would exceed 100 kg during the study, the treatment dose would not change and the patient continue on study. Thus, a flat dose of 45 mg was administered throughout the study. As per the posology in the approved SmPC of Stelara EU, "*for patients with a body weight > 100 kg the initial dose is 90 mg administered subcutaneously, followed by a 90 mg dose 4 weeks later, and then every 12 weeks thereafter. In these patients, 45 mg was also shown to be efficacious. However, 90 mg resulted in greater efficacy*." In study FYB202-03-01, a total of 16 patients from 392 evaluable patients (4.08%) had body weight increase > 100 kg, from which 9 had the body weight increase > 100 kg at the end of the study, i.e. at week 52, 5 patients had a body weight increase > 100 kg at week 12 and 2 patients had a body weight increase > 100 kg at week 28. The CHMP noted that no increase of the body weight > 100 kg was recorded before week 12, when the primary endpoint was measured. In addition, the number of patients with body weight increase > 100 kg was small, hence, it was considered unlikely to have had a relevant impact on the interpretation of the results of the study.

A total of 392 patients were randomised to receive study treatment; 197 patients were randomised to receive FYB202 and 195 patients Stelara EU.

A total of 17 major protocol deviations led to the exclusion of 13 patients from the per-protocol analysis set. Both groups had similar numbers of patients with major protocol deviations (6 patients in the FYB202 and 7 patients in the Stelara EU group). The protocol deviations are unlikely to have had an impact on the validity of the results.

A small number of patients discontinued from the study and the numbers of discontinuations were generally balanced across FYB202 and Stelara treatment groups. Hence, the reasons for screen failure or discontinuation from treatment from the study are unlikely to have impacted the validity of the results.

A total of 375 patients were re-randomised at Week 28; 189 patients on FYB202 stayed on FYB202 as per study design, 97 patients on Stelara EU were re-randomised to Stelara EU (Stelara EU-Stelara EU), and 89 patients on Stelara EU were re-randomised to FYB202 (Stelara EU-FYB202). Following the re-randomisation of 375 patients, 372 patients completed the study until Week 52; 187 patients on FYB202-FYB202, 97 patients on Stelara EU approved Stelara EU, and 88 patients on Stelara EU-FYB202.

The primary efficacy endpoint was the percent change from baseline in PASI LS means at week 12 timepoint. This is considered sufficiently sensitive to detect potential clinically meaningful differences in efficacy. Further, the continuous variable PASI score has been recommended over the dichotomous endpoint PASI75. However, in terms of sensitivity to detect differences between the FYB202 and Stelara, the CHMP highlighted that during the scientific advice (EMA/CHMP/SAWP/775190/2018), the CHMP suggested that an earlier time point (e.g. week 8) would be preferred over the 12-week time point, as the timing of the primary efficacy endpoint at 12 weeks is near the top of the dose-response curve. Hence, an earlier time point at week 8

might be a more sensitive time to detect any product-related differences. Nevertheless, the week 12 timepoint is considered sensitive enough and the issue was not further pursued.

Data available from the clinical study showed that the primary efficacy endpoint, percent change from baseline in the psoriasis area and severity index (PASI) at Week 12 met the pre-defined equivalence margin. Sensitivity analyses also reported equivalence.

The applicant presented data on a number of relevant secondary efficacy endpoints in which the comparability of FYB202 to Stelara EU was shown across all secondary efficacy endpoints. These included PASI improvement over time, percentages of patients reaching PASI 75 and PASI 90 up to Week 52, improvement of PGA over time as well as improvement of patients' quality of life [DLQI] and itching [I-VAS for worst and average itching]). The number of patients achieving a PASI 75 or PASI 90 response was generally similar for both treatments throughout the study. A high and comparable proportion of all patients (98.5% in each group) achieved a PASI 75 response. Greater than 80% of patients recorded a PASI 90 response. PGA and (worst and average) I-VAS improvements were similar for both FYB202 and Stelara. The median scores observed indicated that patients were "clear of disease" (PGA) or experienced "no pruritus" (I-VAS). In addition, there was an overall improvement in the quality of life as measured by the DLQI, which was similar for both FYB0202 and Stelara in that the overall effect of psoriasis on the patient's life changed from a "very large" effect at baseline to a "small effect" at Week 28. There was a significant improvement in the signs and symptoms of psoriasis for both treatment groups, which was broadly comparable for FYB202 and Stelara in terms of the % affected BSA.

No major differences were noted between efficacy variables across the secondary endpoint evaluations and overall, both products were considered clinically similar based on the data presented.

In the context of the transition from the reference product Stelara to FYB202 following the Week 28 evaluation, there was no relevant negative impact observed on clinical efficacy. Overall, clinical efficacy was maintained after transition in all parameters tested until the end of the observation period. There was no difference between the two treatment groups who continued on their initial treatment following the transition period.

The impact of the immunogenicity of FYB202 versus Stelara on clinical efficacy is based on the percent change in PASI score in ADA-negative patients at week 12 and over 52 weeks. The analysis was made on the safety set and the use of MMRM. Upon the CHMP's request, the applicant provided an updated analysis of the effect of FYB202 versus Stelara on the percent change in PASI at week 12 using the PPS. Both analyses support the proof of biosimilarity of FYB202 and Stelara, with both confidence intervals being well contained in the equivalence margin of ± 11%.

Based on the available results, the equivalence from a clinical efficacy perspective of FYB202 to the Stelara EU is shown.

2.6.7. Conclusions on the clinical efficacy

A confirmatory randomised, Phase III, double-blind, multicentre clinical study (FYB202-03-01) was performed to compare the clinical efficacy of FYB202 and the EU reference product Stelara (45mg s.c. injections) in adult patients with moderate to severe plaque PsO. The study was adequately powered, included a study

population sensitive for detecting potential differences between the biosimilar and the reference product and had relevant endpoints.

The primary efficacy analysis for the primary endpoint showed a similar difference for the percent improvement in PASI score between FYB202 and Stelara EU treatment groups; the 95% CI was within the prespecified equivalence margin of (-11, +11). All sensitivity analyses performed supported the results of the primary analysis. The secondary endpoints are supportive of clinical efficacy equivalence.

The CHMP concluded that the equivalence from a clinical efficacy perspective of FYB202 to the Stelara EU is demonstrated.

2.6.8. Clinical safety

Safety data on FYB202 is available from three clinical studies (Study FYB202-01-01, study FYB202-01-02 and Study FYB201-03-01), where safety was assessed as part of the secondary study objectives. Safety evaluation included adverse events (AEs), serious AEs (SAEs), treatment-emergent adverse events (TEAEs), adverse events of special interest (AESI), local tolerability, vital signs, and laboratory evaluations, as well as immunogenicity.

Study FYB202-01-01 and study FYB202-01-02 were conducted in healthy subjects following single dose administration. Subjects were monitored for 112 days until the end of the study visit. A single pooled safety analysis of healthy patients of both phase 1 studies was completed. Study FYB201-03-01 was conducted in patients with moderate to severe plaque psoriasis following multiple dose administration. Subjects were monitored for 52 weeks until the end of the study visit.

2.6.8.1. Patient exposure

Overall Extent of Exposure

A total of 555 subjects received at least 1 dose of FYB202 across the 3 clinical studies.

Study FYB202-01-01 & Study FYB202-01-02

In total, in the phase 1 studies FYB202-01-01 & FYB202-01-02, the pooled safety analysis set (SAF) comprised 806 healthy volunteers; FYB202 n=269, EU-STELARA n=268, and US-STELARA n = 269; study FYB202-01-01 n = 315, & study FYB202-01-02 n=491.

In Study FYB202-01-01, 315 subjects were treated with a single SC injection of either FYB202 (105 subjects), EU-STELARA (105 subjects), or US-STELARA (105 subjects) at a dose level of 45 mg. In Study FYB202-01-02, 491 subjects were enrolled, randomised, and treated with a single SC injection of either FYB202 (164 subjects), EU-STELARA (163 subjects), or US-STELARA (164 subjects) at a dose level of 45 mg. The follow-up period was until 112 days.

Study FYB202-03-01

In Period 1 (Week 0 to Week 28), subjects were randomized to receive the assigned treatment (FYB202 or Stelara) at Weeks 0, 4, and 16. 392 patients with psoriasis were enrolled, randomised and treated: 197 patients in the FYB202 group and 195 patients in the EU-Stelara group.

At week 28, re-randomisation occurred according to responder status. 375 patients were re-randomised and 12 were not (9 non-responders and 3, other reason; lost to follow-up, AE Renal cancer metastatic, AE Cholestasis, Hepatitis toxic). 375 patients received 2 further injections at Week 28 and Week 40; 189 patients in the FYB202-FYB202 group, 97 patients in the EU-Stelara- EU-Stelara group, and 89 patients switched from Stelara EU to FYB202. The end-of-study visit took place in Week 52.

The SAF, which is the same as the full analysis set (FAS), comprises all patients treated with study medication at least once, n=392, 197 patients treated with FYB202 and 195 patients treated with Stelara EU. The re-randomised analysis set (RRAS) consisted of all patients who were re-randomised and treated with study medication at least once, at Week 28 or later, n=375, (189 patients treated with FYB202 and 186 patients treated with Stelara EU).

Demographics and Baseline Characteristics

Across the studies, demographic characteristics and baseline disease characteristics were comparable across the treatment groups. Prior and concomitant medications were balanced across the treatment groups across the studies.

2.6.8.2. Adverse events

Study FYB202-01-01 & Study FYB202-01-02: TEAEs in Healthy Subjects

In both studies pooled analysis set (n=806)**,** 583 subjects (72.7%) reported 1679 TEAEs. 186 subjects (69.1%) reported 543 TEAEs after the administration of FYB202, 198 subjects (73.9%) reported 548 TEAEs after the administration of Stelara-EU and 199 subjects (74%) reported 588 TEAEs after the administration of Stelara-US.

In study FYB202-01-01, 211 subjects (67.0%) reported 660 TEAEs. Sixty-six (66) subjects (62.9%) reported 196 TEAEs after administration of FYB202, 75 subjects (71.4%) reported 233 TEAEs after administration of EU-approved Stelara and 70 subjects (66.7%) reported 231 TEAEs after administration of US-licensed Stelara.

In study FYB202-01-02, 372 subjects (75.8%) reported 1019 TEAEs. 120 subjects (73.1%) reported 347 TEAEs after the administration of FYB202, 123 subjects (75.5%) reported 315 TEAEs after the administration of EU-approved Stelara and 129 subjects (78.7%) reported 357 TEAEs after the administration of US-licensed Stelara.

In total for both phase 1 studies, the severity of most TEAEs was mild or moderate which was comparable across the groups. The frequency of mild TEAEs across groups was; FYB202: 86 (32%) subjects, Stelara EU: 102 (38.1%) and Stelara US: 103 (38.3%). The frequency of moderate TEAEs across groups was; FYB202: 97 (36.1%) subjects, Stelara EU: 92 (34.3%) and Stelara US: 94 (34.9%). There were 9 subjects that experienced severe TEAEs; 3 events in FYB202, 4 events in Stelara EU, and 4 events in Stelara US group. All were considered unlikely to be related to the study drug except 1 severe AE of ALT and AST increased in the Stelara US group. 3 severe events were reported as SAEs, all occurring in Stelara EU.

TEAEs occurring in ≥ 5% of subjects in any treatment group reported during the study are provided in Table 42 below.

Table 42 TEAEs by MedDRA SOC and PT in at least 5% of healthy volunteers - data pooled SAF (n=315) Study FYB202-01-01 and SAF (n-491) Study FYB202-01-02.

MedDRA System Organ Class MedDRA Preferred Term	FYB202 (N=269) n (%)	Stelara EU (N=268) n (%)	Stelara US (N=269) n (%)
Any TEAE	186 (69.1)	198 (73.9)	199 (74.0)
Infections and infestations Nasopharyngitis Rhinitis COVID-19	90 (33.5) 49 (18.2) 6 (2.2) 16 (5.9)	91 (34.0) 44 (16.4) 17 (6.3) 10 (3.7)	96 (35.7) 58 (21.6) 15 (5.6) 10 (3.7)
Nervous system disorders Headache	67 (24.9) 61 (22.7)	79 (29.5) 73 (27.2)	91 (33.8) 83 (30.9)
General disorders and administration site conditions	49 (18.2)	42 (15.7)	53 (19.7)
Gastrointestinal disorders Diarrhoea	41 (15.2) 11 (4.1)	45 (16.8) 14 (5.2)	38 (14.1) 11 (4.1)
Investigations	39 (14.5)	30 (11.2)	31 (11.5)
Respiratory, thoracic and mediastinal disorders Oropharyngeal pain	25 (9.3) 15 (5.6)	39 (14.6) 21 (7.8)	21 (7.8) 14 (5.2)
Musculoskeletal and connective tissue disorders	28 (10.4)	28 (10.4)	27 (10.0)
Skin and subcutaneous tissue disorders	16 (5.9)	20 (7.5)	14 (5.2)
Injury, poisoning and procedural complications	13 (4.8)	8 (3.0)	20 (7.4)
Reproductive system and breast disorders	11 (4.1)	9 (3.4)	18 (6.7)

MedDRA = Medical Dictionary for Regulatory Activities, N = number of patients per group, n = number of patients per category, SAF = safety analysis set, TEAE = treatment-emergent adverse event.

