CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

761379Orig1s000

MULTI-DISCIPLINE REVIEW

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

BIOSIMILAR MULTIDISCIPLINARY EVALUATION AND REVIEW

Application Type	351(k) BLA
Application Number	BLA 761379
Received Date	September 28, 2023
BsUFA Goal Date	September 28, 2024
Division/Office	Division of Dermatology and Dentistry (DDD)/Office of Immunology and Inflammation (OII) in collaboration with the Division of Rheumatology and Transplant Medicine (DRTM)/OII and Division of Gastroenterology (DG)/OII
Review Completion Date	See DARRTS stamped date
Product Code Name	FYB202
Proposed Nonproprietary Name[1]	ustekinumab-aauz
Proposed Proprietary Name[1]	Otulfi
Pharmacologic Class	IL12/23 blocker
Applicant	Fresenius Kabi USA, LLC
Applicant Proposed Indication(s)	• moderate to severe plaque psoriasis (PsO) in adults and pediatric patients (6 years or older) who are candidates for phototherapy or systemic therapy • active psoriatic arthritis (PsA) in adults and pediatric patients (6 years or older) • moderately to severely active Crohn's disease (CD) in adults • moderately to severely active ulcerative colitis (UC) in adults
Recommendation on Regulatory Action	Approval of FYB202 as biosimilar to US-Stelara. Provisional determination that FYB202 is interchangeable with US-Stelara (ustekinumab). Approval for interchangeability is precluded due to unexpired first interchangeable exclusivity for Wezlana.

[1]Section 7 of the Biosimilar Multidisciplinary Evaluation and Review discusses the acceptability of the proposed nonproprietary and proprietary names, which are conditionally accepted until such time that the application is approved.

Table of Contents

Table of Tables

Table of Figures

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OBP = Office of Biotechnology Products
OPMA = Office of Pharmaceutical Manufacturing Assessment
OPDP = Office of Prescription Drug Promotion
OSI = Office of Scientific Investigations
OSE = Office of Surveillance and Epidemiology
OTBB = Office of Therapeutic Biologics and Biosimilars
DEPI = Division of Epidemiology
DMEPA = Division of Medication Error and Prevention Analysis
DRISK = Division of Risk Management
DPMH = Division of Pediatric and Maternal Health

Glossary

AC	Advisory Committee
ADA	Anti-drug Antibodies
AE	Adverse Event
BLA	Biologics License Application
BMER	Biosimilar Multidisciplinary Evaluation and Review
BMI	Body Mass Index
BPD	Biosimilar Biological Product Development
BsUFA	Biosimilar User Fee Agreements
CD	Crohn's disease
CDER	Center for Drug Evaluation and Research
CDRH	Center for Devices and Radiological Health
CDTL	Cross-Discipline Team Leader
CFR	Code of Federal Regulations
CI	Confidence Interval
CMC	Chemistry, Manufacturing, and Controls
CRF	Case Report Form
CRO	Contract Research Organization
CRP	C-reactive Protein
CSC	Computational Science Center
CTD	Common Technical Document
CUHF	Comparative Use Human Factors
CV	Coefficient of Variation
DEPI	Division of Epidemiology
DIA	Division of Inspectional Assessment
DLQI	Dermatology Life Quality Index
DMC	Data Monitoring Committee
DMA	Division of Microbiology Assessment
DMEPA	Division of Medication Error Prevention and Analysis
DPMH	Division of Pediatric and Maternal Health
DRISK	Division of Risk Management
eCTD	Electronic Common Technical Document
EU-Stelara	EU-approved Stelara
FDA	Food and Drug Administration
FISH	Fluorescence In Situ Hybridization
GCP	Good Clinical Practice
GMR	Geometric Mean Ratio
HF	Human Factors
ICH	International Conference on Harmonization
IND	Investigational New Drug
ITT	Intention to Treat
I-VAS	Itching Visual Analogue Scale
LLOQ	Lower Limit of Quantitation
MAPP	Manual of Policy and Procedure

mITT	Modified Intention to Treat
MOA	Mechanism of Action
NAb	Neutralizing Antibody
NCI-CTCAE	National Cancer Institute – Common Terminology Criteria for Adverse Events
NCT	National Clinical Trial
OBP	Office of Biotechnology Products
OCP	Office of Clinical Pharmacology
OPDP	Office of Prescription Drug Promotion
OSE	Office of Surveillance and Epidemiology
OSI	Office of Scientific Investigations
OSIS	Office of Study Integrity and Surveillance
PASI	Psoriasis Area and Severity Index
PD	Pharmacodynamics
PeRC	Pediatric Review Committee
PGA	Physician's Global Assessment
PK	Pharmacokinetics
PMC	Postmarketing Commitments
PMR	Postmarketing Requirements
PREA	Pediatric Research Equity Act
PHS	Public Health Service
PLR	Physician Labeling Rule
PLLR	Pregnancy and Lactation Labeling Rule
PsA	Psoriatic Arthritis
PsO	Plaque Psoriasis
REMS	Risk Evaluation and Mitigation Strategies
ROA	Route of Administration
SAE	Serious Adverse Event
SAP	Statistical Analysis Plan
SOC	System Organ Class
SOP	Standard Operating Procedures
TEAE	Treatment-Emergent Adverse Events
UC	Ulcerative Colitis
ULOQ	Upper Limit of Quantitation
URRA	Use-related Risk Analysis
US-Stelara	US-licensed Stelara

Signatures

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	Signature:		

1. Executive Summary

1.1. Product Introduction

Fresenius Kabi USA, LLC[2] (also referred to as "Applicant" in this review) has submitted a biologic license application (BLA) under section 351(k) of the Public Health Service Act (PHS Act) for FYB202, a proposed interchangeable biosimilar to US-licensed Stelara (US-Stelara, ustekinumab).

FYB202 is a recombinant human immunoglobulin isotype class G subclass 1 kappa monoclonal antibody (mAb) that binds to the p40 protein subunit of the IL-23 and IL-12 cytokines to neutralize IL-23 and IL-12 mediated signaling. Interleukin-12 stimulates natural killer cells and drives the differentiation of CD4+ T cells toward the T helper 1 (Th1) phenotype; IL-23 induces the T helper 17 (Th17) pathway.

Fresenius Kabi USA, LLC is seeking licensure of FYB202 for the same indications for which US-licensed Stelara is approved:

- Adult patients with
  - Moderate to severe plaque psoriasis (PsO) who are candidates for phototherapy or systemic therapy
  - Active psoriatic arthritis (PsA)
  - Moderately to severely active Crohn's disease (CD)
  - Moderately to severely active ulcerative colitis (UC)
- Pediatric patients 6 years and older with
  - Moderate to severe plaque psoriasis (PsO), who are candidates for phototherapy or systemic therapy
  - Active psoriatic arthritis (PsA)

The applicant is seeking licensure for FYB202 injection as follows:

- FYB202, 45 mg/0.5 mL prefilled syringe (PFS) for subcutaneous use as interchangeable with US-Stelara 45 mg/0.5 mL PFS for subcutaneous use.
- FYB202, 90 mg/mL PFS for subcutaneous use as interchangeable with US-Stelara 90 mg/mL PFS for subcutaneous use.
- FYB202, 130 mg/26 mL single-dose vial for intravenous (IV) use as interchangeable with US-Stelara 130 mg/26 mL single-dose vial for IV use.

The strengths, dosage form and routes of administration of FYB202 will be the same as those approved for Stelara. In this submission, the Applicant is not seeking licensure of FYB202 in a 45 mg/0.5 mL single-dose vial for subcutaneous use. US-Stelara is

[2] At the time of submission, Formycon AG owned BLA 761379. During the review cycle, Formycon AG informed the FDA that they transferred ownership of BLA 761379 to Fresenius Kabi USA, LLC on April 23, 2024. FDA acknowledged the change in ownership prior to licensure via an acknowledgement letter to the new applicant. For the purposes of this review, Fresenius Kabi USA, LLC will be referred to as "the Applicant".

available in a 45 mg/0.5 mL single-dose vial for subcutaneous use for weight-based dosing of pediatric patients with a body weight of less than 60 kg. Section 2 of the labeling for FYB202 will note that there is no dosage form of the product that allows weight-based dosing for pediatric patients below 60 kg. Please see Section 10 below for more information on the Applicant's plans to develop the 45 mg/0.5 mL single-dose vial.

Although the Division of Dermatology and Dentistry (DDD) is the lead division for this application and provided the written clinical review, clinical input pertaining to their respective indications was obtained from the Division of Gastroenterology (DG) and the Division of Rheumatology and Transplant Medicine (DRTM) during the course of the review.

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

Not applicable.

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

FYB202 has the same mechanism(s) of action as US-Stelara.

FYB202 product is a sterile liquid solution available in a sterile, single dose, preservative-free solution for subcutaneous (SC) injection in a prefilled syringe (PFS) containing 45 mg/0.5 mL FYB202 or 90 mg/mL FYB202 and a single-dose vial containing 130mg/26mL (5mg/5mL) for IV infusion.

The routes of administration, dosage forms, and strengths of FYB202 are the same as those approved for US-Stelara. In this submission, the Applicant is not seeking licensure of the 45mg/0.5mL vial for subcutaneous use. Therefore, the proposed presentations of FYB202 only support the dosing regimens of patients with plaque psoriasis or psoriatic arthritis 6 years and older who weigh at least 60 kg and adult patients with Crohn's disease and ulcerative colitis. The 45 mg/0.5 mL PFS and 90mg/1mL PFS of FYB202 support the dosing regimens of adult and pediatric patients ≥ 6 years of age with moderate to severe plaque psoriasis and psoriatic arthritis and body weight ≥ 60 kg and adults with Crohn's disease and ulcerative colitis (maintenance). The single-dose vial containing 130mg/26mL (5mg/mL) supports the IV induction dosing regimen for adult patients with Crohn's disease and ulcerative colitis.

Additionally, the conditions of use for which the Applicant is seeking licensure for FYB202 as an interchangeable biosimilar to US-Stelara have been previously approved for US-Stelara.

1.4. Inspection of Manufacturing Facilities

Adequate descriptions of the facilities, equipment, environmental controls, cleaning, and contamination control strategy were provided for (b) (4) proposed for drug substance manufacture and (b) (4) proposed for drug product manufacture of the prefilled syringe and vial presentations, respectively. A 704(a)(4) document review was performed by OPQAIII and OPMA for the drug substance manufacturing facility, (b) (4), and found satisfactory. A pre-license inspection of the drug product manufacturing facility, (b) (4) was conducted in (b) (4) found satisfactory. A pre-license inspection of the drug product manufacturing facility, (b) (4) was waived. A device-related inspection of (b) (4) was recommended by CDRH, was performed in (b) (4) and closed in (b) (4) and found satisfactory following resolution of observations conveyed during the inspectional activities. All proposed manufacturing and testing facilities are acceptable based on their current CGMP compliance status and recent relevant inspectional coverage.

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

The Applicant provided adequate data to establish the scientific bridge to justify the relevance of data generated from the comparative clinical study FYB202-03-01, which used EU-Stelara as the comparator, for the assessment of biosimilarity:

- The Office of Pharmaceutical Products, OPQ, CDER has determined, and I agree, that based on the data provided by the Applicant, the analytical component of the scientific bridge between FYB202, US-Stelara, and EU-Stelara was established.
- The Office of Clinical Pharmacology (OCP) has determined, and I agree, that based on the data provided by the Applicant, the PK data established the PK component of the scientific bridge.

1.6. Biosimilarity and Interchangeability Assessment

Table 1. Summary and Assessment of Biosimilarity and Interchangeability

Comparative Analytical Studies[3]

[3]Refer to the Product Quality Review, including the Comparative Analytical Assessment (CAA) Chapter therein for additional information regarding comparative analytical studies.

Summary of Evidence	• FYB202 is highly similar to US-Stelara notwithstanding minor difference in clinically inactive components. • The strengths, dosage form, and routes of administration of FYB202 are the same as those of US-Stelara. • The analytical component of the scientific bridge between FYB202, US-Stelara, and EU-Stelara was established to support the relevance of the data generated from studies using EU-Stelara as the comparator to the assessment of biosimilarity.
Assessment of Residual Uncertainties	• There are no residual uncertainties from the product quality assessment.
Animal/Nonclinical Studies	
Summary of Evidence	• The information in the pharmacology/toxicology assessment supports the demonstration of biosimilarity.
Assessment of Residual Uncertainties	• There are no residual uncertainties from the pharmacology/toxicology assessment.
Clinical Studies	
Clinical Pharmacology Studies	

Summary of Evidence	• PK similarity between FYB202, US-Stelara, and EU-Stelara was evaluated in healthy adult subjects (Study FYB202-01-02) and supports a demonstration of no clinically meaningful differences between FYB202 and US-Stelara. • PK similarity between FYB202, US-Stelara, and EU-Stelara provides the PK component of the scientific bridge to support the relevance of comparative data generated using EU-Stelara in Study FYB202-03-01 to the assessment of biosimilarity. • The incidence of anti-drug antibodies (ADA) and neutralizing antibody (Nab) formation for FYB202 was numerically lower compared to those of US-Stelara and EU-Stelara in healthy subjects in the PK similarity Study FYB202-01-02 and was also numerically lower compared to that of EU-Stelara in subjects with psoriasis in the comparative clinical Study FYB202-03-01. • The incidence of positive ADA and reactive Nab was generally similar after the single transition from EU-Stelara to FYB202. • However, the numerical differences in ADA and Nab incidences in Studies FYB202-01-02 and FYB202-03-01 are not considered to be clinically significant and do not preclude the conclusion of no clinically meaningful differences between FYB202 and US-Stelara, as the systemic exposure between the treatment groups are comparable.
Assessment of Residual Uncertainties	• There are no residual uncertainties from a clinical pharmacology perspective.
Additional Clinical Studies	

Summary of Evidence	• In Study FYB202-03-01, there were no meaningful differences in terms of efficacy between FYB202 and EU-Stelara. The frequency of treatment emergent adverse events, serious events, and events leading to discontinuation of study drug had no meaningful differences between the treatment arms. • Given the scientific bridge was established (based on the analytical and PK comparisons) between FYB202, US-Stelara, and EU-Stelara to justify the relevance of the data generated with EU-Stelara as the comparator, the collective evidence from submitted clinical studies, including the comparative clinical study FYB202-03-01, supports a demonstration of no clinically meaningful differences between FYB202 and US-Stelara in the studied indication (plaque psoriasis, PsO).
Assessment of Residual Uncertainties	• There are no residual uncertainties from the clinical or statistical perspective.
Switching Study	
Summary of Evidence	• FDA determined that a switching study is not necessary to support a demonstration of interchangeability for FYB202. • The Applicant has provided adequate data and information to support a demonstration that the risk in terms of safety or diminished efficacy of alternating or switching between use of FYB202 and US-Stelara is not greater than the risk of using US-Stelara without such alternation or switch.
Assessment of Residual Uncertainties	• There are no residual uncertainties from the clinical perspective.
Any Given Patient Evaluation	
Summary of Evidence	• The analytical data and clinical data support a demonstration that FYB202 can be expected to produce the same clinical result as that of US-Stelara in any given patient. The Applicant has provided adequate data and information to support a demonstration that FYB202 can be expected to produce the same clinical result as that of US-Stelara in any given patient.