Study FYB202-01-01 & Study FYB202-01-02: Treatment-Related Adverse Events in Healthy Subjects

In total for both phase 1 studies, TEAEs with suspected relationship to the study intervention were reported in 145 subjects (53.9%) in the FYB202 group, 161 (60.1%) in the Stelara EU group, and 159 (59.1%) in the Stelara US group.

In study FYB202-01-01, 544 TEAEs with suspected relationship to the study intervention were reported in 195 subjects (61.5%); 58 subjects (55.2%) in the FYB202 group, in 71 (67.6%) in the Stelara EU group, and 66 (62.9%) in the Stelara US group. The majority of TEAEs related to study intervention were mild/moderate severity. There was 1 severe TEAE (ALT and AST increased) that was possibly related to the study drug, Stelara US.

In study FYB202-01-02, 531 TEAEs with suspected relationship to the study intervention were reported in 270 subjects; 87 subjects reported 174 (32.8%) AEs in the FYB202 group, 90 subjects reported 174 (32.8%) in the Stelara EU group, and 93 subjects reported 183 (34.5%) AEs in the Stelara US group. The intensity of

IMP-related AEs was mild in 381 out of 531 cases (71.75%), and moderate in 150 out of 531 cases (28.25%). There were no severe AEs with a suspected relationship to the study intervention.

Related TEAEs occurring in ≥ 5% of subjects in any treatment group reported during the study are provided in the Table below. The most frequently reported TEAEs in all treatment groups at the PT level were 'headache' and 'nasopharyngitis'. The TEAE of 'injection site pain' was slightly higher in the FYB202 group, 10 subjects (3.7%), compared to Stelara EU 2 (0.7%) and Stelara US 6 (2.2%). Otherwise FYB202 TEAEs by PT were comparable to Stelara.

Table 43 TEAEs with a Suspected Relationship to Study Intervention by MedDRA System Organ Class and Preferred Term in at least 2% of Healthy Volunteers – SAF (N=315) of Study FYB202-01-01 and SAF (N=491) of Study FYB202-01-02, Data Pooled

MedDRA System Organ Class MedDRA Preferred Term	FYB202 (N=269) n (%)	Stelara EU (N=268) n (%)	Stelara US (N=269) n (%)
Any TEAE	145 (53.9)	161 (60.1)	159 (59.1)
Infections and infestations	62 (23.0)	65 (24.3)	66 (24.5)
Nasopharyngitis	36 (13.4)	34 (12.7)	35 (13.0)
Rhinitis	5 (1.9)	16 (6.0)	13 (4.8)
Oral herpes	5 (1.9)	2 (0.7)	7 (2.6)
Nervous system disorders	48 (17.8)	62 (23.1)	72 (26.8)
Headache	45 (16.7)	57 (21.3)	69 (25.7)
Dizziness	5 (1.9)	7 (2.6)	3 (1.1)
General disorders and administration site	41 (15.2)	36 (13.4)	46 (17.1)
Injection site erythema	6 (2.2)	10 (3.7)	6 (2.2)
Fatigue	7 (2.6)	4 (1.5)	10 (3.7)
Injection site haematoma	6 (2.2)	7 (2.6)	6 (2.2)
Injection site pain	10 (3.7)	2 (0.7)	6 (2.2)
Gastrointestinal disorders	30 (11.2)	34 (12.7)	27 (10.0)
Diarrhoea	11 (4.1)	13 (4.9)	11 (4.1)
Nausea	6 (2.2)	12 (4.5)	4 (1.5)
Vomiting	4 (1.5)	6 (2.2)	3 (1.1)
Abdominal pain	6 (2.2)	2 (0.7)	2 (0.7)
Respiratory, thoracic and mediastinal	15 (5.6)	28 (10.4)	18 (6.7)
Oropharyngeal pain	12 (4.5)	16 (6.0)	12 (4.5)
Cough	4 (1.5)	5 (1.9)	6 (2.2)
Investigations	15 (5.6)	21 (7.8)	19 (7.1)
Alanine aminotransferase increased	6 (2.2)	7 (2.6)	4 (1.5)
Musculoskeletal and connective tissue	11 (4.1)	13 (4.9)	15 (5.6)
Back pain	4 (1.5)	7 (2.6)	4 (1.5)
Skin and subcutaneous tissue disorders	15 (5.6)	14 (5.2)	7 (2.6)
Reproductive system and breast disorders	3 (1.1)	3 (1.1)	6 (2.2)

MedDRA = Medical Dictionary for Regulatory Activities, N = number of patients per group, n = number of patients per category, SAF = safety analysis set, TEAE = treatment-emergent adverse event. Source: Table 15 Summary of Clinical Safety

Study FYB201-03-01: TEAEs in Patients

The safety results are presented in 2 separate time periods:

- Period 1 - From Baseline to Week 28, IP administration at Weeks 0, 4, 16
- Period 2 – From Week 28 to Week 52, IP administration at Weeks 28, 40

Period 1 - From Baseline to Week 28

A total of 158 (40.3%) subjects reported 274 TEAEs. The incidence of subjects who experienced AEs was similar between treatment groups; 78 (39.6%) patients in the FYB202 group and 80 (41.0%) patients in the Stelara EU group.

The intensity of most AEs was mild (FYB202: 51 [25.9%] patients, Stelara EU: 44 [22.6%] patients) or moderate (FYB202: 25 [12.7%] patients, Stelara EU: 35 [17.9%] patients). Three patients reported severe TEAEs: 2 (1.0%) patients treated with FYB202 (Hand fracture, Rash) and 1 (0.5%) patient treated with Stelara EU (Multiple injuries and Road traffic accident). The events Multiple injuries and Road traffic accident were also considered SAEs.

TEAEs occurring in ≥ 2% of subjects in any treatment group before re-randomisation are provided in the Table below. The most frequently reported types of TEAEs by SOC were infections and infestations, General Disorders and Administration Site Conditions, and Investigations. The most frequently reported TEAEs at the PT level were Injection site pain, Nasopharyngitis and Covid-19.

FYB202 treated patients had the highest frequency for SOC 'General Disorders and administration site conditions', 'infection and infestations', 'Musculoskeletal and connective tissue disorders' and 'Skin and subcutaneous tissue disorders'. This was driven by PT injection site pain, nasopharyngitis, arthralgia and pruritus. Of these FYB202-treated patients had a notably higher frequency of PT 'Injection site pain''.

Overall, the incidences and frequency of the majority of the TEAEs by SOC and PT were comparable apart from PT injection site pain.

Table 44 TEAEs by MedDRA SOC and PT in at least 2% of patients before re-randomisation (SAF,n=392) Study FYB202-03-01

MedDRA System Organ Class **MedDRA Preferred Term**	**FYB202 (N=197) n (%)**	**Stelara EU (N=195) n (%)**
Any TEAE	78 (39.6)	80 (41.0)
Infections and infestations Nasopharyngitis Covid-19	30 (15.2) 9 (4.6) 7 (3.6)	24 (12.3) 5 (2.6) 5 (2.6)
General disorders and administration site conditions Injection site pain Injection site reaction	32 (16.2) 22 (11.2) 4 (2.0)	21 (10.8) 15 (7.7) 4 (2.1)
Investigations C-reactive protein increased	12 (6.1) 3 (1.5)	18 (9.2) 5 (2.6)
Injury, poisoning and procedural complications	4 (2.0)	8 (4.1)
Metabolism and nutrition disorders	2 (1.0)	10 (5.1)

Nervous System Disorders Headache	4 (2.0) 3 (1.5)	6 (3.1) 5 (2.6)
Musculoskeletal and connective tissue disorders Arthralgia	7 (3.6) 4 (2.0)	2 (1.0) 0 (0.0)
Gastrointestinal disorders	3 (1.5)	5 (2.6)
Skin and subcutaneous tissue disorders	5 (2.5)	2 (1.0)
Vascular disorders Hypertension	1 (0.5) 0 (0.0)	6 (3.1) 6 (3.1)

MedDRA = Medical Dictionary for Regulatory Activities, N = number of patients per group, n = number of patients per category, SAF = safety analysis set, TEAE = treatment-emergent adverse event.
Source: Table 10 Summary of Clinical Safety

Period 2 - From Week 28 to Week 52

After rerandomization, a total of 67 (17.9%) subjects experienced TEAEs; 33 (17.5%) patients with FYB202-FYB202, 16 (16.5%) patients with Stelara EU-Stelara EU, and 18 (20.2%) patients with Stelara EU-FYB202.

Most TEAEs were of mild severity; in the FYB202-FYB202 group 21 (11.1%) patients, in the Stelara EU-Stelara EU group 12 (12.4%) patients. Moderate severity AEs were reported in 10 (5.3%) patients in the FYB202-FYB202 group, in 3 (3.1%) patients in the Stelara EU- Stelara EU arm, and in 7 (7.9%) patients in the Stelara EU-FYB202 arm. There were 3 (0.8%) severe TEAEs; 2 (1.1%) in the FYB202-FYB202 arm [Appendicitis perforated and Covid-19], and 1 (1%) in the Stelara EU-Stelara EU arm [Pulmonary embolism and Respiratory failure]. All severe TEAEs were serious, with no suspected causal relationship to the study intervention.

TEAEs occurring in ≥ 2% of subjects in any treatment group before re-randomisation are provided in **Table 44** below. The most frequently reported type of TEAEs by SOC were infections and infestations. The most frequently reported TEAEs at the PT level were Covid-19, Nasopharyngitis and Upper respiratory infection. Overall, the incidences and frequency of the majority of the TEAEs by SOC and PT were comparable.

Table 45 TEAEs by MedDRA SOC and PT in at least 2% of patients after re-randomisation (RRAS, n=375) Study FYB202-03-01

MedDRA System Organ Class MedDRA Preferred Term	**FYB202 - FYB202 (N=189) n (%)**	**Stelara EU - Stelara EU (N=97) n**	**Stelara EU - FYB202 (N=89) n (%)**
Any TEAE	33 (17.5)	16 (16.5)	18 (20.2)
Infections and infestations Covid-19 Nasopharyngitis Upper respiratory tract infection	23 (12.2) 13 (6.9) 6 (3.2) 3 (1.6)	13 (13.4) 6 (6.2) 2	12 (13.5) 5 (5.6) 3 (3.4) 2 (2.2)
Metabolism and nutrition disorders Hyperglycaemia	2 (1.1) 0 (0.0)	1 (1.0) 1 (1.0)	2 (2.2) 2 (2.2)

MedDRA = Medical Dictionary for Regulatory Activities, N = number of patients per group, n = number of patients per category, SAF = safety analysis set, TEAE = treatment-emergent adverse

Study FYB201-03-01: Treatment Related Adverse Events in Patients

Period 1 - From Baseline to Week 28

A total of 58 (14.8%) patients experienced TEAEs with a suspected causal relationship to study intervention. The incidence was comparable between treatment groups; 32 [16.2%] patients in the FYB202 group and 26 [13.3%] patients in the Stelara EU group.

There was 1 severe related TEAE in the FYB202 group related to the one event of Rash. This patient experienced a severe rash on day 8 of the study after the first injection of FYB202. The patient recovered after 13 days. The patient was subsequently discontinued from the study before the week 4 dose due to protocol deviation. The sponsor requested the patient discontinue from study for safety reasons.

TEAEs with a suspected causal relationship to study intervention in any treatment group before re-randomisation are provided in the Table below. The most frequently reported MedDRA was Injection site pain with more events and more affected patients in the FYB202 group than in the Stelara EU group; 32 events in 22 (11.2%) patients with FYB202 and 18 events in 15 (7.7%) patients with Stelara EU. This difference is mainly driven by events after the first injection. Overall, the incidences and frequency of the majority of the TEAEs by SOC and PT were comparable, apart from an imbalance of injection site pain.

Table 46-TEAEs with a suspected causal relationship to study intervention by MedDRA System Organ Class and Preferred Term before Re-randomization (SAF, N=392)

MedDRA System Organ Class **MedDRA Preferred Term**	**FYB202 (N=197) n (%)**	**Stelara EU (N=195) n**
Any related TEAE	32 (16.2)	26 (13.3)
General disorders and administration site conditions	29 (14.7)	21 (10.8)
Injection site pain	22 (11.2)	15 (7.7)
Injection site reaction	4 (2.0)	4 (2.1)
Injection site erythema	2 (1.0)	2 (1.0)
Injection site induration	2 (1.0)	0 (0.0)
Induration	1 (0.5)	0 (0.0)
Injection site swelling	1 (0.5)	0 (0.0)
Infections and infestations	1 (0.5)	2 (1.0)
Cystitis	1 (0.5)	0 (0.0)
Laryngitis	0 (0.0)	1 (0.5)
Upper respiratory tract infection	0 (0.0)	1 (0.5)
Nervous system disorders	2 (1.0)	1 (0.5)
Dizziness	1 (0.5)	1 (0.5)
Headache	1 (0.5)	1 (0.5)
Gastrointestinal disorders	0 (0.0)	1 (0.5)
Cheilosis	0 (0.0)	1 (0.5)
Hepatobiliary disorders	0 (0.0)	1 (0.5)
Cholestasis	0 (0.0)	1 (0.5)
Hepatitis toxic	0 (0.0)	1 (0.5)

Investigations White blood cell count increased	1 (0.5) 1 (0.5)	0 (0.0) 0 (0.0)
Skin and subcutaneous tissue disorders **Rash**	1 (0.5) 1 (0.5)	0 (0.0) 0 (0.0)

MedDRA = Medical Dictionary for Regulatory Activities, N = number of patients per group, n = number of patients per category, SAF = safety analysis set, TEAE = treatment-emergent adverse event, Source: Table 12 Summary of Safety

Period 2 - From Week 28 to Week 52

After re-randomization, there were 4 (1.1%) patients with TEAEs with a suspected causal relationship to study intervention; 2 (1.1%) patients treated with FYB202-FYB202 [injection site pain, injection site induration], 2 (2.2%) patients treated with Stelara EU-FYB202 [injection site pain, injection site reaction, nasopharyngitis], and none with Stelara EU-Stelara EU.

2.6.8.3. Serious adverse event/deaths/other significant events

Deaths

In the clinical development program of FYB202, one death occurred in study FYB202-01-01. A 39-year-old female subject died from severe glioblastoma, 99 days after the single subcutaneous injection of Stelara-EU 45 mg. The relationship of this event was assessed as unlikely to be related to the study intervention by the Investigator.

Serious AEs in Healthy Subjects: Study FYB202-01-01 & study FYB202-01-02

In total there were 6 serious adverse events (SAEs) in both phase 1 studies; see **Table 46** below. All were assessed as unlikely related to the study intervention by the Investigator.

Table 47 SAEs in phase 1 studies FYB202-01-01 & FYB202-01-02

Study	Last treatment before SAE onset	MedDRA PT of SAE	Relationship by Investigator	Patient outcome
FYB202-01-01	Stelara EU	Migraine	Unlikely	Resolved without sequelae
	Stelara EU	Glioblastoma	Unlikely	Fatal
FYB202-01-02	FYB202	Concussion	Unlikely	Recovered
	Stelara EU	Hypersensitivity	Unlikely	Recovered
	Stelara US	Road traffic accident	Unlikely	Recovering
	Stelara US	Abortion incomplete	Unlikely	Recovered

Serious AEs in Patients: Study FYB202-03-01

A total of 11 subjects experienced 15 SAEs. Before re-randomisation there were 4 SAEs in 3 (1.5%) patients in the FYB202 group and 6 SAEs in 3 (1.5%) patients in the Stelara EU group. After re-randomisation there were 5 (1.3%) serious TEAEs; 3 (1.6%) in the FYB202- FYB202 group, 1(1%) in the Stelara EU-Stelara EU group and 1 (1.1%) in the Stelara EU-FYB202 group. All were assessed as unlikely related to the study intervention by the Investigator. See the table below for further details.

Table 48 SAEs in Study FYB202-03-01

Study	Treatment	MedDRA PT of SAE	Relationship by Investigator	Patients's outcome
FYB202-03-01 Period 1	FYB202*	Covid-19 pneumonia	Unlikely	Recovered
		Pulmonary embolism	Unlikely	Recovered
	Stelara EU*	Renal cancer metastatic	Unlikely	Not recovered
	FYB202	Covid-19	Unlikely	Recovered
	FYB202 #	Pneumothorax spontaneous	Unlikely	Recovered
	Stelara EU #	Road traffic accident	Unlikely	Not reported
		Multiple injuries	Unlikely	Not reported
	Stelara EU	Bile duct stone	Unlikely	Recovered
		Pancreatitis acute	Unlikely	Recovered
		Cholelithiasis	Unlikely	Recovered
FYB202-03-01 Period 2	FYB202-FYB202	Carpal tunnel syndrome	Unlikely	Recovered
	FYB202-FYB202	Appendicitis perforated	Unlikely	Recovered
	FYB202-FYB202	Covid-19	Unlikely	Recovered
	Stelara EU- Stelara EU	Respiratory failure	Unlikely	Recovered
	Stelara EU -FYB202*	Congenital anomaly	Unlikely	Not recovered

***** Study intervention was discontinued # Study intervention was interrupted

AESI - Study FYB202-01-01 & study FYB202-01-02:

No adverse events of special interest (AESIs) were defined for Study FYB202-01-01 & study FYB202-01-02. Local tolerability was assessed and will be presented here.

Local tolerability

In Study FYB202-01-01, 25 healthy volunteers had mild injection site events that were documented as TEAEs; FYB202: 10 subjects, Stelara EU: 6 subjects, Stelara US: 9 subjects. All TEAEs were recovered/resolved by the end of the study. 15 subjects had mild injection site haematoma that was documented as TEAEs; 5 in each treatment group. 18 subjects documented pain of any severity at the injection site via visual analogue scale (FYB202:8, Stelara EU:3, Stelara US:7). VAS distances had a higher range for FYB202; FYB202: 1 mm to 45 mm, Stelara EU: 3 mm to 9 mm, Stelara US: 1 mm to 12 mm.

In Study FYB202-01-02, 63 subjects had injection site reactions that were documented as AEs of mild intensity; FYB202: 21 subjects, Stelara US: 16 subjects, Stelara US: 23 subjects. FYB202 had the most frequent reaction of injection site pain, 7 subjects compared to 1 subject Stelara EU and 3 subjects Stelara US. All TEAEs resolved. A total of 29 out of 491 (5.91%) subjects documented pain of any severity at the injection site via VAS (FYB202: 9, Stelara EU: 9, Stelara US: 11). VAS distances had a higher range for FYB202; FYB202: 1 mm to 33 mm, Stelara EU: 1 mm to 20 mm, Stelara US: 1 mm to 7 mm.

AESI - Study FYB201-03-01:

AESIs based on the prescribing information for Stelara were defined as:

- Serious infections
- All malignancies, in particular, non-melanoma skin cancer

- Systemic and respiratory hypersensitivity reactions
- Serious skin conditions
- Injection site reactions (ISRs)

Patients treated with FYB202 reported 43 events in 30 (15.2%) patients and patients treated with Stelara EU reported 25 events in 22 (11.3%) patients.

Serious infections: Before re-randomisation, there was one patient with a serious infection (Covid-19) in the FYB202 group. After re-randomisation, there was one patient with a serious infection (Covid-19) in the FYB202-FYB202 group.

All malignancies, in particular non-melanoma skin cancer: Before re-randomisation, there was one patient with a malignancy (Renal cancer metastatic) in the Stelara EU group. No case of non-melanoma skin cancer was identified.

Systemic and respiratory hypersensitivity reactions & Serious skin conditions: No cases were identified.

There were no AESIs with a relationship to study interventions for serious infection, all malignancies, systemic and respiratory hypersensitivity reactions and serious skin conditions.

The investigator suspected a causal relationship to study interventions for all Injection site reactions AESIs. Before re-randomisation, the incidence of injection site events in patients treated with FYB202 was 29 (14.7%) versus 21 (10.8%) in patients treated with Stelara EU. After re-randomisation, there were three patients with injection site events all treated with FYB202; 2 in the FYB202-FYB202 group and 1 in the Stelara EU-FYB202 group. The table below outlines the injection site reactions before rerandomization.

AEs with PT Injection site pain occurred more frequently in the FYB202 group (32 events in 22 (11.2%) patients) than in the Stelara EU group (18 events in 15 (7.7%) patients) with the largest difference after the first administration. At 45 minutes after the first administration the number of patients with ISRs was higher in the FYB202 group 7.1% compared to Stelara EU 3.6%. Most of these TEAEs subsided after 1 day. All were rated as mild intensity. Patients rated the severity of injection site pain using a VAS scoring FYB202 between 0.4 to 1.1 mm on average and Stelara EU between 0.2 to 0.5 mm on average.

Table 49 Injection Site Reactions AESI before rerandomization (SAF N=392)

AESI Category **MedDRA System Organ Class** MedDRA Preferred Term	**FYB202** **(N=197)** **N (%) E**	**Stelara EU** **(N=195)** **N (%) E**
Injection Site Reaction **General Disorders and Administration Site Conditions**	29 (14.7) 42	21 (10.8) 24
Injection Site Pain	22 (11.2) 32	15 (7.7) 18
Injection Site Reaction	4 (2) 4	4 (2.1) 4
Injection Site Erythema	2 (1) 2	2 (1) 2
Injection Site Induration	2 (1) 2	2 (1) 2
Induration	1 (0.5) 1	0 (0) 0
Injection Site Swelling	1 (0.5) 1	0 (0) 0

2.6.8.4. Laboratory findings

Study FYB202-01-01:

Fifty-seven (57) TEAEs were associated with clinically significant abnormal laboratory findings. The most frequently reported TEAEs were increases in ALT and increased blood creatine phosphokinase.

The percentage of subjects with increased CK was higher after administration of FYB202 (6.7%) compared to Stelara-EU (1.9%) and Stelara-US (2.9%). There were 5 cases of severe CK increase: 3 FYB202 group, 1 Stelara EU and 1 Stelara US. None of the TEAEs of increased CK were considered drug-related by investigator.

The percentage of subjects with increased ALT was comparable after the administration of FYB202 and Stelara-EU (both 6.7%) which was higher compared to Stelara-US (3.8%). Of these TEAEs 17 were considered drug-related; FYB202: 4.8%, Stelara EU: 5.7%, Stelara US: 2.9%. There was 1 case of severe ALT increase in Stelara US group which was considered possibly drug-related, Stelara US.

There were no notable differences in values of vital signs, ECG results or physical examination between the FYB202 and Stelara treatment groups.

Study FYB202-01-02:

89 TEAEs were associated with clinically significant abnormal laboratory findings, 36 of these were considered drug-related; 10 events in FYB202, 14 events in Stelara EU and 12 events in Stelara US. The most frequently reported drug-related TEAEs by PT were C-reactive protein increased and abnormal urine analysis. There were no notable differences between the FYB202 and Stelara treatment groups.

There were no notable differences in values of vital signs, ECG results or physical examination between the FYB202 and Stelara treatment groups.

Study FYB202-03-01:

A total of 50 TEAEs were associated with clinically significant abnormal laboratory findings; of which 34 were mild and 36 were moderate AEs. Before re-randomisation under SOC Investigations, there were 13 events reported in 12 (6.1%) patients in the FYB202 group and 24 events reported in 18 (9.2%) patients in the Stelara EU group. The most frequently reported TEAEs by PT was C-reactive protein increased; FYB202: 1.5%, Stelara US: 2.6%. Otherwise, TEAEs occurred in 1 or 2 patients in the groups.

After re-randomisation, 1 event of GGT increased in 1 (0.5%) patient in the FYB202-FYB202 group and 4 events in 1 (1.0%) patient in the Stelara EU-Stelara EU group (blood creatinine increased, blood urea increased, blood uric acid increased and GRF decreased) and none in the Stelara EU-FYB202 group fulfilled these criteria.

The Investigator suspected no causal relationship between any haematology, clinical chemistry, urinalysis AE and study intervention.

There were no notable differences in values of vital signs, ECG results or physical examination between the FYB202 and Stelara treatment groups.

2.6.8.5. In vitro biomarker test for patient selection for safety

Not applicable.

2.6.8.6. Safety in special populations

Section not applicable for biosimilars.

The applicant, for completeness, discussed the cases of pregnancies that occurred during the drug development programme.

Three pregnancies occurred in Study FYB202-01-02. Two pregnancies were detected during the study and were reported as major protocol deviations. In both cases, the pregnancies were terminated by elective abortion (no congenital anomalies reported). One of these pregnancies was also reported as SAE (Abortion incomplete) because pharmacological abortion with mifepristone resulted in an incomplete abortion which required hospitalisation and uterine curettage. At the end-of-study visit, one further pregnancy was detected. The outcome of the pregnancy was followed up until the delivery of a healthy child.