Assessment of Residual Uncertainties	• There are no residual uncertainties from the clinical perspective.
Extrapolation	
Summary of Evidence	• DDD, DG, and DRTM teams have determined that the Applicant has provided adequate scientific justification (based on mechanism of action, PK, immunogenicity, and toxicity) to support extrapolation of data and information submitted, including clinical data from the studied population (PsO), to support licensure of FYB202 as an interchangeable biosimilar, under section 351(k) of the PHS Act, for the following indications for which US-licensed Stelara has been previously approved: o Moderate to severe plaque psoriasis in adult patients and pediatric patients 6 years of age and older who are candidates for phototherapy or systemic therapy o Active psoriatic arthritis in adult patients and pediatric patients 6 years of age and older o Moderately to severely active Crohn's disease in adults o Moderately to severely active ulcerative colitis in adults
Assessment of Residual Uncertainties	• There are no residual uncertainties regarding the extrapolation of data and information to support licensure of FYB202 as an interchangeable biosimilar to US-Stelara for the above indications.

1.7. Conclusions on Approvability

In considering the totality of the evidence submitted, the data submitted by the Applicant demonstrate that FYB202 is highly similar to US-licensed Stelara, notwithstanding minor differences in clinically inactive components, and that there are no clinically meaningful differences between FYB202 and US-licensed Stelara in terms of the safety, purity, and potency of the product. The data and information provided by the Applicant are sufficient to demonstrate that FYB202 can be expected to produce the same clinical result as US-licensed Stelara in any given patient and that the risk in terms of safety or diminished efficacy of alternating or switching between use of FYB202 and US-licensed Stelara is not greater than the risk of using US-licensed Stelara without such alternation or switch. The information submitted by the Applicant, including adequate justification for extrapolation of data and information, demonstrates that FYB202 Stelara is biosimilar to US-Stelara, and supports a provisional determination under section 351(k)(4) of the Public Health Service (PHS) Act that FYB202 is interchangeable with US-Stelara, as

follows:

- FYB202, 45 mg/0.5 mL PFS for subcutaneous use is an interchangeable biosimilar with US-Stelara 45 mg/0.5 mL PFS for subcutaneous use,
- FYB202, 90 mg/mL PFS for subcutaneous use is an interchangeable biosimilar with US-Stelara 90 mg/mL PFS for subcutaneous use, and
- FYB202, 130 mg/26 mL single-dose vial for intravenous (IV) use is interchangeable biosimilar with US-Stelara 130 mg/26 mL single-dose vial for IV use

for each of the following indications for which US-licensed Stelara has been previously approved and for which the Applicant is seeking licensure of FYB202:

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

In this submission, the Applicant is not seeking licensure of FYB202 in a 45 mg/0.5 mL single-dose vial for subcutaneous use. US-Stelara is available in a 45 mg/0.5 mL single-dose vial for subcutaneous use for weight-based dosing of pediatric patients with a body weight of less than 60 kg. Section 2 of the labeling for FYB202 will note that there is no dosage form of the product that allows weight-based dosing for pediatric patients below 60 kg. Please see Section 10 below for more information on the Applicant's plans to develop the 45 mg/0.5 mL vial.

The data and information provided by the Applicant are sufficient to demonstrate that FYB202 can be expected to produce the same clinical result as the US-licensed reference product in any given patient.

At this time, FDA is unable to approve FYB202 injection 45 mg/0.5 mL PFS for subcutaneous use as interchangeable with US-Stelara injection 45 mg/0.5 mL PFS for subcutaneous use, FYB202 injection 90 mg/mL PFS for subcutaneous use as interchangeable with US-Stelara injection 90 mg/mL PFS for subcutaneous use, or FYB202 injection 130 mg/26 mL single-dose vial for intravenous use as interchangeable with US-Stelara injection 130 mg/26 mL single-dose vial for intravenous use, because of unexpired First Interchangeable Exclusivity (FIE) for BLAs 761285/761331 for Wezlana (ustekinumab-auub) 45 mg/0.5 mL injection for subcutaneous use, 90 mg/mL injection for subcutaneous use, and 130 mg/26 mL injection for intravenous use (hereinafter "the Wezlana products"). FDA has previously determined that FIE for the Wezlana products will expire on April 30, 2025.[4] Fresenius is expected to submit an amendment seeking approval of its FYB202 45 mg/0.5 mL injection for subcutaneous use, FYB202 90mg/mL

[4] https://purplebooksearch.fda.gov/

injection for subcutaneous use, and 130 mg/26 mL injection for intravenous use products as interchangeable no more than six months prior to the expiration of FIE for the Wezlana products.

Therefore, the FDA review team recommended that BLA 761379 be administratively split to facilitate an approval action for FYB202 as a biosimilar product and a provisional determination that FYB202 is an interchangeable biosimilar product, as described above.

The CDTL and Division Signatory agree with the above assessment and recommendation.

Author:
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Cross-Discipline Team Leader (CDTL)

2. Introduction and Regulatory Background

2.1. Summary of Presubmission Regulatory History Related to Submission

The Division of Dermatology and Dentistry (DDD) had several interactions with the Applicant during the development of FYB202 under IND 141478. Key discussions are detailed below:

- A Biosimilar Biological Product Development (BPD) Type 2 meeting held on February 13, 2019, focused on the overall development plan for FYB202 and analytical data needed to support the development of FYB202 as a proposed biosimilar to US-licensed Stelara. This discussion included a proposed study design to support biosimilarity (bridging study and comparative clinical study). The Agency also made the following recommendations:
    - The Agency agreed, in principle, that the proposed approach for evaluating the analytical similarity between FYB202 and US-licensed Stelara may be suitable to support a 351(k) BLA. However, the FDA stated that additional data and information would be needed to assess the adequacy of their proposed analytical similarity assessment plan, including their approach for establishing quality ranges for individual quality attributes in their 3-way bridging study between FYB202, US-licensed Stelara and EU-approved Stelara and summary information on each batch included in the analytical summary assessment.
    - The Agency did not agree with proposal to address analytical differences due to batch age by normalizing analytical results based on the mean rate of change for a given attribute over time.
    - For attributes proposed to be pooled, provide sufficient analytical data

from each of the different US-licensed Stelara formulations, strengths, and presentations included in the Sponsor's assessment to justify pooling data from different formulations, strengths, and container closure systems.
    - To demonstrate that FYB202 is highly similar to US-licensed Stelara, the pre-specified analytical similarity criteria should be established based only on US-licensed Stelara data rather than a combination of US-licensed Stelara and EU-approved Stelara.
    - The Sponsor proposed a 2-arm study bridging study (FYB202-01-01) comparing FYB202 and EU-Stelara only. The Agency stated that a 3-way bridging study (including US-Stelara) is necessary if their comparative clinical study only has EU-Stelara and FYB202 arms.
    - The size of the proposed safety database for the comparative clinical study (FYB202-03-01) is not sufficient to allow for detecting clinically meaningful differences in long term safety between the two products.
    - For the primary efficacy endpoint of percentage improvement in PASI score from baseline to Week 12, the recommended similarity margin is ±10%.
    - The data included in the original 351(k) application should include all information necessary for the review team to begin its review, including the data from the single transition. It may be possible to submit a subset of data in the 120-day safety update that would not be expected to change any conclusions regarding the approvability of your BLA; however, the Agency recommended that the Sponsor request a BPD Type 4 meeting to discuss any proposals for submitting data in the 120-day safety update.
    - As part of their human factors development plan, the Agency recommended the Sponsor conduct a comprehensive use-related risk analysis to determine the necessity of a human factors (HF) validation study.

- On May 1, 2019, the Sponsor opened the IND with a Special Protocol Assessment (SPA) for their proposed bridging study. The Agency issued a letter of No Agreement because the design and planned analysis of the proposed study did not adequately address the objectives necessary to support a regulatory submission.

- On July 31, 2020, the Sponsor submitted the proposed protocols for a 3-arm study bridging study (FYB202-01-01) and the comparative clinical study (FYB202-03-01), incorporating the Agency's recommendations from the February 13, 2019 BPD Type B meeting. Although no US subjects would be participating in the studies, the protocols were submitted for review. The most significant changes from previous versions included:

    - For Study FYB202-01-01, the Sponsor amended the study to assess 3 pairwise comparisons (FYB202 vs. US-Stelara; FYB202 vs. EU-Stelara; EU-Stelara vs. US-Stelara) of the co-primary endpoints. They also increased the number of subjects.

  - For Study FYB202-03-01, the timing of the single transition was moved from Week 28 to Week 16.
  - The Sponsor will submit the entire dataset (up to Week 52) for the comparative clinical study in the initial BLA submission.

- On November 22, 2021, a BPD Type 3 meeting was held to discuss the current comparative analytical assessment including additional analysis and clinical study results from bridging study. Specifically, the AUC0-inf parameter in the FYB202 treatment arm fell outside of the upper pre-defined bioequivalence margin, and the Sponsor requeste (b) (4) the Agency disagreed with the Sponsor's proposal and recommended that the Sponsor conduct a new 3-way PK similarity study between FYB202, US-Stelara and EU-Stelara.

- On March 18, 2022, the Agency provided BPD Type 2 Written Response Only (WRO) comments regarding the Sponsor's inquiry about the need for a Human Factors Validation Study. The Agency agreed with the Sponsor's determination that they did not need to submit human factors validation study results as part of the marketing application.

- On July 19, 2023, a pre-BLA meeting was held to discuss the Sponsor's future BLA submission. The Agency found the description of the contents of the Sponsor's proposed BLA submission acceptable, while noting that the iPSP for IND 141478 was still under review.

- On September 1, 2023, the FDA sent an advice/information request letter to the Sponsor's IND sharing its updated scientific thinking that a switching study would generally be considered unnecessary to support a demonstration of interchangeability for proposed ustekinumab interchangeable biosimilar products.

- In response to the FDA's September 1, 2023, letter, the Applicant submitted a BLA on September 28, 2023, seeking approval as an interchangeable biosimilar. The application included a scientific justification for how the data and information in the application met the standards for licensure as an interchangeable biosimilar as described in section 351(k)(4) of the PHS Act.

2.2. Studies Submitted by the Applicant

Refer to the Product Quality review, including the Comparative Analytical Assessment (CAA) Chapter for information regarding comparative analytical studies provided to support a demonstration of biosimilarity.

Table 2. FYB202 Clinical Studies Submitted

Study Identity	Study Objective	Study Design	Study Population	Treatment Groups
PK Similarity Studies				
FYB202-01-01	Primary and Secondary: Demonstrate PK similarity of FYB202 with EU-Stelara and US-Stelara; and EU-Stelara with US-Stelara Secondary: Safety and tolerability	Double-blind, randomized, parallel-group, active-controlled, single-dose, 3-arm	Healthy adults, weighing between 60-90 kg inclusive	FYB202: 105 US-Stelara: 105 EU-Stelara: 105 45mg SC, single-dose PFS
FYB202-01-02	Primary and Secondary: Demonstrate PK similarity of FYB202 with EU-Stelara and US-Stelara; and EU-Stelara with US-Stelara Secondary: Safety and tolerability	Double-blind, randomized, parallel-group, active-controlled, single-dose, 3-arm	Healthy adults, weighing between 60-90 kg inclusive	FYB202: 164 US-Stelara: 163 EU-Stelara: 164 45mg SC, single-dose PFS
Comparative Clinical Study				
FYB202-03-01	Primary: Evaluate and compare percent improvement in PASI score over 12 weeks between FYB202 and EU-Stelara Secondary: Evaluate and compare efficacy, safety, and immunogenicity of FYB202 compared EU-Stelara	Double-blind, randomized, parallel-group, active-controlled with single switch	Adults with moderate to severe chronic plaque PsO	FYB202: 197 EU-Stelara: 195 45mg SC at Weeks 0, 4, and 16 After single switch at Week 28 FYB202-FYB202: 189 EU-Stelara-EU-Stelara: 97 EU-Stelara-FYB202: 89 45mg SC, single-dose PFS

Source: Reviewer.

Authors:
Felisa Lewis, MD, MPH
Clinical Reviewer

Snezana Trajkovic, MD
Clinical Team Leader

3. Summary of Conclusions of Other Review Disciplines

3.1. Office of Pharmaceutical Quality (OPQ)

The Office of Pharmaceutical Quality, CDER, recommends approval of BLA 761379 for FYB202 manufactured by Fresenius Kabi USA, LLC. The data submitted in this application are adequate to support the conclusion that the manufacture of FYB202 is well-controlled and leads to a product that is pure and potent. The comparative analytical data support a demonstration that FYB202 is highly similar to US-licensed Stelara, notwithstanding minor differences in clinically inactive components. It is recommended that this product be approved for human use under conditions specified in the package insert.

3.2. Devices

FYB202 injection is a sterile liquid solution with the following proposed strengths in a prefilled syringe (PFS):

- Injection: 45 mg/0.5 mL in a single-dose prefilled syringe
- Injection: 90 mg/mL in a single-dose prefilled syringe

The FYB202 PFS container closure system consists of a (b) (4) glass syringe with a staked-in stainless steel (b) (4) needle (b) (4) with a rigid needle shield and a (b) (4) rubber stopper (b) (4) .

3.2.1. Center for Devices and Radiological Health (CDRH)

Based on assessment of device constituent parts of the combination product, CDRH recommends approval.

3.2.2. Division of Medication Error Prevention and Analysis (DMEPA1)

The Applicant submitted a Comparative Analyses and justification for not submitting a Human Factors (HF) Validation study and Comparative Use Human Factors (CUHF) study results to support their marketing application for FYB202 injection, 45 mg/0.5 mL and 90 mg/mL as a proposed biosimilar and interchangeable biosimilar to US-Licensed Stelara. Based on DMEPA1's review of the Applicant's submission, including the Comparative Analyses and the user interface, DMEPA1 determined that the Applicant does not need to submit a human factors validation and comparative use human factors study results to support their marketing application. DMEPA1 has determined, and we agree, that the proposed PFSs are approvable from DMEPA1's perspective.