One pregnancy occurred in Study FYB202-03-01 with a congenital anomaly/birth defect (SAE). This patient had a major protocol deviation connected to this AE. The subject stopped the initial contraceptive and started using condoms and emergency contraceptives instead. Site staff were not informed. The subject became pregnant while receiving study medication. Pregnancy was not detected by history or urine pregnancy testing at V5/wk28 or V6/W40. After the 5th injection of ustekinumab a home self-pregnancy test returned positive. This was not reported. At 26 weeks gestational age, 55 days after the 5th injection (week 40) of 45 mg ustekinumab as FYB202, the patient gave birth to 2 live female infants via Caesarean section, after the pregnancy with twins was confirmed by a maternity hospital the day previous. 56 days after birth, both infants were self-breathing, no gene defects were identified, and no other findings except cranial malformation (hypertelorism, slight exophthalmos and cranium developmental anomaly) were noted in both children. The first child also had an absence of the left leg V digit and an additional digit on the right leg. No further follow-up information is available. The event of congenital anomaly of twins was assessed as unexpected and unlikely to be related to the study drug.

2.6.8.7. Immunological events

Bioanalytical methods

PK Assay, ADA Assay and Nab assays are discussed in Section 2.6.3. .

Study FYB202-01-01:

ADA/NAb formation

Overall, ADA incidence from baseline to Day 112 was 15.2% for FYB202 compared to 36.5% for Stelara EU and 34.3% for Stelara US. NAb incidence from baseline to Day 112 was 8.6% for FYB202 compared to 22.1% for Stelara EU and 22.9% for Stelara US. The majority of treatment-emergent ADA signals were classified as treatment-induced and persistent. ADA prevalence was maximal on Day 14 for Stelara US. Whereas for FYB202 & Stelara EU, ADA and NAb prevalence was at a maximum at Day 112, with Stelara EU also having a peak in ADA positivity at D14.

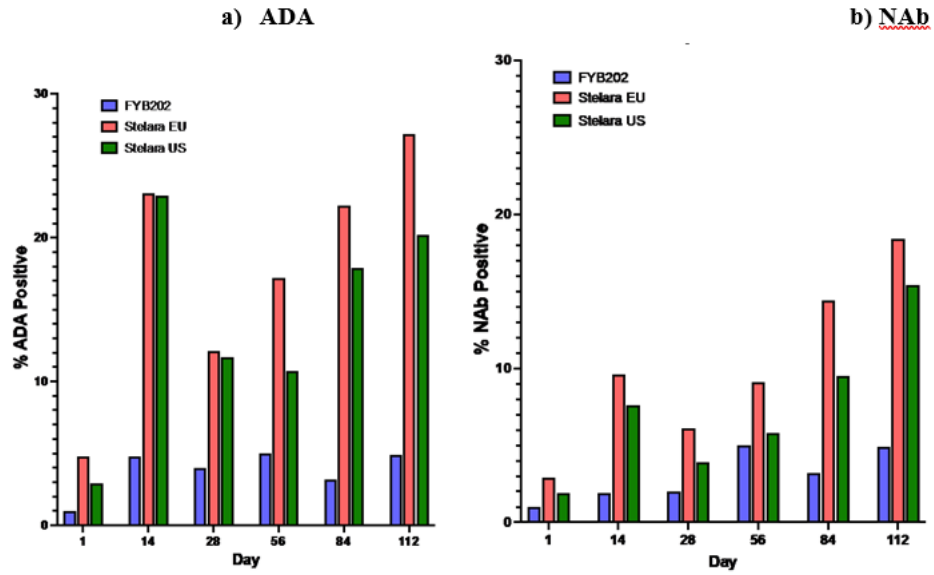
Table 49 and **Figure 23** outline the proportion of subjects with confirmatory positive ADA & NAB over the study period.

Table 50 ADA/NAb prevalence and ADA titer vs. time from Baseline to Day 112 (Safety analysis set FYB202-01-01)

Category	Sample timepoint					
	Day 1	**Day 14**	**Day 28**	**Day 56**	**Day 84**	**Day 112**
FYB202 (N=105)						
Evaluable (n)	105	105	99	101	94	102
ADA positive (n)(%)	1 (1)	5 (4.8)	4 (4)	5 (5)	9 (9.6)	12 (11.8)
NAb positive (n)(%)	1 (1)	2 (1.9)	2 (2)	5 (5)	3 (3.2)	5 (4.9)
ADA titer: Median Geom. mean Max	80 80.0 80	80 93.3 118	132.5 144.1 310	118 263.0 2160	341 367.5 10200	409 481.6 26300
Stelara EU (N=105)						
Evaluable (n)	105	104	99	99	90	103
ADA positive (n)(%)	5 (4.8)	24 (23.1)	12 (12.1)	17 (17.2)	20 (22.2)	28 (27.2)
NAb positive (n)(%)	3 (2.9)	10 (9.6)	6 (6.1)	9 (9.1)	13 (14.4)	19 (18.4)
ADA titer: Median Geom. mean Max	136 128.7 158	152.5 213.7 1420	148.5 226.7 1200	142 208.2 4210	150 359.4 17800	226 325.1 17100
Stelara US (N=105)						
Evaluable (n)	105	105	103	103	95	104
ADA positive (n)(5)	3 (2.9)	24 (22.9)	12 (11.7)	11 (10.7)	17 (17.9)	21 (20.2)
NAb positive (n)(%)	2 (1.9)	8 (7.6)	4 (3.9)	6 (5.8)	9 (9.5)	16 (15.4)
ADA titer: Median Geom. mean Max	135 117.2 149	144 198.4 2210	157 193.6 634	450 470.7 6180	146 363.1 30300	263 428.3 19500

n = number of evaluable subjects within the specified category or total number of subjects per visit, % = number of evaluable subjects within the specified category / total number of subjects per visit, N = total number of subjects in the analysis set and treatment group, ADA = anti-drug antibody. Source: Table 52 ISI. Shaded boxes represent peak values of ADA and NAb positivity and ADA GMT.

Figure 23 ADA and NAb prevalence vs. time from baseline to Day 112 in Study FYB202-01-01 – SAS



ADA = anti-drug antibody; NAb = neutralizing antibody

Safety:

The analysis of the relationship of ADA status to safety parameters focused on AESIs only. No AESIs were defined for Study FYB202-01-01. This is an assessment as set out in the ISI SAP. The following groups of AEs are of special interest for Phase 1: Drug hypersensitivity reactions, anaphylaxis and Injection Site Reactions.

The majority of patients who experienced AESI were ADA-negative. For the ADA-negative subjects, the incidence of any AESI was 21.3% for FYB202 compared to 16.9% for Stelara EU and 18.1% for Stelara US. The incidence of AESI by PT was of similar frequency between both groups, apart from injection site pain and pruritis being higher in the FYB202 group, 5.6% and 5.6%, respectively, compared to Stelara EU (1.4%, 2.8%) and Stelara US (4.2%, 0%), respectively.

There were only 2 ADA-positive subjects (12.5% of the total) with AESI in the FYB202 group, compared to 6 subjects (18.2%) in each of the Stelara EU & Stelara US treatment groups. The incidence of AESI by PT was of similar frequency between both groups, apart from PT injection site haematoma being higher in the Stelara EU group (12.1%), compared to FYB202 (6.3%) and Stelara US (0%), along with PT cough being higher in Stelara US group (12.1%), compared to 0% in the other 2 groups.

There were no reports of hypersensitivity reactions or anaphylaxis in either treatment group during the study period.

Study FYB202-01-02:

ADA/NAb formation

Overall, ADA incidence from baseline to Day 112 was 19% for FYB202 compared to 42.3% for Stelara EU and 50.6% for Stelara US. NAb incidence from baseline to Day 112 was 9.8% for FYB202 compared to 15.3% for Stelara EU and 17.7% for Stelara US. The majority of treatment-emergent ADA signals were classified as treatment-induced. Approximately 50% of the ADA signals induced by Stelara EU and Stelara US fulfilled the "transient" classification, while the majority of the signals induced by FYB 202 were classified as "persistent".

Despite this, the proportion of patients with persistent positive ADA from baseline to D112 remains lower in the FYB202 group (10.4%) compared to Stelara EU (19%) & Stelara US (25.6%).

For Stelara EU and Stelara US, ADA prevalence peaked at Day 10, with 30.2 % and 32.7 % ADA positive respectively. In the FYB202 group, ADA prevalence increased steadily from baseline to End-of-Study, with 15.5 % ADA-positive subjects at Day 112. The time point of highest incidence of subjects with a positive NAb result was Day 112 in all three treatment groups (FYB202: 7.93%, EU-Stelara: 9.20%, US-Stelara: 10.37%). The overall ADA geometric mean titres were slightly higher for FYB202 compared to the two reference products; 321.46 (FYB202), 200.79 (EU-Stelara) and 249.42 (US-Stelara). All three groups had different time points for peak ADA GMTs.

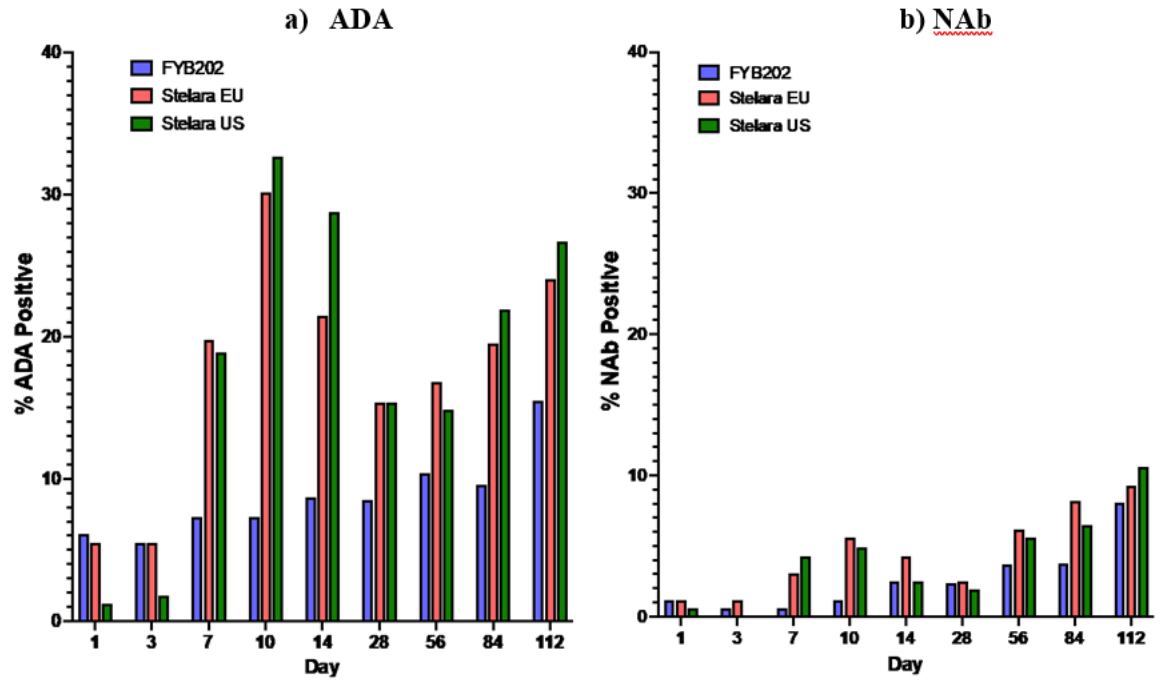
Table 51 and **Figure 24** outline the proportion of subjects with confirmatory positive ADA & NAb over the study period.