3.3. Office of Study Integrity and Surveillance (OSIS)

The Division requested that the Office of Study Integrity and Surveillance (OSIS) conduct clinical site inspections at the sites in Table 4. OSIS had the following comments:

- Declined to inspect Site 01 due to limited resources available to complete the inspection prior to the user fee goal date.
- Site 02 – There were minor data discrepancies discussed with the Primary Investigator (PI) at the time of inspection and in a follow-up response that did not rise to the level of reporting on Form FDA 483. The inspector concluded the data was accurately reported and there was no impact on the data integrity of the study.
- Site 03 – There were 2 minor data entry errors that deviated from protocol procedure. These discrepancies were discussed with the PI at the time of inspection and did not rise to the level of reporting on Form FDA 483. The inspector concluded the data was accurately reported and there was no impact on the data integrity or subject safety for the study.
- Declined to inspect Site 04 because the site closed in August 2023. However, the site was inspected in May 2023, with no objections.
- OSIS conducted a remote regulatory assessment (RRA) of Site 05. Two objectionable conditions were found. Based on the evaluation of RRA observations, exhibits, and written response to the observations by (b) (4) OSIS concluded that there are no concerns with reliability of measured concentration data from 101 runs and the results of neutralizing antibodies analyzed in subject samples from study # FYB202-01-02.

Table 3. Inspection Sites

(Name, Address, Phone number, email, fax#)	Site #	Protocol ID	No. of Subjects (SAFPOP)	Purpose	Date of OSIS Review	Date of Previous Inspection	Comments/ Conclusion
SocraTec Probandenstation Erfurt Mainzerhofplatz 14 Erfurt, Germany 49-361-60205-44 PI: Dr. Juliane Körner	01	FYB202-01-02	228	Clinical; routine inspection	N/A	Aug 2012	Unable to inspect due to limited resources available
CRS Clinical Research Services Berlin GmbH Associates, Inc. Sellerstrasse 31, Gebäude P300 Berlin, Germany	02	FYB202-01-02	252	Clinical; routine inspection	Jul 2024	N/A	See text.

49-30-859949-160 PI: Mares-Elaine Strempler							
CRS Clinical Research Services Mannheim GmbH Grenadierstr. 1 Mannheim, Germany 49-621-15045-144 PI: Dr. Brigitte Kalsch	03	FYB202-01-02	212	Clinical; routine inspection	June 2024	May 2014	See text.
CTC North GmbH & Co. KG Martinistrasse 64, 3. OG Hamburg, Germany +49 40 22667-825 PI: Dr. Anastasia Kelidou	04	FYB202-01-02	161	Clinical; routine inspection	N/A	May 2023	Declined to inspect; site closed after August 2023
(b) (4)	N/A	FYB202-01-02	N/A	Analytical; routine inspection	(b) (4)		See text.

Source: Reviewer.

3.4. Office of Scientific Investigations (OSI)

The sites in Table 4 were selected because there was insufficient domestic data (largest sites are outside of the US). Both sites participated in Study FYB202-03-01 (the comparative clinical study). The inspections did not find significant concerns regarding the oversight of the clinical trial or Good Clinical Practice (GCP) or regulatory compliance. Based on the results of these inspections, data generated by the inspected clinical investigators appear acceptable in support of the proposed application.

Table 4. Clinical Inspection Sites

(Name, Address, Phone number, email, fax#)	Site #	Protocol ID	No. of Subjects (SAFPOP)	Endpoint	Inspection Type
Kapinska-Mrowiecka, Monika Ul.Henryka Sienkiewicza 23 KRAKOW, NA 30-033 POL Phone: +48124223171	311	FYB202-03-01	25	Arithmetic mean of Percent (%) Improvement in PASI score from baseline to week 12	Y-Insp

+48124223271 m.kapinska.mrowiecka@gmail.com allmedpl@gmail.com pulkaallmed@gmail.com Fax:+48124291073					
Pirowska, Magdalena Ul.Rogozinskiego 6/Lokal U3 KRAKOW, NA 31-559 POL Phone: +48600858891 +48696049029 m.pirowska@diamondclinic.eu barbara@diamondclinic.eu	312	FYB202-03-01	27	Arithmetic mean of Percent (%) improvement in PASI score from baseline to week 12	Y-Insp

Source: Reviewer.

Author:
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Cross-Discipline Team Leader (CDTL)

4. Nonclinical Pharmacology and Toxicology Evaluation and Recommendations

4.1. Nonclinical Executive Summary and Recommendation

The FDA has determined that animal testing is unnecessary to support a demonstration of biosimilarity between FYB202 and US-Stelara. No animal studies using FYB202 and US-Stelara were conducted by the Applicant. The Applicant provided adequate scientific justification (based on the totality of the comparative analytical assessment of FYB202 to US-Stelara, no critical residual impurities identified for FYB202, and no novel excipients used for the FYB202 formulation) to support that no comparative *in vivo* animal studies are needed to support a demonstration of biosimilarity between FYB202 and US-Stelara.

The Applicant conducted extractables studies for the two different container closure systems (CCSs) of the drug product and performed toxicological assessment. Overall, the levels of extractables and potential leachables from the two CCSs are acceptable from a nonclinical perspective. There are no outstanding issues from a Pharmacology/Toxicology perspective.

This BLA is approvable from a nonclinical perspective. There are no recommended nonclinical postmarketing commitments or postmarketing requirements for this BLA.

4.1.1. Nonclinical Residual Uncertainties Assessment

There were no nonclinical residual uncertainties.

4.2. Product Information

Product Formulation

The proposed product has two different formulations. One is a solution for subcutaneous injection that contains 45 mg/0.5 mL or 90 mg/mL FYB202, packaged in pre-filled glass syringes with a fill volume of 0.5 or 1.0 mL, respectively. The other is a solution for intravenous infusion that contains 130 mg/26 mL (5 mg/mL) FYB202, packaged in glass vials. Composition of the 45 mg/0.5mL and 90 mg/mL solution for subcutaneous injection is summarized in the following table.

Table 5: Composition of solution for subcutaneous injection, 45 mg/0.5 mL and 90 mg/mL

Component	Function	Quantity per mL	Quantity per 45 mg pre-filled syringe	Quantity per 90 mg pre-filled syringe
FYB202	Active ingredient	90 mg	45 mg	90 mg
L-Histidine	(b) (4)	1.024 mg	0.512 mg	1.024 mg
Sucrose		76 mg	38 mg	76 mg
Polysorbate 80		0.04 mg	0.02 mg	0.04 mg
Hydrochloric acid		q.s.* adjustment to pH 6.0	q.s. adjustment to pH 6.0	q.s. adjustment to pH 6.0
Water for injection		q.s. to 1 mL	q.s. to 0.5 mL	q.s. to 1 mL

Source: Reviewer.
*q.s. = *quantum satis*

(b) (4) The final composition of the 130 mg/26 mL (5 mg/mL) solution is summarized in the following table.

Table 6: Composition of solution for intravenous infusion, 130 mg/26 mL (5 mg/mL)

Component	Function	Quantity per mL	Quantity per 26 mL vial
FYB202	Active ingredient	5 mg	130 mg
L-Histidine	(b) (4)		(b) (4)
L-Histidine HCl monohydrate*			
Sucrose		85 mg	2210 mg
Polysorbate 80		0.4 mg	10.4 mg
L-methionine		0.4 mg	10.4 mg
EDTA disodium salt dihydrate (b) (4)		0.02 mg	(b) (4)

[redacted]			(b) (4)
Water for injection	(b) (4)	q.s. to 1 mL	q.s. to 26 mL

Source: Reviewer.

* (b) (4)

Comments on Excipients

The compositions of the 90 mg/mL solution for subcutaneous injection for US-Stelara and FYB202 are listed in the following table for comparison.

Table 7: Comparison between compositions of US-Stelara and FYB202, 90 mg/mL and 45 mg/0.5 mL solution for subcutaneous injection

Component	US-Stelara		FYB202	
	Quantity per mL	Quantity per 0.5 mL	Quantity per mL	Quantity per 0.5 mL
US-Stelara or FYB202	90 mg	45 mg	90 mg	45 mg
L-Histidine	1 mg	0.5 mg	1.024 mg	0.512 mg
L-Histidine HCl monohydrate			--	
Sucrose	76 mg	38 mg	76 mg	38 mg
Polysorbate 80	0.04 mg	0.02 mg	0.04 mg	0.02 mg
Hydrochloric acid	--		q.s. adjustment to pH 6.0	
Water for injection	q.s. to 1 mL	q.s. to 0.5 mL	q.s. to 1 mL	q.s. to 0.5 mL

Source: Reviewer.

The compositions of the 130 mg/26 mL (5 mg/mL) solution for intravenous infusion for US-Stelara and FYB202 are listed in the following table for comparison.

Table 8: Comparison between compositions of US-Stelara and FYB202, 130 mg/26 mL (5 mg/mL) solution for intravenous infusion

Component	US-Stelara	FYB202
	Quantity per mL	Quantity per mL
US-Stelara or FYB202	5 mg	5 mg
L-Histidine	(b) (4)	(b) (4)
L-Histidine HCl monohydrate		
Sucrose	85 mg	85 mg
Polysorbate 80	0.4 mg	0.4 mg
L-methionine	0.4 mg	0.4 mg
EDTA disodium salt (b) (4)	0.02 mg	0.02 mg
Hydrochloric acid	--	(b) (4)
Water for injection	q.s. to 1 mL	q.s. to 1 mL

Source: Reviewer.

The compositions of US-Stelara and FYB202 formulations are almost identical, with the same final pH value. Therefore, there are no nonclinical safety concerns about the composition of the 90 mg/mL solution for subcutaneous injection or the 130 mg/26 mL (5 mg/mL) solution for intravenous infusion.

Overall, the excipients in FYB202 are the same and present in the same levels as the excipients in US-Stelara.

Comments on Impurities of Concern

There are no impurities of toxicological concern.

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5. Clinical Pharmacology Evaluation and Recommendations

5.1. Clinical Pharmacology Executive Summary and Recommendation

The Applicant submitted a Biologics License Application (BLA) seeking approval as a biosimilar of US-licensed Stelara (ustekinumab) for several indications including moderate to severe plaque psoriasis (Ps) and active psoriatic arthritis (PsA) in patients 6 years of age and older; and moderate to severe active Crohn's disease (CD) and moderate to severe active ulcerative colitis in adults only.

Ustekinumab, a human IgG1κ monoclonal antibody, is a human interleukin-12 and -23 antagonist. The proposed dosing regimen for each indication is age- and weight-based.

The proposed product has the same dosage form (injection), routes of administration [subcutaneous (SC)], dosing regimen and presentations [pre-filled syringe (PFS) and single-dose vial] as US-Stelara (ustekinumab injection, 45 mg/0.5 mL and 90 mg/mL, BLA 125261, license holder: Centocor Ortho Biotech, Inc., and ustekinumab injection, 130 mg/26 mL, BLA 761044, license holder: Janssen Biotech, Inc.).The FYB202 45 mg/0.5 mL vial is under development.

Table 9. Clinical Pharmacology Major Review Issues and Recommendations

Review Issue	Recommendations and Comments
Pharmacokinetics	• Study FYB202-01-02 was a 3-way PK similarity study between FYB202, EU-Stelara and US-Stelara in healthy subjects following a single dose of 45 mg given by SC administration. • PK similarity has been demonstrated between FYB202, EU-Stelara and US-Stelara which supports a demonstration of no clinically

	meaningful differences between FYB202 and US-Stelara. • PK similarity between FYB202, EU-Stelara and US-Stelara provides the PK component of the scientific bridge to support the relevance of comparative clinical similarity data generated using EU-Stelara to the assessment of biosimilarity.
Pharmacodynamics	• Not Applicable
Immunogenicity	• In the PK similarity study (FYB202-01-02) the incidence of positive anti-drug antibodies (ADA) and reactive neutralizing antibodies (NAb) was higher in the EU-Stelara and US-Stelara arms compared to the biosimilar product FYB202. • Similar trend was observed in the clinical similarity study (FYB202-03-01) with ADA positive and reactive NAb incidence being higher in the EU-Stelara arm compared to FYB202. It is noted that the incidence of positive ADA and reactive NAb was generally similar after single transition from EU-Stelara to FYB202. ADA titer concentrations were also generally similar between FYB202 and EU-Stelara. • The efficacy in subjects that were ADA positive and NAb positive was lower than ADA negative and NAb negative subjects; however, the efficacy was fairly comparable between FYB202 and EU-Stelara arms regardless of immunogenicity status.

The clinical development program for FYB202 includes three clinical studies:

1. Pharmacokinetic (PK) similarity study - FYB202-01-01: “A Randomized, double-blind, single-dose, 3-arm, parallel-group phase 1 study to demonstrate pharmacokinetic equivalence of FYB202 and Stelara (ustekinumab) administered as a single subcutaneous injection to healthy volunteers.”

2. Pharmacokinetic (PK) similarity study - FYB202-01-02: “A Randomized, double-blind, single-dose, 3-arm, parallel-group phase 1 study to demonstrate pharmacokinetic equivalence of FYB202 and Stelara (ustekinumab) administered as a single subcutaneous injection to healthy volunteers – RUSTIC”

3. Clinical similarity study - FYB202-03-01: “A Randomized, 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"

The clinical pharmacology review for this BLA primary focuses on the PK similarity study (Study FYB202-01-02) which provided a scientific bridge to support using EU-Stelara in the comparative clinical study (Study FYB202-03-01) as these studies provided primary supportive evidence for demonstration of the biosimilarity of FYB202. A summary of the first PK similarity study, Study FYB202-01-01, will be provided in this review for completeness; however, this failed PK similarity study would have limited regulatory utility. Study FYB202-01-01 was a randomized, double-blind, single-dose, three-arm, parallel-group study in healthy subjects conducted to demonstrate pairwise PK similarity between FYB202, EU-Stelara, and US-Stelara, following the administration of a single SC dose of 45 mg in 0.5 mL solution. The upper limits of the 90% confidence intervals (CIs) exceeded 125% for the area under the serum drug concentration-time curve from time 0 to infinity ($AUC_{0\text{-}inf)}$ comparisons of FYB202 to EU-Stelara and FYB202 to US-Stelara.

The Applicant conducted a root cause analysis to identify reasons for the failure to demonstrate PK similarity in Study FYB202-01-01. It was found that the clinical batches of FYB202 used in the study had a higher protein content compared to EU-Stelara and US-Stelara batches. The Applicant conducted post-hoc statistical analysis following dose correction to adjust for different protein contents of clinical batches used in Study FYB202-01-01 and respective 90% CI for the pairwise comparison of $AUC_{0\text{-}inf}$ were contained within the no boundary effect of 80-125%. The results from this post-hoc analysis suggest that the protein content difference may have impacted the PK comparisons between FYB202, US-Stelara, and EU-Stelara.

Subsequently, Study FYB202-01-02 was conducted with FYB202 batches containing a similar protein content compared to US-Stelara and EU-Stelara batches. Refer to Section 14.3 (Clinical Pharmacology Appendices) for details on FYB202-01-01. Based on these justifications, FDA considers Study FYB202-01-02 more appropriate to comparatively assess PK between the products.