Table 51 ADA/NAb prevalence and ADA titre vs. time from Baseline to Day 112 in Study FYB202-01-02 – Safety Analysis Set

Category	Sample timepoint								
	Day 1	Day 3	Day 7	Day 10	Day 14	Day 28	Day 56	Day 84	Day 112
FYB202 (N=164)									
Evaluable (n)	164	163	164	164	161	164	164	157	162
ADA positive (n)(%)	10 (6.1)	9 (5.5)	12 (7.3)	12 (7.3)	14 (8.7)	14 (8.5)	17 (10.4)	15 (9.6)	25 (15.5)
NAb positive (n)(%)	2 (1.2)	1 (0.6)	1 (0.6)	2 (1.2)	4 (2.5)	4 (2.4)	6 (3.7)	6 (3.8)	13 (8.1)
ADA titer: Median Geom. mean Max	 137.0 177.9 4580	 140.0 174.9 2830	 141.5 206.2 4280	 144.0 296.2 19900	 123.5 267.6 30600	 402.3 151.5 35800	 158.0 389.2 20500	 380.0 654.5 25500	 159.0 365.5 12100
Stelara EU (N=163)									
Evaluable (n)	163	163	162	162	163	162	162	159	162
ADA positive (n)(%)	9 (5.5)	9 (5.5)	32 (19.8)	49 (30.2)	35 (21.5)	25 (15.4)	27 (16.8)	31 (19.5)	39 (24.1)
NAb positive (n)(%)	2 (1.2)	2 (1.2)	5 (3.1)	9 (5.6)	7 (4.3)	4 (2.5)	10 (6.2)	13 (8.2)	15 (9.3)
ADA titer: Median Geom. mean Max	 114.0 114.6 154	 117.0 119.7 212	 122.5 143.6 10200	 141.0 227.5 89900	 157.0 245.6 49000	 129.0 166.0 27700	 127.0 153.3 10600	 265.0 274.6 6640	 148.0 256.8 4190
Stelara US (N=164)									
Evaluable (n)	164	164	164	162	163	162	161	155	162
ADA positive (n)(%)	2 (1.2)	3 (1.8)	31 (18.9)	53 (32.7)	47 (28.8)	25 (15.4)	24 (14.9)	34 (21.9)	43 (26.7)
NAb positive (n)(%)	1 (0.6)	0 (0)	7 (4.3)	8 (4.9)	4 (2.5)	3 (1.9)	9 (5.6)	10 (6.5)	17 (10.6)
ADA titer: Median Geom. mean Max	 103.0 100.4 126	 112.0 103.6 124	 145.0 211.6 7120	 244.0 295.5 50100	 150.0 249.5 33800	 146.0 191.5 5920	 142.5 224.8 8880	 140.0 240.7 17700	 149.0 310.6 16900

Shaded boxes represent peak values of ADA and NAb positivity and ADA GMT.

Figure 24 ADA and NAb prevalence vs. time from baseline to Day 112 in Study FYB202- 01-02 – SAS



ADA = anti-drug antibody; NAb = neutralizing antibody

Safety

The analysis of the relationship of ADA status to safety parameters focused on AESIs only. No AESIs were defined for Study FYB202-01-01. This is an assessment as set out in the ISI SAP. The following groups of AEs are of special interest for Phase 1: Drug hypersensitivity reactions, anaphylaxis and Injection Site Reactions.

The majority of patients who experienced AESI were ADA-negative. For the ADA-negative subjects, the incidence of any AESI was 16.7% for FYB202 compared to 25% for Stelara EU and 13.3% for Stelara US. The incidence of AESI by PT was of similar frequency between both groups, apart from injection site erythema and rash being higher in the Stelara EU group, (10% and 4%), respectively, compared to FYB202 (2.9%, 0.7%) and Stelara US (2.4%, 1.2%), respectively.

Out of the 25 ADA-positive subjects in the FYB202 treatment group, there were 5 subjects with an AESI (20% of total), compared to 7 out of 63 ADA-positive subjects (11.1% of total) for Stelara EU and 10 out of 81 ADA positive subjects (12.3% of total) for Stelara US. The incidence of AESI by PT was of similar frequency between both groups, apart from PTs of injection site erythema, injection site pain, cough and dermatitis bullous being higher in the FYB202 group (8%, 8%, 4% and 4%, respectively), compared to Stelara EU (0%, 0%, 1.6%, 0%) and Stelara US (4.9%, 1.2%, 1.2%,0%), respectively.

There was one report of hypersensitivity reaction in an ADA-positive subject who received Stelara EU. The SAE was assessed as severe and unlikely related to the drug.

Study FYB202-03-01:

ADA/NAb formation

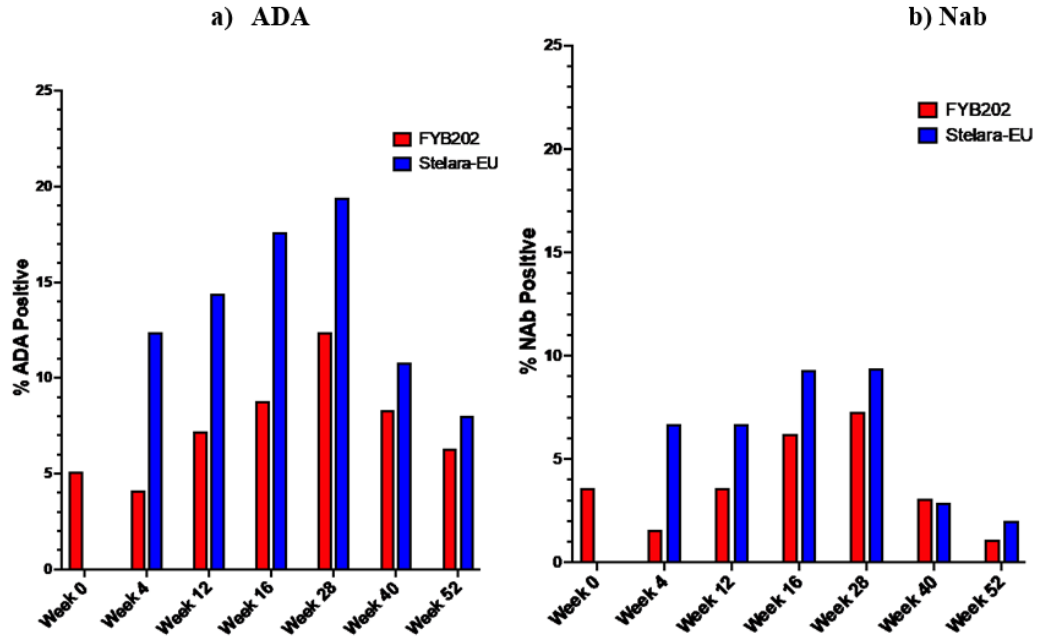
Overall, ADA incidence from baseline to Week 52 was 14.9% for FYB202 compared to 29.2% for Stelara EU. NAb incidence from baseline to Week 52 was 9.7% for FYB202 compared to 18.9% for Stelara EU. ADA and NAb prevalence in both treatment groups was maximal at Week 28; 12.6% for FYB202 vs. 19.5% for Stelara EU. At Week 52, ADA prevalence was 6.3% for FYB202 compared to 8% for patients treated with Stelara EU during the complete study period.

Table 52 ADA/NAb prevalence and ADA titre vs. time from Week 0 to Week 16 in Study FYB202-03-01 – SAS (n=392)

Category	Pre-treatment	Week 4	Week 12	Week 16
FYB202 (N=197)				
Evaluable (n)	196	193	194	194
ADA positive (n) (%)	10 (5.1)	8 (4.1)	14 (7.2)	17 (8.8)
NAb positive (n) (%)	7 (3.6)	3 (1.6)	7 (3.6)	12 (6.2)
Titer geomean (CV)	108.78 (69.54)	157.18 (131.62)	147.97 (74.32)	179.35 (97.77)
Stelara EU (N=195)				
Evaluable (n)	195	194	194	193
ADA positive (n)(%)	0 (0)	24 (12.4)	28 (14.4)	34 (17.6)
NAb positive (n)	0 (0)	13 (6.7)	13 (6.7)	18 (9.3)
Titer geomean (CV)	-	160.47 (163.09)	190.03 (138.0)	189.31 (168.14)

n = number of patients within the specified category or total number of patients per visit, % = number of patients within the specified category / total number of patients per visit, N = total number of patients in analysis set and treatment group, ADA = anti-drug antibody; NAb = neutralizing antibody. Source: Table 12-19 CSR. Shaded boxes represent peak values of ADA and NAb positivity and ADA GMT.

Figure 25 ADA and NAb prevalence vs. time from Week 0 to Week 52 in Study FYB202-03-01 – Safety Analysis Set



ADA = anti-drug antibody; NAb = neutralizing antibody. Source ISI Study FYB202-03-01

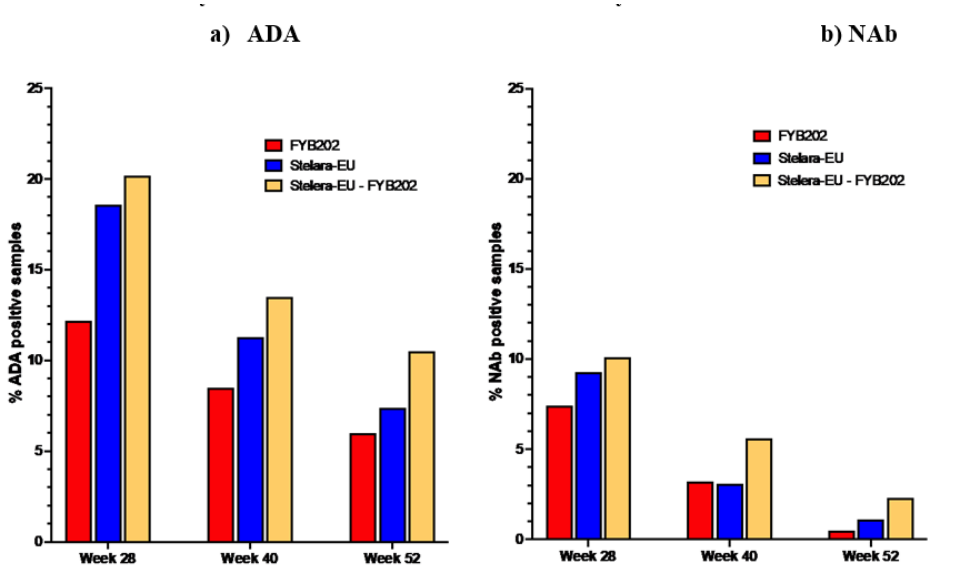
Table 53 ADA/NAb prevalence and ADA titre vs. time from Week 28 to Week 52 in Study FYB202-03-01 – RRAS (n=375)

Category	Sample timepoint (predose)		
	Week 28	Week 40	Week 52
FYB202- FYB202 (N=189)			
Evaluable (n)	189	189	183
ADA positive (n) (%)	23 (12.2)	16 (8.5)	11 (6.0)
NAb positive (n) (%)	14 (7.4)	6 (3.2)	1 (0.5)
Titer geomean (CV)	221.86 (133.57)	233.33 (189.43)	290.54 (319.08)
Stelara EU – Stelara EU (N=97)			
Evaluable (n)	97	97	94
ADA positive (n) (%)	18 (18.6)	11 (11.3)	7 (7.4)
NAb positive (n) (%)	9 (9.3)	3 (3.1)	1 (1.1)
Titer geomean (CV)	158.26 (89.09)	212.87 (106.95)	217.24 (142.23)

Stelara EU –FYB202 (N=89)			
Evaluable (n)	89	89	86
ADA positive (n) (%)	18 (20.2)	12 (13.5)	9 (10.5)
NAb positive (n) (%)	9 (10.1)	5 (5.6)	2 (2.3)
Titer geomean (CV)	267.59 (179.11)	191.41 (120.71)	200.73 (175.46)

n = number of patients within the specified category or total number of patients per visit, % = number of patients within the specified category / total number of patients per visit, N = total number of patients in analysis set and treatment group, ADA = anti-drug antibody; NAb = neutralizing antibody. Source: Table 12-20 CSR. Shaded boxes represent peak values of ADA and NAb positivity and ADA GMT.

Figure 26 ADA and Nab prevalence vs. time from Week 28 to Week 52 by eCRF visit in Study FYB202-03-01 - RRAS



ADA = anti-drug antibody; NAb = neutralizing antibody. Source Figure 41 ISI Report Study FYB202-03-01

Based on a cumulative analysis of treatment induced ADA, treatment with Stelara EU induced ADAs in more patients than treatment with FYB202; 54 (27.7%) in Stelara EU compared to 20 (10.4%) in FYB202. This has a difference of -17.33% with 95% CI: [-25.15%; -9.51%] between the treatment groups from Week 0 to 28.

Impact of transition from Stelara EU to FYB202 on ADA/NAb response dynamics

At week 28, before re-randomisation and pre-dose differences in ADA prevalence were observed between groups: (12.2% for FYB202, 18.6% for Stelara EU-Stelara EU and 20.2% for Stelara-FYB202). The incidence of ADA and NAb positivity was higher for the Stelara EU-FYB202 switch group at all time points after re-randomisation; see table above. Yet, the ADA and NAb positivity declined after re-randomisation for all groups. ADA titre distributions across the treatment groups were comparable at Week 40 and Week 52.

After rerandomization, no patients who were ADA negative at Week 28 became ADA positive following the transition from Stelara EU to FYB202 at Week 28. For patients who remained on Stelara EU, two patients who were ADA negative at Week 28 seroconverted to ADA positive status at Week 40. For patients who remained on FYB202, one patient who was ADA negative at Week 28 seroconverted to ADA positive status at Week 40.

Safety

The relationship between ADA status and AESI was assessed.

The majority of patients who experienced AESI were ADA-negative. For the ADA-negative subjects, the incidence of any AESI was 18% for FYB202 compared to 10.8% for Stelara EU. The incidence of AESI under SOC General disorders and administration site conditions was 16.9% for FYB202 compared to 10.1% for Stelara EU. The incidence of PT injection site pain was 12.8% for FYB202 compared to 5.8% for Stelara EU. Other AESI were of similar frequency between both groups.