PK similarity was established in the second PK similarity study (FYB202-01-02) through the three pair-wise comparisons between FYB202, EU-Stelara, and US-Stelara following the administration of a single fixed SC dose of 45 mg. The 90% CI for the least square (LS) geometric means ratios (GMRs) for area under the serum drug concentration-time curve from time 0 to infinity ($AUC_{0\text{-}inf}$) and maximum serum drug concentration (C_{max}) were contained within the pre-specified no effect boundary of 80% to 125% (Table 2). The observed PK similarity between FYB202, EU-Stelara, and US-Stelara provides the PK component of the scientific bridge to support the relevance of the comparative clinical study data generated using EU-Stelara as the comparator to the assessment of biosimilarity.

Higher incidences of anti-drug antibodies (ADA) and reactive neutralizing antibodies (NAb) were observed in healthy subjects that received EU-Stelara and US-Stelara (Study FYB202-01-02) and subjects with plaque psoriasis that received EU-Stelara

(Study FYB202-03-01) in comparison to FYB202. In Study FYB202-03-01, the incidence of positive ADA and reactive NAb was nearly similar after single transition from EU-Stelara to FYB202. Although patients treated with FYB202 had higher mean C_{trough} at early timepoints compared to patients treated with EU-Stelara, it was noted that the C_{trough} levels for both treatment groups were comparable at steady-state starting from Week 16. ADA titer concentrations were generally similar between FYB202 and EU-Stelara, and higher ADA titer levels result in lower serum drug concentrations in both treatment groups.

PK similarity was established between FYB202, EU-Stelara and US-Stelara based on Study FYB202-01-02 results. These results support a demonstration that FYB202 has no clinically meaningful differences from US-Stelara and the PK component of the scientific bridge that justifies the relevance of comparative data generated in the comparative clinical study using EU-Stelara. The numerical differences in ADA and Nab incidences in Studies FYB202-01-02 and FYB202-03-01 are not considered to be clinically significant and do not preclude the conclusion of no clinically meaningful differences between FYB202 and US-Stelara, as the systemic exposure between the treatment groups are comparable.

Recommendations:

This BLA is acceptable from a Clinical Pharmacology perspective.

5.1.1. Clinical Pharmacology Residual Uncertainties Assessment

There are no residual uncertainties from the Clinical Pharmacology perspective.

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

In the PK similarity study in healthy subjects FYB202-01-02, following SC administration of FYB202, EU-Stelara, or US-Stelara, the 90% CIs for the GMRs of FYB202 to EU-Stelara, FYB202 to US-Stelara, and EU-Stelara to US-Stelara for the tested PK parameters (i.e., $AUC_{0\text{-}inf}$ and C_{max}) were all within the PK similarity acceptance interval of 80% to 125%. These pairwise comparisons met the pre-specified criteria for PK similarity between FYB202, EU-Stelara, and US-Stelara; thus, the PK portion of the scientific bridge was established to support the relevance of the data generated using EU-Stelara.

5.3. Human Pharmacokinetic and Pharmacodynamic Studies

5.3.1. PK Assessments

PK Similarity Study FYB202-01-02

Clinical Pharmacology Study Design Features

Study FYB202-01-02 was a randomized, double-blind, single-dose, three-arm, parallel-group study to demonstrate pairwise PK similarity between FYB202 vs EU-Stelara, FYB202 vs US-Stelara, and EU-Stelara vs US-Stelara in healthy Caucasian males and females subjects and to evaluate the clinical safety, tolerability, and immunogenicity. The single SC dose administered was 45 mg in 0.5 mL solution. Randomization was stratified according to study site, sex, and 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).

Pharmacokinetic blood samples (4 mL each) were collected from subjects to determine the serum concentration of study drug and to evaluate the PK similarity of the three Investigational Products (IPs). The blood sampling time points were as follow: pre-dose, 6,12,18, and 24 hours post-dose and on Day 3, 4, 5, 6, 7, 8, 9, 10, 12, 14, 17, 21, 28, 35, 42, 49, 56, 63, 70, 84, 98, and 112.

Clinical Pharmacology Study Endpoints

The primary PK parameters for the three IPs comparisons were C_{max} and $AUC_{0\text{-}inf}$. PK similarity was evaluated for each of the three pairwise comparisons without adjustment for multiplicity. PK similarity was concluded when the respective 90% CIs for the LS GMR for C_{max} and $AUC_{0\text{-}inf}$ were completely included in the pre-defined no effect boundary of 80–125%.

Bioanalytical PK Method and Performance

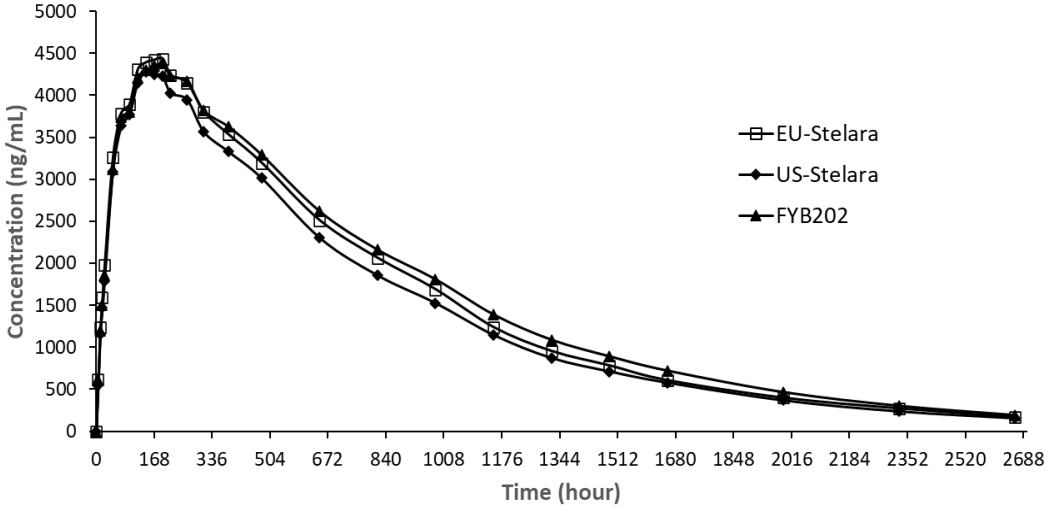
The bioanalytical studies were developed and validated by (b) (4) to determine the concentration of study drug in human serum samples by enzyme-linked immunosorbent assay (ELISA). The lower limit of quantification of the ELISA method was 40 ng/mL in neat human plasma. The bioanalytical method was developed based on the FDA Bioanalytical Method Validation Guidance for Industry (2018) and was found acceptable. Refer to Clinical Pharmacology Appendices (Section 14.3) for detailed review of the bioanalytical method(s) validation and performance.

PK Similarity Assessment

Overall, 491 healthy male and female subjects were randomized (159 subjects to FYB202, 160 subjects to EU-Stelara, and 159 subjects to US-Stelara) into the study and included. All randomized subjects were included in the evaluation of safety data including immunogenicity analysis. In total, 13 subjects were excluded from the PK analysis set due to major protocol deviations including 5 subjects that prematurely dropped out. The PK analysis set comprised 478 subjects.

The mean serum concentration-time profiles for study drug following the SC administration of 45 mg of the IPs are depicted in Figure 1.

Figure 1. Mean Serum Concentration vs. Time Profiles After Subcutaneous Administration of 45 mg (Single Dose 0.5 mL) of FYB202, EU-Stelara, and US-Stelara (Linear Scale, all subjects)



Source: Reviewer's Analysis

The PK similarity results are presented in Table 10. The GMRs and 90% CIs of C_{max} and $AUC_{0\text{-}inf}$ were within the pre-specified no effect boundary of 80% to 125%. Therefore, the PK data obtained from Study FYB202-01-02 supports the conclusion of PK similarity between FYB202, EU-Stelara, US-Stelara following subcutaneous administration of 45 mg (single dose 0.5 mL).

The sponsor also performed explorative subgroup analyses without formal testing for PK similarity based on the status of ADA and NAb. The GMRs and 90% CIs of C_{max} and $AUC_{0\text{-}inf}$ were within in the no effect boundary of 80% to 125% (Data not shown).

Table 10. Summary of Statistical Analyses for Assessment of Pairwise Pharmacokinetic Similarity between FYB202, EU-Stelara and US-Stelara (Study FYB202-01-02)

Parameter	N Observations	Point Estimate (%)	90% Confidence interval		CV_{ANCOVA} (%)
			Lower limit (%)	Upper limit (%)	
	FYB202 vs. EU-Stelara				
$AUC_{(0\text{-}inf)}$	318	102.85	96.84	109.23	33.41
C_{max}	319	97.22	92.05	102.67	30.2
	FYB202 vs. 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
	EU-Stelara vs. 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

Source: Study FYB202-01-02 Report, TT 36

OSIS inspection:
The biopharmaceutical inspection was requested for four clinical sites and one bioanalytical site of study FYB202-01-02. OSIS conduct a biopharmaceutical inspection for the bioanalytical site and two clinical sites and found no concerns for either site regarding reliability of the data for inspected study FYB202-01-02. OSIS declined to conduct an inspection for two clinical sites and recommended accepting data for Agency review based on the recent inspectional history of the sites (See Section 3.3).

5.3.2. Comparative Clinical Study FYB202-03-01

Comparative Clinical Study Design Features

Study FYB202-03-01 was a randomized, double-blind, parallel-group study to compare the efficacy, safety, and immunogenicity of FYB202 and EU-Stelara in patients with moderate-to-severe plaque psoriasis. Eligible subjects received subcutaneous injections of FYB202 and EU-Stelara 45 mg at Weeks 0 and 4 and at 12-week intervals thereafter (Weeks 16, 28, and 40). End of the study was at Week 52.

At Week 28, after receiving treatment at Week 0, 4 and 16, the patients were assessed for Psoriasis Area and Severity Index (PASI) response. Patients not achieving a ≥75% improvement from baseline in PASI score (PASI 75) at Week 28 were considered non-responders. Study responders who achieved PASI 75 response at Week 28 were rerandomized: patients who initially received EU-Stelara were rerandomized 1:1 so that 50% of patients in the original EU-Stelara arm received FYB202 and 50% continued to receive EU-Stelara at Weeks 28 and 40. Patients originally randomized to FYB202 continued to receive FYB202 at Weeks 28 and 40. Non-responders were discontinued from study intervention, but followed until end-of-study and underwent all study-related assessments.

Clinical Pharmacology Study Endpoints

Pharmacokinetic endpoint was study drug C_{trough} at Weeks 4, 12, 16, 28, 40 and 52, and the change in C_{trough} from Week 28 through Week 52 in patients following a single transition from EU-Stelara to FYB202.

Bioanalytical PK Method and Performance

The bioanalytical studies were developed and validated by (b) (4) to determine the concentration of FYB202 / Ustekinumab in human serum samples by enzyme-linked immunosorbent assay (ELISA). The lower limit of quantification of the ELISA method was 40 ng/mL in neat human plasma. The bioanalytical method was developed based on the FDA Bioanalytical Method Validation Guidance for Industry (2018) and was found acceptable. Refer to Clinical Pharmacology Appendices (Section 14.3) for detailed review of the bioanalytical method(s) validation and performance.

PK Assessment

The summary of C_{trough} levels from baseline to Week 52 include data of patients keeping to their initial randomized treatment and data of patients after rerandomization at Week 28 following a single transition from EU-Stelara to FYB202 (Table 11). High variability was observed at Week 4 and 12 compared to lower variability observed at Weeks 16, 28, 40, and 52 (Figure 2). Although patients treated with FYB202 had higher mean C_{trough} at early timepoints compared to patients treated with EU-Stelara, the C_{trough} levels for both treatment groups were generally comparable at steady-state starting from Week 16.

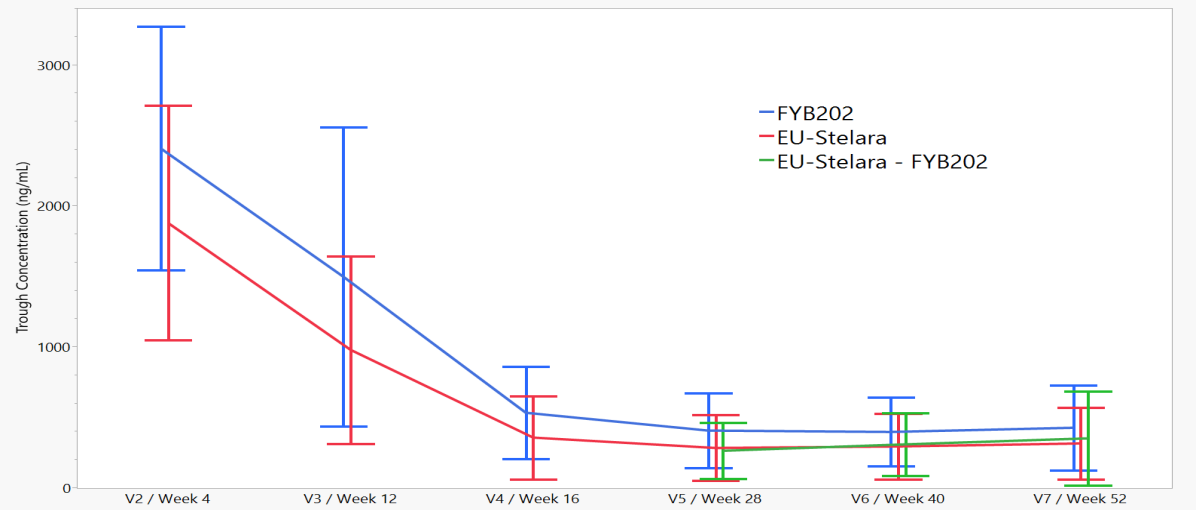
Table 11. C_{trough} Ustekinumab Concentrations at Weeks 0 to 52 from Study FYB202-03-01

Initial Randomization		
Analysis Visit	**FYB202 (N=197)**	**EU-Stelara (N=195)**
Baseline V1/ Week 0		
N	195	195
Mean (SD)	23.91 (53.01)	20.88 (12.25)
Geometric mean (CV)	20.45 (27.02)	20.23 (16.27)
V2 / Week 4		
N	194	193
Mean (SD)	2404.24 (863.61)	1905.96 (855.90)
Geometric mean (CV)	2195.01 (56.9)	1617.38 (84.77)
V3 / Week 12		
N	194	191
Mean (SD)	1497.53 (1063.44)	997.44 (674.49)
Geometric mean (CV)	1206.64 (85.22)	727.43 (126.4)
V4 / Week 16		
N	193	194
Mean (SD)	529.76 (328.23)	350.30 (277.10)
Geometric mean (CV)	411.68 (100.77)	227.12 (153.22)
V5 / Week 28		
N	191	192
Mean (SD)	403.98 (267.45)	272.02 (216.64)
Geometric mean (CV)	314.02 (96.35)	176.69 (150.43)
V6 / Week 40		
N	192	101
Mean (SD)	393.74 (244.39)	292.06 (233.35)
Geometric mean (CV)	300.02 (106.85)	191.68 (147.02)
V7 / Week 52		
N	182	92
Mean (SD)	423.39 (300.74)	312.16 (254.96)
Geometric mean (CV)	318.56 (104.98)	210.18 (137.26)
Rerandomization		
	EU-Stelara - FYB202 (N=89)	
V5 / Week 28 N	89	
Mean (SD)	262.60 (197.37)	
Geometric mean (CV)	172.43 (149.08)	
V6 / Week 40		
N	89	
Mean (SD)	262.60 (197.37)	

Geometric mean (CV)	208.26 (140.96)
V7 / Week 52	
N	84
Mean (SD)	348.19 (334.45)
Geometric mean (CV)	235.68 (132.56)

Source: Study FYB202-03-01 Report Body, Table 12-24 and 12-25.

Figure 2. Arithmetic Mean (SD) - Trough Concentration over Time (Linear Scale)



Error bars represent standard deviation (SD).
Source: Reviewer's analysis. Data source: ADPC.xpt

In summary, C_{trough} levels had their initial peak at Week 4, then reached steady state by Week 16

5.4. Clinical Immunogenicity Assessments

5.4.1. Study FYB202-01-02

Design features of the clinical immunogenicity assessment

For immunogenicity assessments, blood samples (4 mL each) were withdrawn as follows: pre-dose, Day 3, 7, 10, 14, 28, 56, 84, and 112.

Incidence of ADA and NAb

FYB202 showed a lower percentage of ADA-positive subjects compared to EU-Stelara (19.5% vs. 42.3%), and US-Stelara (19.5% vs. 50.6%). Similar trend was observed for the NAb response. The percentage of subjects with reactive NAb was 9.8%, 15.3%, and 17.7% after the administration of FYB202, EU-Stelara, and US-Stelara, respectively (Table 12).

Table 12. Assessment of ADA and NAb by Treatment Group in Study FYB202-01-02

Analysis Visit	FYB202 (N=164)	EU-Stelara (N=163)	US-Stelara (N=164)
ADA			
Baseline	10 (6.1%)	9 (5.5%)	2 (1.2%)
From baseline to Days 112	31 (19.5%)	69 (42.3%)	83 (50.6%)
NAb			
Baseline	2 (1.2%)	2 (1.2%)	1 (0.6%)
From baseline to Day 112	16 (9.8%)	25 (15.3%)	29 (17.7%)

Source: Integrated summary of immunogenicity, Table 60.

The magnitude of ADA titer levels for all three treatment groups ranged from 80.8 to 89900. The geometric mean concentrations of ADA titer appear to increase from Day 1 to Day 112 with similar median ADA titer concentrations from Day 1 to Day 112 for the three Ips. The highest incidence of positive ADA was on Day 112 for FYB202 (15.5%) and Day 10 for EU-Stelara (30.2%) and US-Stelara (32.7%). The highest incidence of reactive NAb was on Day 112 for the three treatment groups (FYB202: 8.1%, EU-Stelara: 9.3%, and US-Stelara: 10.6%) (Table 13).

Table 13. ADA and NAb incidence and ADA Titer Concentrations by Treatment Group from Baseline to Day 112 in Study FYB202-01-02

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	9	12	12	14	14	17	15	25
ADA positive (%)	6.1	5.5	7.3	7.3	8.7	8.5	10.4	9.6	15.5
NAb positive (n)	2	1	1	2	4	4	6	6	13
NAb positive (%)	1.2	0.6	0.6	1.2	2.5	2.4	3.7	3.8	8.1
ADA titer:									
Median	137.0	140.0	141.5	144.0	123.5	402.3	158.0	380.0	159.0
Geom. mean	177.9	174.9	206.2	296.2	267.6	151.5	389.2	654.5	365.5
Max	4580	2830	4280	19900	30600	35800	20500	25500	12100
Stelara EU (N=163)									
Evaluable (n)	163	163	162	162	163	162	162	159	162
ADA positive (n)	9	9	32	49	35	25	27	31	39
ADA positive (%)	5.5	5.5	19.8	30.2	21.5	15.4	16.8	19.5	24.1
NAb positive (n)	2	2	5	9	7	4	10	13	15
NAb positive (%)	1.2	1.2	3.1	5.6	4.3	2.5	6.2	8.2	9.3
ADA titer:									
Median	114.0	117.0	122.5	141.0	157.0	129.0	127.0	265.0	148.0
Geom. mean	114.6	119.7	143.6	227.5	245.6	166.0	153.3	274.6	256.8
Max	154	212	10200	89900	49000	27700	10600	6640	4190
Stelara US (N=164)									
Evaluable (n)	164	164	164	162	163	162	161	155	162
ADA positive (n)	2	3	31	53	47	25	24	34	43
ADA positive (%)	1.2	1.8	18.9	32.7	28.8	15.4	14.9	21.9	26.7
NAb positive (n)	1	0	7	8	4	3	9	10	17
NAb positive (%)	0.6	0	4.3	4.9	2.5	1.9	5.6	6.5	10.6
ADA titer:									
Median	103.0	112.0	145.0	244.0	150.0	146.0	142.5	140.0	149.0
Geom. mean	100.4	103.6	211.6	295.5	249.5	191.5	224.8	240.7	310.6
Max	126	124	7120	50100	33800	5920	8880	17700	16900

Abbreviations: ADA=anti-drug antibody; NAb=neutralizing antibody; Geom.=geometric; Max=maximum 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 analysis set and treatment group
Source: Integrated summary of immunogenicity, Table 61

5.4.2. Study FYB202-03-01

Design features of the clinical immunogenicity assessment

The Pharmacokinetic and immunogenicity blood samples at baseline and Weeks 4, 12, 16, 28, 40, and 52 were collected from study subjects to determine the serum study drug trough concentration (C_{trough}) and number of patients with antibodies to ustekinumab and to evaluate change in ustekinumab Ctrough and number of patients with antibodies to ustekinumab from week 28 through week 52 following a single transition from EU-Stelara to FYB202.

Incidence of ADA and NAb

Anti-drug antibodies (ADA) and NAb were selected as the immunogenicity endpoints. Blood samples for immunogenicity assessments were drawn at the study sites prior to the administration of study interventions. Separate samples were collected for ADA and NAb assessments. Samples with confirmed treatment-induced ADA were tested for titer estimation and NAb assessment. Descriptive statistics were summarized for the incidence of ADA and NAb and the ADA titers.

The incidence of ADA from Week 4 to Week 52 was generally higher in the EU-Stelara group compared to FYB202 group. Ten out of 197 (5.1%) subjects in the FYB202 treatment group had an ADA positive result at baseline (pre-treatment) compared to none in the EU-Stelara group (Table 14). Anti-drug antibodies and NAb incidence in both treatment groups was maximal at Week 28 and then declined from Week 28 to Week 52. At Week 52, ADA prevalence was similar for FYB202 (6.3%) and EU-Stelara (8%). The incidence of Nab was similar between the two treatment groups. The geometric mean ADA titer concentrations for FYB202 and EU-Stelara were similar from Week 4 to 52. Moreover, the incidence of ADA and reactive Nab and mean titers were similar following the single transition from EU-Stelara to FYB202 compared to the groups kept to their initial randomized treatment. The number and percent of ADA and NAb positive subjects are listed in Table 14.

Table 14. Patients with ADA, NAb, and Measured Titers at Weeks 0, 4, 12, 16, 28, 40, and 52

	Initial Randomization	
Analysis Visit	**FYB202 (N=197)**	**EU-Stelara (N=195)**
Baseline V1/ Week 0		
N(%)	10 (5.1)	0 (0.0)
Titer Mean (CV)	142.7 (114)	
Titer Geo-mean (CV)	108.78 (69.54)	
NAb Reactive/ Negative N(%)	Re 7 (3.6)/Ne 3 (1.5)	
V2 / Week 4		
N(%)	8 (4.1)	24 (12.4)
Titer Mean (CV)	319.87 (182)	478.15 (243)
Titer Geo-mean (CV)	157.18 (131.62)	160.47 (163.09)
NAb Reactive/ Negative N(%)	Re 3 (1.6)/Ne 5 (2.6)	Re 13 (6.7)/Ne 11 (5.7)
V3 / Week 12		
N(%)	14 (7.2)	28 (14.4)
Titer Mean (CV)	183.78 (72)	377.8 (173)
Titer Geo-mean (CV)	147.97 (74.32)	190.03 (138.0)
NAb Reactive/ Negative N(%)	Re 7 (3.6)/Ne 7 (3.6)	Re 13 (6.7)/Ne 15 (7.7)
V4 / Week 16		
N(%)	17 (8.8)	34 (17.6)
Titer Mean (CV)	248.41 (87)	529.41 (280)
Titer Geo-mean (CV)	179.35 (97.77)	189.31 (168.14)
NAb Reactive/ Negative N(%)	Re 12 (6.2)/Ne 5 (2.6)	Re 18 (9.3)/Ne 16 (8.3)
V5 / Week 28		
N(%)	24 (12.4)	37 (19.4)
Titer Mean (CV)	368.88 (126)	410 (201)
Titer Geo-mean (CV)	212.63 (133.45)	203.29 (134.10)
NAb Reactive/ Negative N(%)	Re 14 (7.3)/Ne 10	Re 18 (9.4)/Ne 19 (9.9)

	(5.2)	
V6 / Week 40		
N(%)	16 (8.3)	11 (10.8)
Titer Mean (CV)	663.75 (241)	304.81 (99)
Titer Geo-mean (CV)	233.33 (189.43)	212.87 (106.95)
NAb Reactive/ Negative N(%)	Re 6 (3.1)/Ne 10 (5.2)	Re 3 (2.9)/Ne 8 (7.8)
V7 / Week 52		
N(%)	12 (6.3)	8 (8.0)
Titer Mean (CV)	1561 (285)	365.65 (130)
Titer Geo-mean (CV)	292.19 (282.51)	223.12 (126.32)
NAb Reactive/ Negative N(%)	Re 2 (1.1)/Ne 10 (5.3)	Re 2 (2.0)/ Ne 6 (6.0)
Rerandomization		
	EU-Stelara - FYB202 (N=89)	
V5 / Week 28		
N(%)	18 (20.2)	
Titer Mean (CV)	608.22 (186)	
Titer Geo-mean (CV)	267.59 (179.11)	
NAb Reactive/ Negative N(%)	Re 9 (10.1)/Ne 9 (10.1)	
V6 / Week 40		
N(%)	12 (13.5)	
Titer Mean (CV)	305 (114.7)	
Titer Geo-mean (CV)	191.41 (120.71)	
NAb Reactive/ Negative N(%)	Re 5 (5.6)/Ne 7 (7.9)	
V7 / Week 52		
N(%)	9 (10.5)	
Titer Mean (CV)	398.22 (138)	
Titer Geo-mean (CV)	200.73 (175.46)	
NAb Reactive/ Negative N(%)	Re 2 (2.3)/ Ne 7 (8.1)	

Source: Reviewer's analysis and Study FYB202-03-01 Report, Table 12-19 and 12-20.

Shift of ADA and NAb incidence after rerandomization

None of the subjects with ADA negative at Week 28 became ADA positive following transition from EU-Stelara to FYB202. One subject with negative NAb became reactive following transition from EU-Stelara to FYB202 (Table 15).

Table 15. Shift of ADA and NAb Incidence from Week 28 to Week 40 and 52 After Rerandomization

	Analysis Visit and Treatment group			
V5/ Week 28	**V6/ Week 40**		**V7/ Week 50**	
	FYB202 – FYB202 (N=189)			
ADA	Negative	Positive	Negative	Positive
Negative	166	0	158	0
Positive	0	15	3	10
	EU-Stelara – FYB202 (N=89)			
	Negative	Positive	Negative	Positive
Negative	72	0	70	0
Positive	3	12	1	9
	EU-Stelara – Stelara EU (N=97)			

	Negative	Positive	Negative	Positive
Negative	79	0	76	0
Positive	0	9	0	6
FYB202 – FYB202 (N=189)				
NAb	Negative	Reactive	Negative	Reactive
Negative	7	0	2	0
Reactive	3	5	7	1
EU-Stelara – FYB202 (N=89)				
	Negative	Reactive	Negative	Reactive
Negative	5	1	2	1
Reactive	2	4	5	1
EU-Stelara – EU-Stelara (N=97)				
	Negative	Reactive	Negative	Reactive
Negative	3	0	1	0
Reactive	3	3	4	1

Source: Reviewer's analysis using ADIS.xpt dataset

The number of evaluable subjects with treatment-induced ADA, treatment-boosted ADA, persistent positive, and transient positive status until Weeks 12, 28 and 52 are provided in Table 16. EU-Stelara showed higher number of subjects with treatment-induced ADA, persistent positive, and transient positive status compared to FYB202.

Table 16. Summary of ADA Classification by Treatment Group - Safety Analysis Set

ADA Status	FYB202	EU-Stelara
Week 0 to 12		
Evaluable patients	193	195
Treatment-induced ADA n(%)	9 (4.6)	39 (20)
Treatment-boosted ADA n(%)	0	0
Persistent positive n(%)	7 (3.6)	24 (12.3)
Transient positive n(%)	2 (1)	15 (7.7)
Week 0 to 28		
Evaluable patients	193	195
Treatment-induced ADA n(%)	20 (10.3)	54 (27.7)
Treatment-boosted ADA n(%)	1 (0.5)	0
Persistent positive n(%)	16 (8.3)	38 (19.5)
Transient positive n(%)	4 (2)	16 (8.2)
Week 0 to 52		
Evaluable patients	195	106
Treatment-induced ADA n(%)	21 (10.7)	31 (29.2)
Treatment-boosted ADA n(%)	2 (1)	0
Persistent positive n(%)	13 (6.6)	19 (18)
Transient positive n(%)	8 (4.1)	12 (11.3)

SAF = safety analysis set, n = number of patients within the specified category as part of evaluable patients
Treatment-induced ADA: ADA positive result post-treatment only. Any pre-treatment ADA assessment is either negative or not assessable. Patients with missing pre- treatment ADA samples were not evaluable for the ADA analysis.
Treatment-boosted ADA: Pre-existing ADA that were boosted to a higher level following study treatment, i.e. pre-treatment positive ADA titer that was boosted by at least 2 dilution steps (4-fold) following study treatment.
Persistent positive patient: An evaluable patient with treatment-induced ADAs detected at 2 or more sequential sampling time points during the study (with ≥16 weeks between first and last positive) or with a positive ADA present at the last sampling time point (before completion or early discontinuation of the study or before the end of the observational period).
Transient positive patient: An evaluable patient with at least one post-treatment ADA positive result who does not fulfil the conditions of persistent positive patient, i.e. treatment-induced ADA detected only at one or more time points over a limited period, but not on two or more consecutive time points (with ≥16 weeks between first and last positive).