Out of the 23 patients with AESI, there was only one ADA positive subject (4.3% of total) in the FYB202 group with an AESI (PT: injection site induration) compared to 7 out of 56 patients with ADA positive results (12.5% of total) in the Stelara EU treatment group (all PT: injection site pain).

There were no reports of hypersensitivity reactions or anaphylaxis in either treatment group during the 52-week study period.

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

Study FYB202-01-01 & study FYB202-01-02:

No patients discontinued study intervention due to TEAEs, as a single dose of ustekinumab 45mg was given. No patients were discontinued from the study due to TEAEs.

Study FYB202-03-01:

Six patients discontinued the study intervention due to AEs. Before re-randomisation, there were 5 (1.3%) patients that experienced TEAEs that led to treatment discontinuation and study withdrawal; 2 (1%) in FYB202 arm [pain in extremity, blood pressure increased, Covid-19 pneumonia, pulmonary embolism] and 3 (1.5%) in Stelara EU arm [headache, dizziness, renal cancer metastatic, cholestasis, hepatitis toxic]. The Investigator suspected a causal relationship between the study drug with AEs Headache and Dizziness in one patient (Stelara EU) and Cholestasis and Hepatitis toxic in another patient (Stelara EU). Both were considered moderate severity, non-serious.

After re-randomisation, there was 1 patient who experienced a TEAE (congenital anomaly) that led to treatment discontinuation and study withdrawal in the Stelara EU-FYB202 group. This was assessed as unlikely to be related to the study intervention.

2.6.8.10. Post marketing experience

Not applicable.

2.6.9. Discussion on clinical safety

Patient exposure

The clinical safety of FYB202 was assessed in three clinical studies, two clinical Phase I pharmacokinetic (PK) studies in healthy subjects (FYB202-01-01 and FYB202-01-02) and a clinical Phase III efficacy and safety study in patients with moderate to severe plaque psoriasis (FYB-202-03-01). In the phase 1 studies, the pooled safety analysis set (SAF) comprised 806 healthy volunteers; FYB202 n=269, EU-STELARA n=268, and US-STELARA n = 269; study FYB202-01-01 n = 315, & study FYB202-01-02 n=491. In Study FYB202-03-01, a total of 392 patients were randomized to receive either FYB202 or Stelara-EU; this represents the SAF; 197 patients were treated with FYB202 and 195 patients were treated with Stelara EU. The re-randomized analysis set (RRAS) consisted of all patients who were re-randomized and treated with study medication at least once at Week 28 or later, n=375, (189 patients treated with FYB202 and 186 patients treated with Stelara EU). The duration of exposure and number of doses administered is acceptable to the CHMP.

The demographic and baseline characteristics were comparable across the treatment groups. The medical/surgical histories and medication use were comparable across the treatment groups.

The FYB202 clinical development programme and design of the studies are adequate to evaluate the comparability of FYB202 and its reference product EU-Stelara in terms of safety and immunogenicity.

Adverse events

Study FYB202-01-01 and Study FYB202-01-02

In both studies pooled analysis set (n=806), 583 subjects (72.7%) reported 1679 TEAEs. The frequency of TEAEs was similar across groups, being slightly lower for FYB202; FYB202: 69.1%, Stelara EU: 73.9%, Stelara US: 74%.

Most TEAEs were of mild/moderate intensity. A similar number of severe TEAEs occurred across the groups. One severe TEAE (ALT and AST increased) was considered possibly related to Stelara US in study FYB202-01-01.

In the pooled phase 1 study, the most frequently reported (≥ 5% of subjects) TEAEs by preferred term (PT) in the FYB202 arm were headache (22.7% of subjects), followed by nasopharyngitis (18.2% of subjects), Covid-19 (5.9%) and oropharyngeal pain (5.6% of subjects each). A similar profile was observed for these TEAEs in the EU- and US-STELARA arms, except Covid-19 was slightly higher in the FYB202 group, 16 (5.9%), compared to Stelara EU 10 (3.7%) and Stelara US 10 (3.7%). The most frequently reported (≥ 5% of subjects) TEAEs considered to be related to the IP by PT in the FYB202 arm were headache (16.7% of subjects), followed by nasopharyngitis (13.4% of subjects). A similar profile was observed for these TEAEs in the EU- and US-STELARA arms, except for headache, which was lower in the FYB202 group. Headache and nasopharyngitis corresponded with the known safety profile of ustekinumab. Of the TEAEs by PT that had a notably slightly higher frequency in the FYB202 group, only the TEAE 'injection site pain' with suspected relationship to the study intervention was slightly higher in the FYB202 group, 10 subjects (3.7%), compared

to Stelara EU 2 (0.7%) and Stelara US 6 (2.2%). Otherwise, FYB202 TEAEs by SOC & PT were comparable to Stelara.

There was one death in study FYB202-01-01, Stelara-EU, due to glioblastoma considered unlikely related to the study intervention; this is agreed by the CHMP. There were 6 SAEs in total across both studies; 2 SAEs in FYB202-01-01 and 4 SAEs in FYB202-01-02. Only 1 SAE of concussion occurred in the FYB202 group. All other SAEs occurred in Stelara EU (3) or Stelara US (2). None were considered as related to the study intervention.

In the pooled phase 1 data, the proportion of subjects who experienced TEAEs considered to be related to the investigational product by the Investigator wase comparable across the three treatment groups. Most were considered of mild intensity. In general, the safety profile reported in Studies FYB202-01-01 and FYB202-01-02 for FYB202 is comparable to the EU and US Stelara treatment groups. The FYB202 group had comparable frequencies in overall TEAEs reported. SOC and PT were also comparable, except for injection site pain being slightly higher in the FYB202 group. Overall, the safety profile is consistent with the known safety profile of Stelara and no new safety concerns were identified.

Study FYB202-03-01

In period 1, a total of 158 (40.3%) subjects reported 274 TEAEs. The incidence of subjects who experienced AEs was similar between treatment groups: 78 (39.6%) patients in the FYB202 group and 80 (41.0%) patients in the Stelara EU group.

The majority of the TEAEs were mild or moderate in severity, and these incidences were comparable across the treatment groups. Three patients reported severe TEAEs: 2 (1.0%) patients treated with FYB202 (hand fracture, rash) and 1 (0.5%) patient treated with Stelara EU (multiple injuries and road traffic accident).

The most frequently reported MedDRA by PT was Injection site pain with more events and affected patients in the FYB202 group than in the Stelara EU group; 32 events in 22 (11.2%) patients with FYB202 and 18 events in 15 (7.7%) patients with Stelara EU. This difference is mainly driven by events after the first injection.

The occurrence of AEs with a suspected causal relationship to study intervention was comparable in both treatment groups (FYB202: 16.2%, Stelara EU: 13.3%). There was one severe related TEAE in the FYB202 group related to the one event of rash.

After rerandomization at Week 28, a total of 67 (17.9%) subjects experienced TEAEs. The incidence of subjects who experienced AEs was similar between treatment groups; FYB202-FYB202: 17.5%, Stelara EU-Stelara EU: 16.5%, Stelara EU-FYB202: 20.2%.

Most TEAEs were of mild or moderate severity, which was comparable across groups. There were 3 severe TEAEs; 2 (1.1%) in the FYB202-FYB202 arm (appendicitis perforated and Covid-19), and 1 (1%) in the Stelara EU-Stelara EU arm (pulmonary embolism and respiratory failure). All severe TEAEs were serious with no suspected causal relationship to the study intervention.

In period 2, the most frequently reported TEAEs by SOC were infections and infestations, which were comparable across groups. The most frequently reported TEAE by PT were Covid-19, Nasopharyngitis, and Upper respiratory infection, which were comparable across groups.

After re-randomisation, few AEs with a suspected causal relationship to study intervention were observed; 2 events in 2 (1.1%) patients in the FYB202-FYB202 group (injection site pain and injection site induration) and 3 events in 2 (2.2%) patients in the Stelara EU-FYB202 group (injection site pain, injection site reaction and nasopharyngitis) and none in the Stelara EU-Stelara EU group.

Overall, no deaths were reported in the study. A total of 11 subjects experienced 15 SAEs, occurring similarly across the treatment groups. More SAEs occurred in period 1, this aspect could be explained by the dosing frequency. All SAEs were assessed as unlikely related to the study intervention. A similar proportion of subjects in both arms experienced TEAEs that led to drug interruption or discontinuation and withdrawn from the study. Of these TEAEs leading to treatment discontinuation, 2 were considered possibly related to study intervention; headache and dizziness in one patient (Stelara EU) and cholestasis and hepatitis toxic in another patient (Stelara EU, case discussed under Laboratory and other safety findings). Headache and dizziness are known common adverse effects of Stelara.

In general, the TEAE safety profile reported in Study FYB202-03-01 for FYB202 is comparable to the EU Stelara. The FYB202 group had comparable frequencies in overall TEAEs reported. SOC and PT were also comparable, except for injection site pain being slightly higher in the FYB202 group. Overall, the safety profile is consistent with the known safety profile of Stelara.

AESI

Study FYB202-03-01:

AESIs were reported more frequently in FYB202 compared to Stelara EU; FYB202: 15.2%, Stelara EU: 11.3%. The main events were injection site reactions. The investigator suspected a causal relationship to study interventions for all injection site reactions AESIs. All were rated as mild intensity. Before re-randomisation, the incidence of injection site events was higher in patients treated with FYB202 29 (14.7%) compared to 21 (10.8%) in patients treated with Stelara EU. After the first administration, the injection site reaction was highest for FYB202. After re-randomisation, there were three patients with injection site events; 2 in the FYB202-FYB202 group and 1 in the Stelara EU-FYB202 group; the trend observed in the first period of the study appeared to be maintained. Injection site pain is a known common adverse reaction of Stelara. AEs with PT Injection site pain occurred more frequently in the FYB202 group (32 events in 22 (11.2%) patients) than in the Stelara EU group (18 events in 15 (7.7%) patients) before re-randomisation. All events were considered a mild reaction and more frequently occurred after the first injection. Patients rated the severity of injection site pain using a VAS scoring FYB202 between 0.4 to 1.1 mm on average and Stelara EU between 0.2 to 0.5 mm on average. Considering the VAS score, the CHMP noted that pain at the injection site was documented with high sensitivity meaning that very low scores (<5 mm) were documented as TEAEs. This led to an overestimation of the incidence of injection site pain. The incidence of VAS >5mm during the study period before re-randomisation was 12 of 197 (6.09%) FYB202- and 2 of 195 (1.03%) Stelara EU-treated patients. The incidence of VAS >5mm after the first dose of FYB202 was 8 of 197 (4.06%). The VAS>5mm would correspond to a frequency below 10% with a frequency of common, hence it is aligned with the frequency included in SmPC section 4.8 of Fymskina and of the reference product.

Study FYB202-01-01 & Study FYB202-01-02
AESIs were not defined for these studies, however, local tolerability was assessed. Local tolerability was similar between treatment groups for study FYB202-01-01, except that FYB202 had a slightly higher

numerical incidence of injection site events, injection site pain and higher pain severity as documented by VAS distances. In study FYB202-01-02, local tolerability was again similar except for subjects in the FYB202 group who reported a higher frequency of injection site pain as well as higher pain severity. In a pooled analysis of these studies, injection site pain was reported in 10 of 269 (3.7%) FYB202-, in 2 of 268 (0.7%) Stelara EU-, and in 6 of 269 (2.2%) Stelara US-treated healthy subjects. All reported events of injection site pain were mild in severity. Thus, the incidence after a single SC injection of 45 mg FYB202 was common (3.7%). This is aligned with the frequency reported in SmPC section 4.8 of Fymskina and of the reference product.

Laboratory and Other Safety findings

In studies FYB202-01-02 and FYB202-01-01, the FYB202 treatment group had a lower overall incidence of TEAEs associated with clinically significant abnormal laboratory findings, which were considered drug-related when compared to Stelara groups.

In study FYB202-01-01, the most frequently reported drug-related TEAEs were increases in ALT; 5 subjects [4.8%] reported 7 TEAEs after administration of FYB202, 6 subjects [5.7%] reported 7 TEAEs after administration of Stelara EU and 3 subjects [2.9%] reported 3 TEAE after administration of Stelara US. One subject in the Stelara US group reported severe TEAEs of severe increase of ALT and AST, which was possibly drug-related. Upon further analysis, no relevant difference between treatment groups was found and incidences did not exceed frequencies reported in the placebo groups in healthy volunteers. In a pooled analysis of at least possibly related treatment-emergent adverse events (TEAEs) in healthy volunteers (Studies FYB202-01-01 and FYB202-01-02), ALT increased was reported in 6 of 269 (2.2%) of FYB202-, in 7 of 268 (2.6%) Stelara EU-, and in 4 of 269 (1.5%) Stelara US-treated subjects. These reported incidences do not exceed frequencies reported for placebo groups in healthy volunteer studies.