Only patients who did not have a single transition from EU-Stelara to FYB202 are included in the EU-Stelara summary from Week 0 to 52.
Source: Reviewer's Analysis using ADIST.xpt dataset

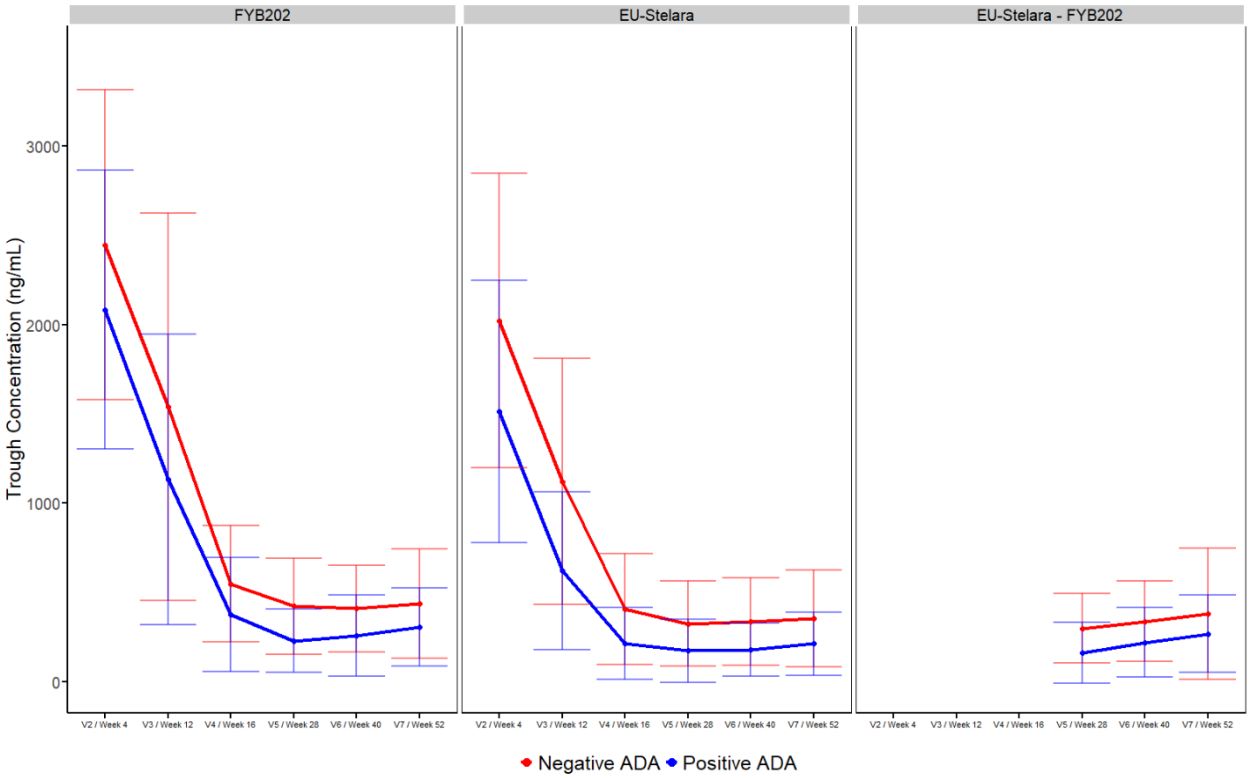
In Summary, EU-Stelara induced ADA in more subjects compared to FYB202 from Week 0 to 28. After rerandomization from Week 28 to 52, the induction of ADA was generally comparable between the two treatment groups. Refer to Clinical conclusions on immunogenicity in Section 6.4.

Impact of ADA and NAb on the PK, PD, safety, and clinical outcomes of the proposed product

Relationship of trough drug serum concentration to ADA status

The trough concentrations (C_{trough}) of FYB202 and EU-Stelara were lower at all timepoints in the ADA positive subpopulation compared to the ADA negative population (Figure 3). 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 C_{trough} of FYB202 vs. EU-Stelara.

Figure 3. Trough Concentrations of FYB202 and EU-Stelara by Treatment Visit and ADA status – Week 4 to Week 52

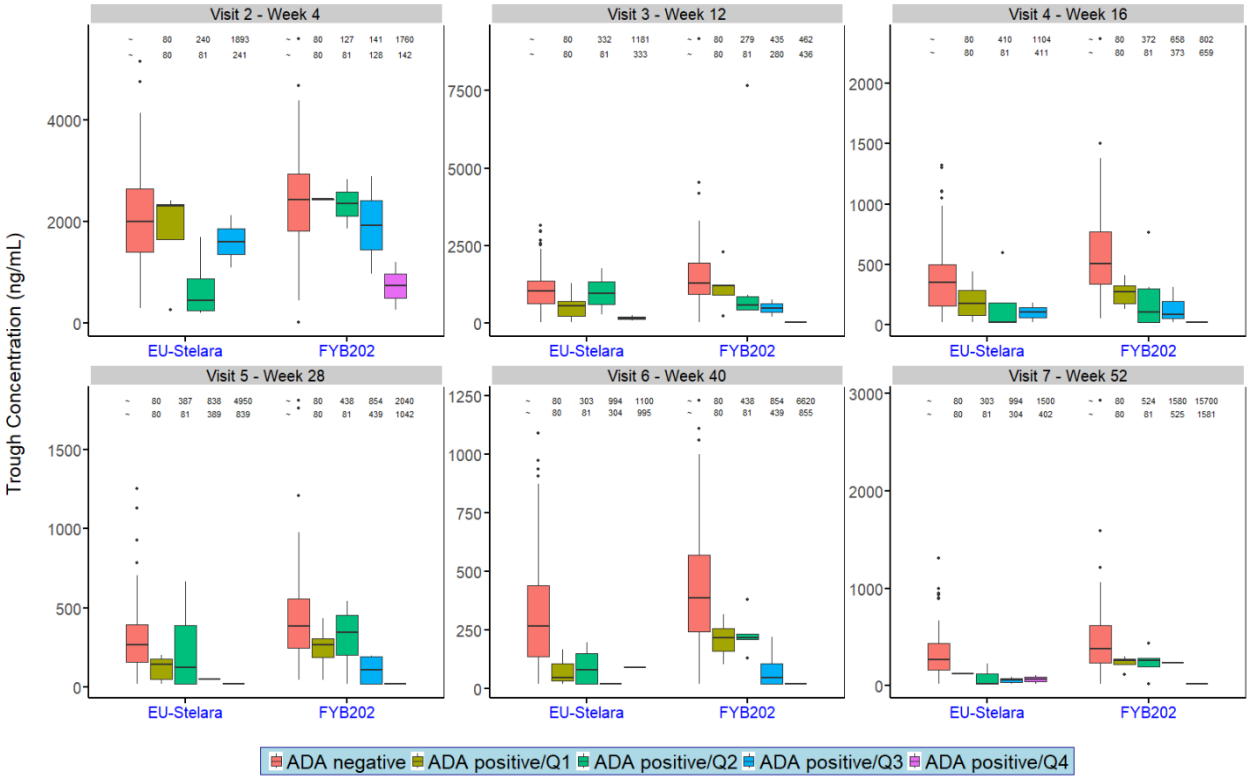


Error bars represent standard deviation.
Source: Reviewer's analysis

ADA titer and trough drug serum concentration

The geometric mean ADA titer concentrations for FYB202 and EU-Stelara were similar from Week 4 to 52. The ADA incidence was higher at Week 28 with similar ADA titer between the two treatment groups; however, ADA titer in the highest quartile (1042 to 2040 for FYB202; 839 to 4950 for EU-Stelara) had the lowest serum drug concentration (Figure 4).

Figure 4. Trough Concentrations of FYB202 and EU-Stelara by ADA Titer and Treatment Visit Week 4 to Week 52



Trough concentrations of FYB202 and EU-Stelara are plotted and stratified based on the quartile of ADA titer concentration with 4 quartiles per treatment group presented as minimum and maximum ADA titer concentrations. Visit 6 and 7 include subjects not participated in the single transition from EU-Stelara to FYB202.
Source: Reviewer's Analysis

Impact of ADA and NAb on Clinical Outcomes

Per the applicant analysis, the mean % improvement in PASI score from baseline to Week 12 was lower for subjects with positive ADA or NAb compared to subjects with negative ADA or NAb in both treatment groups (Table 17).

The lower ADA prevalence detected at Week 12 for FYB202 (7.2%) compared to EU-Stelara (14.4%) had no impact on the primary efficacy endpoint in Study FYB202-03-01. Moreover, there was no difference in the primary efficacy endpoint between NAb positive patients treated with FYB202 (3.6%) compared to EU-Stelara (6.7%) (Table 17).

Table 17. Comparison of % improvement in PASI score from baseline to Week 12 by ADA and NAb status in Study FYB202-03-01

Treatment group / difference	Summary statistics			MMRM Least Squares estimation			
	N	n[a]	Arithmetic mean[a]	n[b]	LS mean[c]	SE LS mean[c]	Two-sided 95% CI
Week 12 – ADA negative							
FYB202	172	172	84.6	172	86.28	2.64	81.09; 91.47
EU-Stelara	141	137	81.3	142	83.04	2.64	77.85; 88.22
Difference: FYB202 – EU-Stelara					3.24	2.2	-1.09; 7.58
Week 12 – ADA positive							
FYB202	21	21	68.8	21	62.15	6.76	48.73; 75.57
EU-Stelara	54	54	74.1	54	66.83	5.77	55.37; 78.28
Difference: FYB202 – EU-Stelara					-4.68	6.38	-17.39; 8.04
Week 12 – NAb negative							
FYB202	180	180	83.6	180	79.82	2.41	75.09; 84.54
EU-Stelara	158	154	80.8	158	77.36	2.4	72.63; 82.08
Difference: FYB202 – EU-Stelara					2.46	2.21	-1.88; 6.8
Week 12 – NAb positive							
FYB202	13	13	73.4	13	74.15	10.25	53.66; 94.65
EU-Stelara	37	37	73.1	37	74.5	10	54.43; 94.57
Difference: FYB202 – EU-Stelara					-0.35	7.96	-16.38; 15.68
Week 28 – ADA negative							
FYB202	172	170	95.9	172	97.41	2.29	92.9; 101.92
EU-Stelara	141	139	94	141	95.67	2.2	91.34; 100
Difference: FYB202 – EU-Stelara					1.74	1.01	-0.24; 3.73
Week 28 – ADA positive							
FYB202	21	20	88	21	81.93	5.38	71.21; 92.65
71.21; 95.65EU-Stelara	54	54	91	54	83.68	5.18	73.36; 94.01
Difference: FYB202 – EU-Stelara					-1.75	4.2	-10.14; 6.63
Week 28 – NAb negative							
FYB202	180	177	95.5	180	91.59	2	87.64; 95.53
EU-Stelara	158	156	93.6	158	90.17	1.93	86.37; 93.98
Difference: FYB202 – EU-Stelara					1.41	1.03	-0.61; 3.44
Week 28 – NAb positive							
FYB202	13	13	89	13	89.77	9.12	71.43; 108.12
EU-Stelara	37	37	91.3	37	92.68	9.61	73.32; 112.04
Difference: FYB202 – EU-Stelara					-2.91	5.82	-14.62; 8.81

N = total number of patients in the treatment group and analysis set; SE = standard error; n = number of assessments; CI = confidence interval; LS = least squares; MMRM = Mixed Model Repeated Measures. Two-sided 95% confidence interval based on normal approximation.

a Arithmetic mean calculation is based on patients with assessments at Week 12.

b For the calculation of LS means based on the MMRM, patients with missing assessments at all postbaseline visits until week 28 cannot be considered.

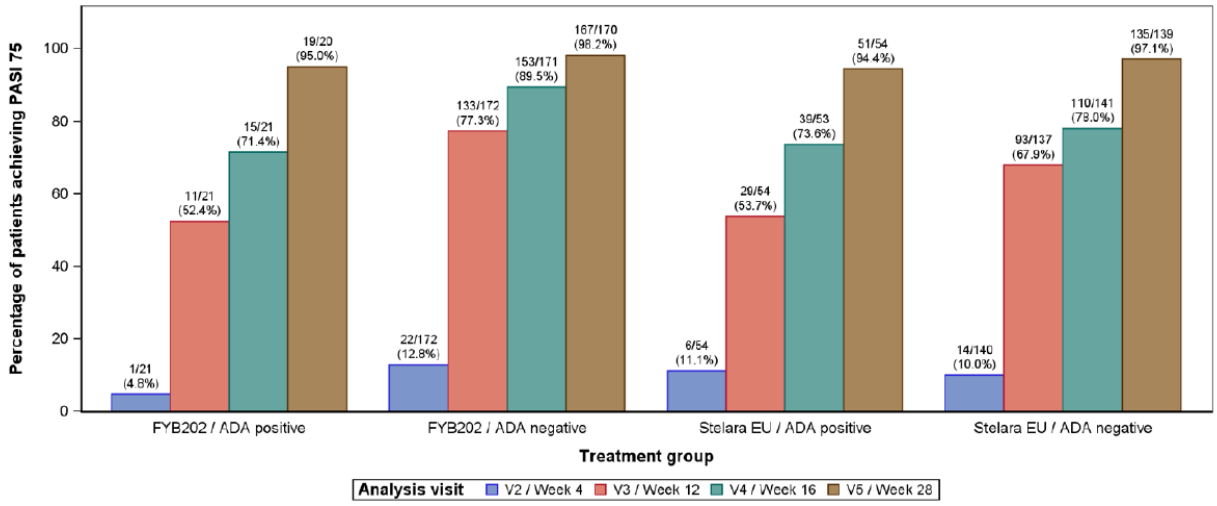
c Estimates are adjusted for baseline PASI score, baseline weight, time since onset of psoriasis and prior inadequate response or intolerance to a systemic biological treatment.

If the confidence interval for difference in LS means is completely contained in the interval [-10%, 10%], FBY202 and EU-approved Stelara are considered equivalent.

Source: Integrated Summary of Immunogenicity, Table 39 and 40.

There was similar proportion of ADA positive and NAb positive patients that reached PASI 75 at Week 12, 28, and 52 in FYB202 and EU-Stelara treatment groups. In comparison to ADA negative patients, the proportion of patients achieving PASI 75 at Week 12 was higher for the ADA positive patients in both treatment groups (Figure 5). The lack of impact on primary efficacy endpoint with the observed difference in ADA and NAb incidence may be explained by the relatively low and similar ADA titers.

Figure 5. Bar Plot of Number of Patients Achieving PASI 75 by Analysis Visit and ADA Status in Study FYB202-03-01



Patients without any post-baseline ADA assessment until Week 28 are not evaluable for ADA and excluded from the analysis.
Source: Integrated Summary of Immunogenicity, Figure 40.

Following a single transition from EU-Stelara to FYB202, there was a small, but minor difference between the three treatment groups in the absolute improvement of PASI score from Week 28 to Week 52. The transition from EU-Stelara to FYB202 did not appear to have a meaningful impact on efficacy (Table 18) and therefore do not preclude a demonstration that FYB202 has no clinically meaningful differences from US-Stelara.

Table 18. Comparison of Absolute Improvement in PASI Score from Week 28 to Week 52 in Study FYB202-03-01 – Re-randomized Analysis Set

Treatment group / difference	Summary statistics			MMRM Least Squares estimation			
	N	n[a]	Arithmetic mean[a]	n[b]	LS mean[c]	SE LS mean[c]	Two-sided 95% CI
Week 52 – All patients (regardless of ADA status)							
EU-Stelara – EU-Stelara	97	92	0.03	97	-0.068	0.309	-0.677 – 0.54
EU-Stelara – FYB202	89	87	-0.14	89	-0.21	0.321	-0.843 – 0.423
Difference					-0.142	0.209	-0.553 – 0.27
Week 52 – ADA negative							
EU-Stelara – EU-Stelara	69	64	-0.02	69	-0.084	0.304	-0.685 – 0.518
EU-Stelara – FYB202	64	63	-0.05	64	-0.077	0.32	-0.709 – 0.555
Difference					0.006	0.236	-0.461 – 0.474
Week 52 – ADA positive							
EU-Stelara – EU-Stelara	28	28	0.16	28	0.198	0.284	-0.374 – 0.769

EU-Stelara – FYB202	25	24	-0.39	25	-0.413	0.304	-1.024 – 0.198
Difference					-0.611	0.417	-1.448 – 0.227

N = total number of patients in the treatment group and analysis set
SE = standard error; n = number of assessments; CI = confidence interval; LS = least squares; Two-sided 95% confidence interval based on normal approximation.
a Arithmetic mean calculation is based on patients with assessments at Week 12.
b For the calculation of LS means based on the MMRM, patients with missing assessments at all postbaseline visits until week 28 cannot be considered.
c Estimates are adjusted for baseline PASI score, baseline weight, time since onset of psoriasis and prior inadequate response or intolerance to a systemic biological treatment.
Source: Integrated Summary of Immunogenicity, Table 48.

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6. Statistical and Clinical Evaluation and Recommendations

6.1. Statistical and Clinical Executive Summary and Recommendation

The applicant (Bioeq GmbH) submitted Biologic License Application (BLA) 761379 to demonstrate biosimilarity of the proposed biosimilar product FYB202 to US-licensed Stelara (ustekinumab), based on the totality of evidence from the analytical, nonclinical, and clinical data. The clinical program includes clinical comparative efficacy and safety study FYB202-03-01 in patients with moderate-to-severe Plaque Psoriasis. The study FYB202-03-01 was a multi-center, randomized, double-masked, 2-arm parallel group, comparative clinical study with a duration of 56 weeks to demonstrate that there is no clinically meaningful difference between FYB202 and EU-approved Stelara in subjects with moderate-to-severe Plaque Psoriasis.

Patients were randomized into one of the two treatment groups in a 1:1 ratio to FYB202 arm or EU-approved Stelara arm. Randomization before the first study intervention was stratified by prior inadequate response or intolerance to a systemic biological treatment in the opinion of the investigator. A total of 392 subjects were randomized to FYB202 arm (N = 197) or EU-approved Stelara arm (N = 195).

The primary efficacy endpoint was the percent improvement in PASI score from baseline to week 12. The primary efficacy analysis was conducted to assess whether there is no clinically meaningful difference between FYB202 and EU-approved Stelara in the primary efficacy endpoint based on the full analysis set (FAS). The pre-specified similarity margin was set as [-10%, 10%].

In terms of the primary efficacy endpoint, the adjusted mean percent improvement in PASI score from baseline to week 12 were comparable between the two treatment groups (79.51% for FYB202 and 76.24% for EU-approved Stelara). In addition, the adjusted mean difference was 3.27% with 90% CIs of (-0.2249%, 6.7699%), which was contained within the similarity margin of [-10%, 10%]. Thus, the study FYB202-03-01

demonstrated the similarity of FYB202 and EU-licensed Stelara for the primary efficacy endpoint.

In summary, the reviewer concludes that this application provides adequate statistical evidence that there is no clinically meaningful difference between FYB202 and EU-approved Stelara in the primary efficacy endpoint according to the prespecified biosimilar margin.

6.1.1. Statistical and Clinical Residual Uncertainties Assessment

There are no residual uncertainties based on the statistical analyses.

6.2. Review of Comparative Clinical Studies with Statistical Endpoints

6.2.1. FYB202-03-01

This section evaluates the efficacy results of Study FYB202-03-01

Data and Analysis Quality

There are no concerns regarding data quality and integrity.

Study Design and Endpoints

Study design

Study FYB202-03-01 was a multi-center, double-blind, parallel-group, active control, randomized study to demonstrate that there is no clinically meaningful difference between FYB202 and EU-approved Stelara in subjects with moderate-to-severe psoriasis regarding efficacy, safety, and immunogenicity.

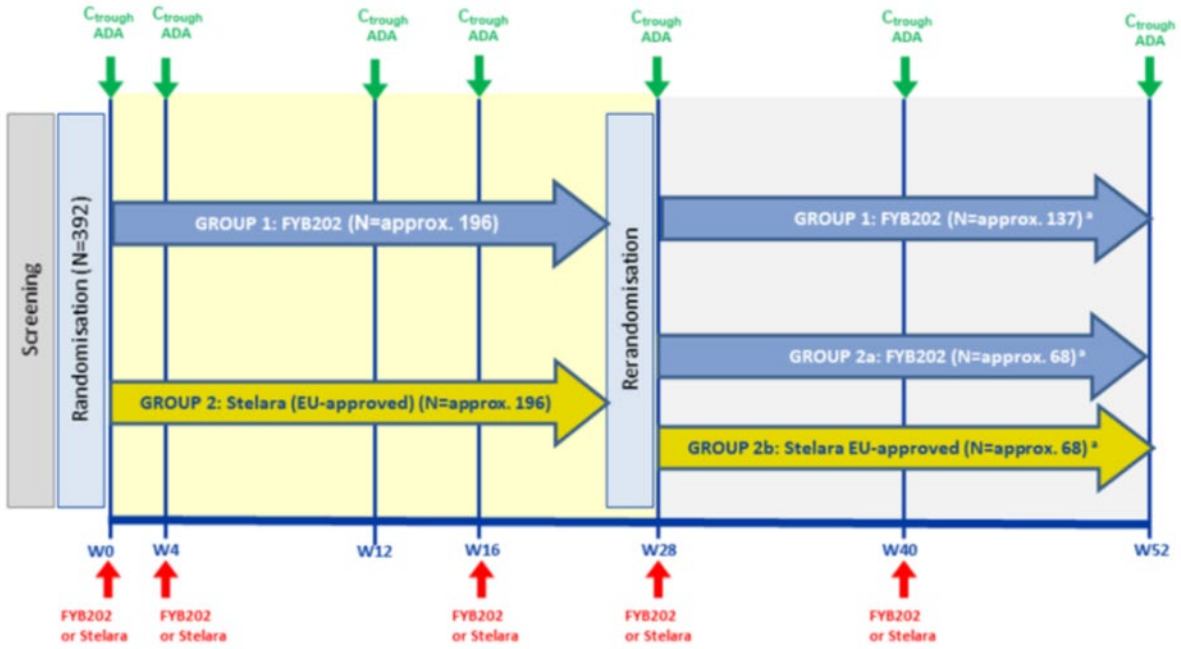
Patients were randomized 1:1 to receive subcutaneous (SC) injections of either FYB202 or EU-approved Stelara 45 mg at weeks 0, 4, 16, 28, and 40. Randomization before the first study intervention was stratified by prior inadequate response or intolerance to a systemic biological treatment in the opinion of the investigator (yes/no).

Patients failing to attain a ≥75% improvement in Psoriasis Area and Severity Index (PASI) score (PASI 75) from baseline at week 28 (estimated approximately 30% of patients) would be categorized as non-responders. These patients would cease the study intervention but would be followed until the study's completion at week 52.

At week 28, patients would be re-randomized in a blinded manner. Those initially assigned to treatment arm EU-approved Stelara would be re-randomized at a 1:1 ratio, with 50% transitioning to FYB202 while the remaining 50% would maintain EU-approved Stelara. Patients originally assigned to FYB202 would continue receiving it without change.

The schedule of activities is presented in Figure 6. The week 12 assessment corresponds to the primary efficacy endpoint evaluation time.

Figure 6. Schematic of the FYB202-03-01 Study Design



[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.
Source: Figure 9-1 of the Clinical Study Report (CSR)

Study endpoints

The primary efficacy endpoint was the percent improvement in PASI score from baseline (week 0) to week 12.

Table 19. Efficacy endpoints

Primary	• **Percent improvement in PASI score from baseline (week 0) to week 12**
Secondary	• 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 • Change per Physician's Global Assessment (PGA) over time. • Improvement of Dermatology Life Quality Index (DLQI) total score from baseline (week 0) at weeks 4, 12, 16, 28, 50, and 52

	• Itching Visual Analogue Scale (I-VAS) at baseline and at weeks 4, 12, 16, 28, 40, and 52 • Changes in PASI 75 and PASI 90 response from week 28 through week 52 in patients following a single transition from EU-approved Stelara to FYB202

Source: Reviewer's summary based on the clinical study report.

Statistical Methodologies

Analysis populations

The statistical analysis plan (SAP) defines the following analysis sets:

- Full analysis set (FAS): All patient randomized and treated with study intervention at least once. Patients are analyzed according to the study intervention they have been randomized to prior to the first study intervention.
- Safety analysis set: All patients treated with study intervention at least once. Patients are generally analyzed according to the study intervention they actually received at week 0 and/or at week 28.
- Per-protocol set (PPS): All patients from the FAS who are solely treated with study intervention from the randomized treatment group until week 28 and have no major protocol deviation that might interfere with the interpretation of the PASI assessment at baseline (week 0) or at week 12. Also, intercurrent events that affected either the availability or the interpretation of the PASI assessment at Week 12 led to the exclusion of a patient from the PPS.
- Re-randomized analysis set (RRAS): All patients who are re-randomized and treated with study intervention at least once at week 28 or later. Patients are analyzed according to the study interventions they actually received at week 0 and at week 28 or later.

The FAS is used as the primary basis for all efficacy evaluations up to and including week 28. After re-randomization, efficacy data are analyzed using the RRAS.

Similarity margin justification

According to the CSR, the similarity margin (-10%, +10%) was determined based on findings from prior studies. In addition, the margin was further investigated by calculating the retained treatment effect of Stelara in trials PHOENIX 1 & 2 (Leonardi et al., 2008; Papp et al., 2008). The results from both studies were combined using meta-analyses. The estimated treatment effect of Stelara was approximately 70%, with the lower limit of the associated 95% confidence interval being 67%. The retained treatment effect was approximately 85.7%, calculated using the provided formula:

$$Retained\ treatment\ effect = \frac{Stelara\ treatment\ effect - similarity\ margin}{Stelara\ treatment\ effect}.$$

Reviewer's comments: The similarity margin was discussed in Biosimilar Biological Product Development (BPD) Type 2 meeting under pre-IND 141478 on February 13, 2019. The applicant's proposal for the margin was (b) (4) *Regarding this proposal, the FDA stated, "For your study design and expected percent improvement in PASI values, we recommend using margins of ± 10%, rather than* (b) (4) *(see the DARRTS entry on March 15, 2019).*

Sample size determination

The sample size calculation was based on the following assumptions in Table 3.

Table 20. Assumptions for sample size calculations

Confidence level	90%
Power	90%
Similarity margin	± 10%
Treatment difference	0%
Standard deviation	30%
Drop-out rate	20%

Source: This table was produced by the reviewer using the information in Table 9-8 of the CSR.

The applicant provided the parameters used in sample size calculation, as outlined in Table 20. Using the assumptions, approximately 196 patients per treatment group are required to achieve 90% power (not included 20% drop-out rate). This calculation assumes similarity testing procedures and a normal distribution of the primary efficacy parameter, with no anticipated difference between the two treatment groups.

Reviewer's comments: The reviewer verified that the study size of 196 was reproducible using the listed assumptions. However, the applicant' assumption regarding the standard deviation of 30% lacks clarity regarding its source.

Analysis of primary efficacy endpoint

The hypotheses to be tested are

$$H_0: |\mu_F - \mu_S| \geq \delta \quad \text{versus} \quad H_A: |\mu_F - \mu_S| < \delta,$$

where μ_F and μ_S are the mean percentage change from baseline to week 12 in PASI score for FYB202 and EU-approved Stelara respectively; δ is the similarity margin ($\delta = 10\%$). To establish the similarity between FYB202 and EU-approved Stelara, the 90% confidence interval (CI) for the mean difference $\mu_F - \mu_S$ is calculated. The null hypothesis H_0 is rejected with a type I error probability $\alpha = 0.05$ if the 90% CI for $\mu_F - \mu_S$ is contained within the interval [-10%, 10%]. Rejecting the null hypothesis H_0 supports the conclusion of similarity between FYB202 and EU-approved Stelara.

The 90% CI for the mean difference $\boldsymbol{\mu_F - \mu_S}$ is constructed using the least-squares mean and error estimates derived from a mixed model repeated measures (MMRM). The MMRM includes baseline variables such as PASI score, weight, duration of psoriasis, prior inadequate response or intolerance to a systemic biological treatment and visit as factors. According to the SAP, the MMRM includes interaction terms between treatment group and visit, as well as between baseline PASI score and visit. Correlations within patients are accounted for using an unstructured variance-covariance matrix. Additionally, the Kenward-Roger degrees of freedom approximation is applied.

Handling of missing data

Per the SAP, MMRM is used for the efficacy analyses. Missing data regarding the primary or secondary efficacy endpoints are not explicitly imputed. Nevertheless, the model is operated under the assumption that the missing data for a patient are similar to the observed values of other patients sharing identical baseline characteristics and experiencing a similar progression from baseline to the relevant visit/week.

Due to the definition of baseline values and the definition of inclusion and exclusion criteria in the protocol, all randomized patients are expected to possess baseline data for the primary and secondary efficacy endpoints. Thus, there should be no necessity to exclude any patient from the MMRM analysis due to missing baseline values. For patients who does not exhibit any post-baseline values until week 28, no course of change from baseline could be assumed, and therefore, these patients are excluded from the primary analysis. The applicant further stated that due to the clinical status of patients it is regarded as very unlikely that no post-baseline assessment of the PASI exists.