In study FYB202-03-01, no TEAEs associated with clinically significant abnormal laboratory findings were considered drug related. FYB202 had a lower overall incidence of TEAEs compared to Stelara-EU. Within study FYB202-03-01, there was an AE of 'Cholestasis and Hepatitis toxic' in one patient in the Stelara EU group led to the discontinuation of the study intervention. These events of Cholestasis and Hepatitis toxic were considered possibly related to the study drug, of moderate severity, non-serious with the outcome not resolved. The patient was ADA-positive. Cholestasis and Hepatitis toxic may have alternative causes. Therefore, the issue was not further pursued.

Clinically significant changes in vitals, physical exam or ECG were reported as TEAEs. No relevant were trends observed for vital signs, physical exam findings or ECG.

Immunogenicity

Immunogenicity was a secondary objective in all studies and was assessed by means of monitoring the development of ADAs and nAbs during the studies.

Study FYB202-01-01

Overall, the ADA and NAB incidence from baseline to Day 112 was lower for FYB202 compared to both Stelara EU and US. ADA prevalence was maximal on Day 14 for Stelara US. Whereas for FYB202 and Stelara EU, ADA and Nab prevalence was maximum at Day 112, with Stelara EU also having a peak in ADA positivity at Day 14. This represents a similar ADA and NAb prevalence pattern related to time in both groups. FYB202

had the highest peak ADA GMT of 481.6 on Day 112 but this was similar to the other two groups at different time points.

In terms of safety, ADA and NAB positivity did not appear to have an effect on AESIs. The frequency of AESI was lower in the FYB202 group for ADA-positive patients. Of note, for ADA-negative subjects, the incidence of injection site pain and pruritis was higher in the FYB202 group.

Study FYB202-01-02

Overall, the ADA and NAb incidence from baseline to Day 112 was lower for FYB202 compared to Stelara EU and Stelara US. For Stelara EU and Stelara US, ADA prevalence peaked at Day 10 and NAb prevalence peaked at D112. In the FYB202 group, ADA and NAb prevalence increased steadily from baseline to End-of-Study, peaking at Day 112. This is a similar ADA and NAb prevalence pattern for FYB202 in this study compared to the first phase 1 study. However, the peak prevalence of ADA positivity differs between FYB202 and Stelara.

The ADA geometric mean titres were higher for FYB202 compared to the two reference products; 321.46 (FYB202), 200.79 (EU-Stelara) and 249.42 (US-Stelara). However, this difference is small and throughout the study period the GMT were comparable at different time points.

Approximately, 50% of the ADA signals induced by Stelara EU and Stelara US fulfilled the "transient" classification, while the majority of the signals induced by FYB 202 were classified as "persistent". The applicant proposed that the reason for this observed difference is uncertain but does not reflect reactivity with NGNA / α-Gal, due to higher NGNA / aGal levels in Stelara. Despite this, the proportion of patients with persistent positive ADA from baseline to D112 remains lower in the FYB202 group (10.4%) compared to Stelara EU (19%) & Stelara US (25.6%).

In terms of safety, the frequency of AESIs was higher in ADA-positive subjects in the FYB202 treatment group compared to the Stelara groups. However, the total event numbers were lower in the FYB202 group. AESI was not defined for this study and is part of the integrated summary of immunogenicity. FYB202 ADA-positive subjects had a higher frequency of PTs of injection site erythema, injection site pain, cough and dermatitis bullous compared to Stelara EU and Stelara US. The CHMP acknowledged the low event numbers, with only 1 or 2 events per PT in the FYB202 group. Hence, no firm conclusion can be drawn.

Study FYB202-01-01 & Study FYB202-01-02

In terms of safety, a pooled analysis was carried out of TEAEs stratified by ADA/NAb. Taking into account the TEAEs identified and the low overall number of affected subjects, there is no apparent significant trend in TEAEs by SOC/PT stratified by antibody status.

Study FYB202-03-01

The overall ADA & NAB incidence from baseline to Week 52 was lower for FYB202 compared to Stelara EU. ADA and NAb prevalence in both treatment groups was maximal at Week 28 and declined from week 28 to week 52. This shows a similar ADA and NAb prevalence pattern related to time. The ADA GMT was comparable between groups.

After switching from Stelara EU to FYB202, there was no seroconversion of patients who were ADA-negative at Week 28. ADA and NAb prevalence was higher for Stelara EU switched to FYB202 compared to patients who did not switch treatments. However, this could have been based on the higher ADA positivity rate in the EU Stelara group before re-randomisation and pre-dose at week 28. The ADA and NAb positivity declined

after re-randomisation for all groups. Hence, it is considered that switching from Stelara EU to FYB202 does not impact immunogenicity negatively.

In terms of safety, there is no apparent significant trend in TEAEs by SOC/PT stratified by antibody status up to week 28 & week 52. Up to week 28, more patients with any TEAE treated with Stelara EU were ADA positive than with FYB202; 25 (46.3%) vs. 6 (28.6%), respectively. This is similar for NAb status and up to week 52. Up to week 28, a similar number of patients with any TEAE were ADA negative between groups; 69 (40.1%) FYB202, 55 (39%) Stelara EU. This is similar for NAb status and up to week 52.

ADA and NAB positivity did not appear to have an effect on AESIs. Out of the ADA-positive subject patients with AESI, there was one patient (4.3% of total) in the FYB202 group with an AESI (PT: injection site induration) compared to 7 out of 56 patients with ADA-positive results (12.5% of total) in the Stelara EU treatment group (all PT: injection site pain). Of note, for ADA-negative subjects, the incidence of injection site pain was higher in the FYB202 group.

More patients treated with FYB202 who experienced injection site pain were ADA negative up to week 52 compared to Stelara EU; 22 (12.8%) vs. 3 (4%), respectively. It is also noted that more patients who experienced injection site pain treated with Stelara EU were ADA positive up to week 52 compared to FYB202; 4 (12.9%) vs. 0 (0%), respectively. There is no apparent correlation between ADA or NAb positivity and the incidence of injection site reactions.

2.6.10. Conclusions on the clinical safety

Overall, the FYB202 clinical development programme and design of the studies was considered adequate to evaluate the comparability of FYB202 and its reference product EU-Stelara in terms of safety. In terms of immunogenicity, subjects (both healthy volunteers and patients) treated with FYB202 had lower overall incidences of ADA and NAb than subjects treated with Stelara. No immunogenicity related difference was observed in the safety profile of the two products. No major or significant differences in safety were detected based on the available data.

Fymskina and the EU reference product Stelara are concluded to be biosimilar in terms of clinical safety.

2.7. Risk Management Plan

2.7.1. Safety concerns

Summary of safety concerns	
Important identified risks	None
Important potential risks	Serious infections (including mycobacterial and salmonella infections) Malignancy Cardiovascular events Serious depression, including suicidality Venous thromboembolism

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

2.7.2. Pharmacovigilance plan

No additional pharmacovigilance activities.

2.7.3. Risk minimisation measures

None.

2.7.4. Conclusion

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

2.8. Pharmacovigilance

2.8.1. Pharmacovigilance system

The CHMP considered that the pharmacovigilance system summary submitted by the applicant fulfils the requirements of Article 8(3) of Directive 2001/83/EC.

2.8.2. Periodic Safety Update Reports submission requirements

The requirements for submission of periodic safety update reports for this medicinal product are set out in the list of Union reference dates (EURD list) provided for under Article 107c(7) of Directive 2001/83/EC and any subsequent updates published on the European medicines web-portal.

2.9. Product information

2.9.1. User consultation

No full user consultation with target patient groups on the package leaflet has been performed on the basis of a bridging report making reference to Stelara 45 mg solution for injection in a pre-filled syringe and Stelara 90 mg solution for injection in a pre-filled syringe. The bridging report submitted by the applicant has been found acceptable.

2.9.2. Labelling exemptions

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

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

2.9.3. Additional monitoring

Pursuant to Article 23(1) of Regulation No (EU) 726/2004, Fymskina (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 include a statement that this medicinal product is subject to additional monitoring and that this will allow quick identification of new safety information. The statement is preceded by an inverted equilateral black triangle.

3. Biosimilarity assessment

3.1. Comparability exercise and indications claimed

The applicant developed FYB202 as a similar biological medical product using the reference product, Stelara, for subcutaneous (SC) and intravenous (IV) use. This abridged application for a proposed biosimilar to Stelara has been submitted under Article 10 (4) of Directive 2001/83/EC as amended by Directive 2004/27/EC. Stelara was originally approved in the European Union on 15.01.2009.

Ustekinumab is a recombinant, fully human immunoglobulin G, subclass 1, κ light chain (IgG1κ) monoclonal antibody (mAb) that binds to the p40 subunit of interleukin (IL)-12 and IL-23, thereby preventing initiation of immune-response signalling pathways.

The reference product Stelara has a number of presentations and strengths approved (45 mg/0.5 mL in vial for SC use; 45 mg/0.5 mL in PFS for SC use; 90 mg/1.0 mL in PFS for SC use; 130 mg/26 mL in vial for IV use).

The applicant is not applying for all presentations of the reference product Stelara. Specifically, the 45 mg/0.5 mL solution in a single-dose vial for subcutaneous injection presentation has not been applied.

The indications applied for Fymskina are the same as those approved for the reference product Stelara at the exception of the paediatric plaque psoriasis initially proposed to be restricted to patients weighing more than 60 kg since paediatric patients who weigh less than 60 kg cannot be dosed with the current presentations of Fymskina. However, the applicant's proposal was not agreed by the CHMP. The agreed indication in paediatric plaque psoriasis is aligned with the one approved for the reference product Stelara. The posology section 4.2 of the SmPC adequately reflects the lack of presentation currently available for Fymskina to dose patients weighing less than 60 kg and that another ustekinumab product 45 mg solution for injection in vials offering weight-based dosing should be used instead.

Quality aspects

The applicant has performed a sound and comprehensive analytical biosimilarity exercise in line with EMA/CHMP/BWP/247713/2012 guidance. A sufficient number of lots, which can be expected to sufficiently reflect the product variability of both the proposed biosimilar and the reference product, was included. The FYB202 batches have been manufactured to the intended clinical or commercial process and batches used in the clinical studies were included. Although the applicant has chosen a comparability approach of ± 3 SD comparability criteria for quantitative data while for the qualitative data, this was evaluated by visual comparison, the analytical results are clearly presented, including chromatograms, spectra, response curves, with detailed summary tables of results for the individual batches and enable an independent assessment of biosimilarity, regardless of the statistical approach taken, which is acceptable.

Clinical pharmacokinetics

A comparative Study FYB202-01-01 failed to demonstrate bioequivalence between FYB202 and EU Stelara. The biosimilarity of FYB202 compared to EU-Stelara was demonstrated in another study FYB202-01-02.

Upon the CHMP's request, the applicant indicated that the differences in protein content may have contributed to the upper boundary of the confidence interval for $AUC_{0\text{-}inf}$ falling outside the 80 – 125% limits in study FYB202-01-01. Also, the higher ADA incidence of Stelara EU possibly influenced the differences in the PK between the products. Moreover, from a quality point of view, the claim of biosimilarity is supported by the analytical similarity exercise. Overall, the CHMP agreed that differences in protein content and incidences of ADA could explain the failure to demonstrate PK biosmilarity in study FYB202-01-01. Further, the applicant performed a comparative analysis (FYB202 vs EU Stelara) of pooled data from Study FYB202-01-01 and Study FYB202-01-02, in which the PK biosimilarity was demonstrated. It is agreed that the PK populations included in both studies are comparable. The applicant was asked to further elaborate on the pooled analysis by providing a tipping point analysis, calculating the largest possible (nominal) coverage probability of the confidence interval that would (just) still be within the acceptance range and the EMA MWP was consulted. The results of the tipping point analysis are reassuring, in line with the Points to Consider on Application with 1. Meta-analyses; 2. One pivotal study.

Clinical efficacy

A confirmatory phase III clinical study for the biosimilar FYB202 was performed to establish equivalence to the reference product Stelara. Study FYB202-03-01 was a comparative efficacy, safety, immunogenicity, and PK study comparing FYB202 versus EU Stelara in adult patients with moderate to severe PsO.

In the context of this biosimilar application, the overall design and conduct of the phase III clinical study were considered acceptable and generally in line with EMA SA recommendations.

Equivalence, based on reported results, is demonstrated for the primary efficacy endpoint of percent change from baseline in PASI at week 12 using the +/- 11% equivalence margins stipulated. The results appear robust to several sensitivity scenarios.

The CHMP concluded that clinical comparability is demonstrated between FYB202 and Stelara in the confirmatory phase III clinical study based on the data provided, which is broadly supportive of clinical efficacy equivalence across primary and secondary endpoints in psoriasis patients.

The CHMP concluded also that comparability in the absorption and elimination phases is established for the SC route of administration, hence, the extrapolation of the SC data to the IV administration route is concluded.

3.2. Results supporting biosimilarity

Quality aspects

Overall, a comprehensive analytical similarity exercise has been performed for both the PFS and the vial presentations of FYB202 against the EU reference product, Stelara. Although the applicant has chosen a comparability approach of ± 3 SD comparability criteria for key attributes, the analytical results are clearly presented, including chromatograms, spectra, and response curves, with detailed summary tables of results for the individual batches and enable an independent assessment of biosimilarity regardless of the statistical approach taken, which is acceptable. The results of the individual tests generally support a conclusion of biosimilarity. Overall, the claim of biosimilarity is supported.

Clinical pharmacokinetics

In terms of PK similarity, FYB202-01-02 showed that FYB202 is similar to Stelara EU with respect to both primary endpoints, AUC0-inf and Cmax. Geometric mean ratios (90% CIs) of AUC0-inf were 102.85% (96.84–109.23%) for the comparison of FYB202 against EU-Stelara. Geometric mean ratios (90% CIs) of Cmax were 97.22% (92.05–102.67%) for the comparison of FYB202 against EU-Stelara. The inter-subject variability as reflected by CV ANCOVA was between ~30% and ~35% for both primary endpoints, which is in accordance with the estimated variability at the time of study design. Differences in t_{max} between treatment groups based on the non-parametric comparison were not detected.

Clinical efficacy

The applicant conducted a confirmatory randomised, Phase III, double-blind, multicentre clinical study (FYB202-03-01) to compare the clinical efficacy of the proposed biosimilar FYB202 and the EU reference product Stelara (45mg s.c. injections) in adult patients with moderate to severe plaque PsO. The study was adequately powered, included a study population sensitive for detecting potential differences between the biosimilar and the reference product and had relevant endpoints.

The primary endpoint indicating clinical equivalence was met in the phase III clinical study: the adjusted LSMeans difference of the percent change from baseline in PASI at Week 12 for the PPS was −0.6 (SE: 1.62) and the 95% CI of the adjusted treatment difference was [−3.780 to 2.579], which was entirely contained within the pre-defined equivalence margin of [−11%, 11%].

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

Secondary efficacy endpoints such as PASI75, PASI90 response rates, PGA, and DLQI were also similar between the treatment groups at all time points.

The percentage change in PASI from baseline through Week 52 was comparable between FYB202 and Stelara.

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

The CHMP concluded that clinical comparability is demonstrated between FYB202 and Stelara in the confirmatory phase III clinical study based on the data provided, which is supportive of clinical efficacy equivalence across primary and secondary endpoints in psoriasis patients.

Clinical safety

The FYB202 clinical development programme and design of the studies are adequate to evaluate the comparability of FYB202 and its reference product EU-Stelara in terms of safety and immunogenicity.

In the pooled Phase 1 PK studies in healthy volunteers, the proportion of subjects with TEAEs, as well as the proportion of subjects with treatment-related TEAEs, were comparable between groups except for injection site pain being slightly higher in the FYB202 group. The total number of treatment-related TEAEs was lower in the FYB202 group compared to the Stelara treatment groups. There were no deaths, SAEs, or discontinuation due to TEAEs related to the study drug during the study. Overall, most TEAEs were mild in the studies. The most frequently reported TEAEs by PT across all groups was headache followed by nasopharyngitis, which is consistent with the known profile of ustekinumab. Laboratory data, vital signs, and 12-lead ECG parameters were comparable between the two groups.

In the phase III efficacy study, incidences of TEAEs, treatment-related TEAEs, and SAEs were comparable between the FYB202 and Stelara treatment groups, as well as transition groups. AESIs were reported more frequently in FYB202 compared to Stelara EU, primarily injection site reactions. There were no deaths or SAEs related to the study drug. There was one severe related TEAE in the FYB202 group of event ‘Rash’. A similar proportion of subjects experienced TEAEs that led to study discontinuation. Overall, the majority of TEAEs were mild or moderate in severity. The most frequently reported related TEAE was injection site pain with more events and affected more patients in the FYB202 group than in the Stelara EU group during period 1. Laboratory data, vital signs, and 12-lead ECG parameters were comparable between the two groups.

Overall, the safety profile of FYB202 was similar to the known profile of ustekinumab. No relevant differences between FYB202 and reference Stelara were identified based on the available data between FYB202 and EU-Stelara.

Immunogenicity

In the Phase 1 PK studies in healthy volunteers, the ADA and NAB incidences were lower in the FYB202 treatment group compared to the EU-/US-Stelara treatment groups. In the phase III efficacy study, the overall incidences of ADA and NAB results were lower for FYB202 treatment compared to EU-Stelara and EU-Stelara switched to FYB202 treatment groups. There was no apparent correlation between the presence of ADA and the occurrence of TEAE, TESAE, ISR or hypersensitivity reactions.

Overall, no immunogenicity related difference was observed in the safety profile of FYB202 and Stelara.

3.3. Uncertainties and limitations about biosimilarity

Quality aspects

None.

Clinical pharmacokinetics

The PK study FYB202-01-01 failed to demonstrate PK biosimilarity between FYB202 and Stelara since AUC0-inf slightly exceeded the upper limit of the acceptance range of 80.00–125.00 %. A root cause analysis was performed to understand the reasons for the failure. The CHMP agrees that the differences in protein content may have contributed to the upper boundary of the confidence interval for $AUC_{0\text{-}inf}$ falling outside the 80 – 125% limits. Also, the higher ADA incidence of Stelara EU had a possible influence on the differences in the PK between the products. Moreover, from a quality point of view, the claim of biosimilarity is supported by the analytical similarity exercise. A comparative analysis (FYB202 vs EU Stelara) of pooled data from Study FYB202-01-01 and Study FYB202-01-02, both studies including comparable PK populations, provide supportive reassurance of the biosimilarity between FYB202 and Stelara.

Clinical Efficacy

None

Clinical Safety

None

3.4. Discussion on biosimilarity

Quality aspects

The applicant has performed a sound and comprehensive analytical biosimilarity exercise in line with EMA/CHMP/BWP/247713/2012 guidance. A large panel of relevant methods has been used to characterise and compare the most relevant physicochemical and biological quality attributes of the ustekinumab molecule, which is considered sufficient. A comprehensive analytical similarity exercise has been performed for both the PFS and the vial presentations of FYB202 against the EU reference product, Stelara, which demonstrated that the primary and higher order structure, functional binding, and bioactivity of FYB202 are highly comparable to EU Stelara. While there are some notable differences in C-terminal lysine variants, charge variants and glycan map profiles for FYB202 compared to EU Stelara, these have been described in detail, and any potential clinical implications have been adequately discussed. The observed differences are, in general, justified by the

difference in cell lines and are not considered clinically significant hence do not impact the biosimilarity claim. Overall, the claim of biosimilarity is supported.

Clinical pharmacokinetics

In study FYB202-01-01, biosimilarity of FYB202 compared to EU-Stelara was not demonstrated for the co-primary endpoint AUC0-inf by the pre-defined primary analysis, since AUC0-inf exceeded slightly the upper limit of the acceptance range of 80.00–125.00 %. Based on the findings of the root cause analysis, the drug substance set point for protein concentration and drug product fill volume of FYB202 batches were amended for the PK study FYB202-01-02. The biosimilarity of FYB202 compared to EU-Stelara was demonstrated in study FYB202-01-02.

The CHMP agrees that the differences in protein content may have contributed to the upper boundary of the confidence interval for $AUC_{0\text{-}inf}$ falling outside the 80 – 125% limits. Also, the higher ADA incidence of Stelara EU possibly influenced the differences in the PK between the products. Moreover, from a quality point of view, the claim of biosimilarity is supported by the analytical similarity exercise. A comparative analysis (FYB202 vs EU Stelara) of pooled data from Study FYB202-01-01 and Study FYB202-01-02, both studies including comparable PK populations, provide supportive reassurance of the biosimilarity between FYB202 and Stelara.

The CHMP concluded that, from a pharmacology perspective, FYB202 is biosimilar to EU Stelara.

Clinical efficacy

A confirmatory randomised, Phase III, double-blind, multicentre clinical study (FYB202-03-01) was performed to compare the clinical efficacy of the proposed biosimilar FYB202 and the EU reference product Stelara (45mg s.c. injections) in adult patients with moderate to severe plaque PsO. The study was adequately powered, included a study population sensitive to detect potential differences between the biosimilar and the reference product and had relevant endpoints.

The equivalence of efficacy was demonstrated based on the primary endpoint. The 95% CI of the mean difference between the treatment groups in PASI percent change from baseline to week 12 (primary endpoint) was within the prespecified equivalence margin of (-11, +11).

Based on the data provided which are supportive of clinical efficacy equivalence across primary and secondary endpoints in psoriasis patients, the CHMP concluded that clinical comparability is demonstrated between FYB202 and Stelara.

Clinical safety

The FYB202 clinical development programme and design of the studies are adequate to evaluate the comparability of FYB202 and its reference product EU-Stelara in terms of safety and immunogenicity.

Regarding the safety profile, no relevant differences in safety were detected based on the available data between FYB202 and EU-Stelara.

In terms of immunogenicity, subjects (both healthy volunteers and patients) treated with FYB202 had lower ADA and nAb frequencies than subjects treated with Stelara. No immunogenicity related difference was observed in the safety profile of the two products.

3.5. Extrapolation of safety and efficacy

Similarity between Fymskina and Stelara has been satisfactorily demonstrated, based on the totality of the data provided as part of the stepwise approach for biosimilars, including quality and functional characterisation, non-clinical studies and clinical efficacy and safety studies.

Fymskina is intended to be used for the treatment of all approved indications for Stelara. The posology section 4.2 of the SmPC adequately reflects the lack of presentation currently available for Fymskina to dose patients weighing less than 60 kg and that another ustekinumab product 45 mg solution for injection in vials offering weight-based dosing should be used instead.

The pivotal efficacy and safety study was conducted in patients with moderate, to severe plaque psoriasis patients. This selected study population represents the most sensitive population to demonstrate biosimilarity. Additionally, ustekinumab's mechanism of action is similar in each of the approved indications for Stelara (PsO, paediatric PsO, PsA, CD, UC) as the Th1 and Th17 cytokine pathways play a central role in their pathogenesis and are mediated by the ustekinumab targeted and inhibited IL-12 and IL-23. Furthermore, the safety profile for ustekinumab is similar between these indications. Therefore, from the clinical point of view, extrapolation of the efficacy and safety data generated in PsO indication to all indications approved for the reference product is acceptable to the CHMP.

In addition, the CHMP concluded that comparability wass established for the SC route of administration. Hence, the extrapolation of the SC data to the IV administration route is agreed and thus the consequential extrapolation to other indications is also concluded.

3.6. Additional considerations

Not all pharmaceutical presentations and strengths as approved for Stelara in the EU are proposed for Fymskina since only the 45 mg/0.5 mL and 90 mg/1.0 mL prefilled syringe (PFS) presentations and IV 130mg are applied for. The 45 mg/0.5 mL vial presentation, which is suitable for paediatric patients that require less than a full 45 mg dose, is currently not proposed for Fymskina. Hence, there is no dose form for Fymskina that allows weight-based dosing for paediatric patients below 60 kg.

The applicant initially proposed to restrict the paediatric plaque psoriasis indication to patients weighing more than 60 kg since paediatric patients who weigh less than 60 kg cannot be dosed with the current presentations of Fymskina. However, the applicant's proposal was not agreed by the CHMP. The agreed indication in paediatric plaque psoriasis is aligned with the one approved for the reference product Stelara. The posology section 4.2 of the SmPC adequately reflects the lack of presentation currently available for Fymskina to dose patients weighing less than 60 kg and that another ustekinumab product 45 mg solution for injection in vials offering weight-based dosing should be used instead.

3.7. Conclusions on biosimilarity and benefit risk balance

Based on the review of the submitted data, Fymskina is considered biosimilar to Stelara. Therefore, a benefit/risk balance comparable to the reference product can be concluded.

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 Fymskina is favourable in the following indications:

Crohn's Disease

Fymskina 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

Fymskina 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).

Plaque psoriasis

Fymskina 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

Fymskina is indicated for the treatment of moderate to severe plaque psoriasis in children and adolescent patients from the age of 6 years and older, and who are inadequately controlled by, or are intolerant to, other systemic therapies or phototherapies (see section 5.1).

Psoriatic arthritis (PsA)

Fymskina, 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).

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.