Reviewer's comments: Two patients (Subject IDs: (b) (6)) did not exhibit any post baseline values until week 28, and they were excluded from the primary analysis. Note that the primary efficacy analysis is based on data of all patients in the FAS.

Sensitivity analyses for the primary efficacy endpoint

To assess robustness of the primary analysis results of the primary endpoint, the following sensitivity analyses are performed as planned in the SAP.

(S1) MMRM including only data until week 12 under the assumption that patients exhibiting comparable post-treatment values up to Week 28 will demonstrate similar behavior.

(S2) Analysis of covariance (ANCOVA) model including the baseline PASI score, baseline weight, duration of psoriasis as covariates, and prior inadequate response or intolerance to a systemic biological treatment and treatment group as fixed effects; based on observed cases.

(S3) ANCOVA model with using multiple imputation.

(S4) MMRM including patients discontinued study status prior to week 16 as a fixed effect.

(S5) MMRM including patients discontinued study status prior to week 12 as a fixed effect.

(S6) MMRM including patients discontinued study intervention status prior to week 16 as a fixed effect.

(S7) MMRM including patients with any major protocol deviation status as a fixed effect.

(S8) MMRM including patients with any major protocol deviation category as a fixed effect.

(S9) Tipping point analysis; sensitivity parameter $\theta = 0$ as a starting point and increments of 2% in both directions to increase the difference between the treatment groups.

Supplemental analyses for the primary efficacy endpoint

According to SAP, the supplemental estimands outlined below are evaluated using the same statistical methods (MMRM) as those for the primary analysis if at least 10 patients meet the relevant criteria described below:

(S10) Comparison of % improvement in PASI score from baseline to week 12 including data up to and including week 28 – excluding patients with major protocol deviations, which is the analysis based on the PPS at the same time,

(S11) Comparison of % improvement in PASI score from baseline to week 12 including data up to and including week 28 excluding patients from the FAS who discontinue study intervention before week 16 or do not have a week 12 PASI assessment (complete case analysis),

(S12) Comparison of % improvement in PASI score from baseline to week 12 including data up to and including week 28 excluding all assessments following discontinuation of study intervention (while on treatment strategy),

(S13) Comparison of % improvement in PASI score from baseline to week 12 including data up to and including week 28 excluding assessments following a missed study intervention,

(S14) Comparison of % improvement in PASI score from baseline to week 12 including data up to and including week 28 excluding all assessments following major protocol deviations.

Reviewer's comments*: Note that only 4 and 3 patients met the criteria on (S12) and (S13), respectively.*

In addition, the reviewer conducts the following supportive analysis:

(S15) ANCOVA using the PPS: the ANCOVA model in this supportive analysis is the same as that in the sensitivity analysis.

Analysis of secondary efficacy endpoints

Recall that there were four secondary efficacy endpoints based on the PASI score.

1) Percent improvement in PASI score from baseline to weeks 4, 16, 28, 40, and 52.
2) Raw PASI scores at baseline and weeks 4 and 12.
3) Proportion of patients with PASI 75 and PASI 90 responses at weeks 4, 12, 16, 28, 40, and 52.
4) Changes in PASI 75 and PASI 90 response from week 28 through week 52 in patients following a single transition from EU-approved Stelara to FYB202.

The secondary efficacy endpoints based on the PASI score are analyzed as follows:

- The raw PASI scores and the percent improvement in PASI score were summarized. Descriptively.
- The percent improvement in PASI score at the analysis visits Week 4, Week 16 and Week 28 was statistically analyzed using the same MMRM as the one for the primary efficacy endpoint.
- The time course of the PASI 75 and PASI 90 response was presented using bar plots.
- The difference between treatment groups in the response rates of PASI 75 and PASI 90 at each analysis visit from Week 4 to Week 28 were analyzed via a repeated measures logistic regression model.
- The change in PASI 75/PASI 90 response from week 28 to week 40 and week 52 were presented in the terms of shift tables by treatment group for the RRAS.

Recall that the secondary efficacy endpoints, excluding those determined by the PASI score, are as follows:

5) Change per PGA over time,
6) Improvement of DLQI total score from baseline at weeks 4, 12, 16, 28, 50, and 52
7) I-VAS at baseline and at weeks 4, 12, 16, 28, 40, and 52

Change per PGA over time is analyzed as follows:

- The changes in PGA score from baseline are descriptively summarized.

- The same MMRM as one for the primary endpoint was used to analyze the difference in treatment groups with respect to the absolute change from baseline in PGA score at week 4, week 12, week 16, and week 28.

The secondary efficacy endpoint based on the DLQI, and I-VAS were analyzed in an analogous manner as explained in the method for PGA. In addition, the analysis of the I-VAS is carried out separately for the average itch experience and the worst itch experience.

Subgroup analysis

According to SAP, the primary endpoint was analyzed across the subgroups defined by the following factors:

- Prior inadequate response or intolerance to a systemic biological treatment (yes/no)
- Sex (male or female)
- Baseline PASI score (moderate or severe)
- Time since onset of psoriasis (≤ 10 years, > 10 years and ≤ 20 years, and ≥ 20 years)
- Baseline body weight (≤ 75 kg, > 75 kg and < 90 kg, and ≥ 90 kg)

The primary efficacy endpoint analysis using the MMRM was repeated for subgroups of the FAS if the subgroup size allowed the calculation of meaningful confidence intervals.

Subject Disposition

Analysis populations, subject disposition and primary reasons for study discontinuation are summarized in Table 21. A total of 507 subjects were screened. Of these, 392 subjects were randomized to receive study treatment: 197 patients were randomized to receive FYB202 and 195 patients to receive EU-approved Stelara.

No patients were excluded from the FAS or SAF. Thus, both sets comprised a total of 392 patients. There were 13 patients who had a major protocol deviation, these patients were excluded from the PPS. There were 9 (2.3%) patients who were excluded from RRAS because they were non-responders, 5 (1.3%) because they discontinued the study before week 28, and 3 (0.8%) patients because they were not rerandomized due to other reasons.

By week 28, 387 patients completed the study, while 5 patients discontinued the study prematurely. Among those who completed the study, 9 patients were non-responders, and 3 patients were not eligible for rerandomization due to other reasons such as discontinuation due to adverse events or non-attendance at week 28 due to patient non-compliance. Consequently, 375 patients were rerandomized at week 28. Of these, 189 patients originally on FYB202 stayed on FYB202 as per study design (FYB202: FYB202), 97 patients initially on EU-approved Stelara were rerandomized to EU-

approved Stelara (EU-approved Stelara: EU-approved Stelara), and 89 patients on EU-approved Stelara were rerandomized to FYB202 (EU-approved Stelara: FYB202).

Following initial randomization, 380 patients completed the study until week 52. Following rerandomization of 375 patients, 372 patients completed the study until week 52; 187 patients on FYB202: FYB202 group, 97 patients on EU-approved Stelara: EU-approved Stelara group, and 88 patients on EU-approved Stelara: FYB202 group.

Table 21. Analysis Population and Subject Disposition

	FYB202	EU-approved Stelara	Overall
Screened			507
Screening failure			115
Randomized	197	195	392
Safety	197 (100.0)	195 (100.0)	392 (100.0)
FAS	197 (100.0)	195 (100.0)	392 (100.0)
PPS	191 (97.0)	188 (96.4)	379 (96.7)
Excluded from PPS			
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	2 (1.0)	5 (2.6)	7 (1.8)
RRAS	189 (95.9)	186 (95.4)	375 (95.7)
Excluded from RRAS			
Non-responder	4 (2.0)	5 (2.6)	9 (2.3)
Discontinued study before week 28	4 (2.0)	1 (0.5)	5 (1.3)
Not rerandomized for other reason	0 (0.0)	3 (1.5)	3 (0.8)
Completed study up to week 28	193 (98.0)	194 (99.5)	387 (98.7)
Discontinued study			
Withdrew consent	2 (1.0)	0 (0.0)	2 (0.5)
Adverse event	1 (0.5)	1 (0.5)	2 (0.5)
Protocol deviation	1 (0.5)	0 (0.0)	1 (0.3)
Not re-randomized at week 28	4 (2.0)	8 (4.1)	12 (3.1)
Non-responders	4 (2.0)	5 (2.6)	9 (2.3)
Other reason	0 (0.0)	3 (1.5)	3 (0.8)
Re-randomized at week 28	189 (95.9)	186 (95.4)	375 (95.7)
Completed study up to week 52	191 (97.0)	189 (96.9)	380 (96.9)
Discontinued the study after re-randomization	2 (1.0)	1 (0.5)	3 (0.8)
Adverse event	0 (0.0)	1 (0.5)	1 (0.3)
Withdrew consent	1 (0.5)	0 (0.0)	1 (0.3)
Other	1 (0.5)	0 (0.0)	1 (0.3)

Source: This table was produced by the reviewer using Tables 10-2 and 14.1.2.1.1 of CSR.

* The total number may add up to more than this number of subjects because a subject may have multiple reasons.

Demographics and Baseline Characteristics

Demographic and baseline characteristics are summarized in Tables 22 and 23. In general, demographic and baseline characteristics appear to be balanced between the two treatment groups among subjects in the FAS.

Table 22. Demographic Characteristics (FAS)

	FYB202	EU-approved Stelara	Overall
FAS	N = 197	N = 195	N = 392
Demographics			
Age (years)			
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
Gender, n (%)			
Male	117 (59.4%)	117 (60.0%)	234 (59.7%)
Female	80 (40.6%)	78 (40.0%)	158 (40.3%)
Race, n (%)			
White	197 (100.0%)	195 (100.0%)	392 (100.0%)
Ethnicity, n (%)			
Not Hispanic/Latino	197 (100.0%)	195 (100.0%)	392 (100.0%)
BMI (kg/m^2)			
Mean (SD)	26.6 (4.21)	27.4 (4.36)	27.0 (4.30)
Median	26.6	27.2	26.80
Min, Max	18.2, 38.9	16.9, 39.3	16.9, 39.3

Source: This table was produced by the reviewer using the Table 10-3 of CSR.

Table 23. Baseline Psoriasis Characteristics (FAS)

	FYB202	EU-approved Stelara	Overall
FAS	N = 197	N = 195	N = 392
Baseline characteristic			
Time since onset of psoriasis [years]			
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

Time since onset of psoriasis [years] in female patients			
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
Time since onset of psoriasis [years] in male patients			
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
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%)

Source: This table was produced by the reviewer using the Table 10-4 of CSR.

Analysis of Primary Clinical Endpoint(s)

The objective of the primary efficacy analysis was to demonstrate the similarity of FYB202 and EU-approved Stelara in the primary efficacy endpoint: the percent improvement in PASI score from baseline to week 12 with a similarity margin of ± 10%.

Table 24 presents the primary efficacy analysis results. As shown in Table 8, the adjusted mean percent improvement in PASI score from baseline to week 12 were comparable for the two treatment groups (79.51% for FYB202 and 76.24% for EU-approved Stelara). In addition, the mean difference was 3.27% with 90% CIs of (-0.2249%, 6.7699%), which was contained within the similarity margin of [-10%, 10%]. Thus, the similarity was demonstrated for the primary efficacy endpoint.

Table 24. Primary Analysis Results for the Percent Improvement in PASI Score from Baseline to Week 12 (FAS)

FAS	FYB202 (N = 197)	EU-approved Stelara (N = 195)
Baseline PASI		
n	197	195
Mean (SD)	24.07 (8.484)	24.75 (9.999)
Median (Range)	21.60 (12.3, 52.8)	21.80 (12.0, 63.3)
PASI at Week 12		
n	194	191
Mean (SD)	4.13 (5.684)	5.04 (6.435)
Median (Range)	2.40 (0.0, 39.2)	2.40 (0.0, 38.2)
% improvement of PASI at Week 12		
Mean (SD)	83.00 (18.882)	79.29 (23.037)
Median (Range)	88.11 (17.4, 100.0)	86.67 (0.0, 100.0)
Adjusted % improvement of PASI at Week 12[1]		
LS mean (SE)	79.51 (2.48)	76.24 (2.44)
LS mean difference (SE)	3.27 (2.121)	
90% CI for the mean difference	**(-0.225, 6.770)**	

[1] MMRM used all available percent improvements in PASI score from baseline until week 28 for all patients in the FAS for model estimation.
[1] Estimates are adjusted for baseline PASI score, baseline weight, time since onset of psoriasis and prior inadequate response or intolerance to a systemic biological treatment.
Source: Reviewer's analysis.

Potential Effects of Missing Data

The study evaluated robustness of the primary analysis results by conducting different sensitivity analyses. Table 25 shows the summary of sensitivity analysis results. The sensitivity analysis results were consistent with the primary analysis results, leading to the same conclusion for a robust interpretation of the similarity finding.

Reviewer's comments: The reviewer included MMRM including patient discontinued study intervention prior to week 16 as additional fixed effect in sensitivity analysis as outlined in the SAP. However, the applicant did not include this sensitivity analysis in their evaluation.

Table 25. Sensitivity Analyses for the Primary Efficacy Endpoint (FAS)

Method	LS Mean (SE)	Difference (FYB202 – Stelara)

	FYB202	Stelara	Mean (SE)	90% CI
(S1) MMRM [1] using data up to week 12	81.16 (4.096)	78.04 (4.000)	3.12 (2.149)	(-0.431, 6.656)
(S2) ANCOVA [2]	80.31 (4.241)	77.16 (4.140)	3.15 (2.147)	(-0.394, 6.685)
(S3) ANCOVA [2] using MI	80.30 (4.241)	77.14 (4.142)	3.16 (2.153)	(-0.381, 6.702)
(S4) MMRM [1] including patient discontinuation of study status prior to week 16 as additional fixed effect	67.67 (12.445)	64.34 (12.495)	3.33 (2.122)	(-0.169, 6.829)
(S5) MMRM [1] including patient discontinuation of study status prior to week 12 as additional fixed effect	67.67 (12.445)	64.34 (12.495)	3.33 (2.122)	(-0.169, 6.829)
(S6) MMRM [1] including patient discontinuation of study treatment status prior to week 16 as additional fixed effect	79.51 (2.479)	76.24 (2.437)	3.27 (2.121)	(-0.225, 6.770)
(S7) MMRM [1] including patient any major protocol deviation status as additional fixed effect	77.87 (3.046)	74.67 (2.967)	3.20 (2.125)	(-0.301, 6.705)
(S8) MMRM [1] including major protocol deviation category as additional fixed effect	78.45 (4.069)	75.18 (3.975)	3.27 (2.129)	(-0.239, 6.782)

[1] Estimates are adjusted for baseline PASI score, baseline weight, time since onset of psoriasis and prior inadequate response or intolerance to a systemic biological treatment.
[2] Estimates are adjusted for baseline PASI score, baseline weight, time since onset of psoriasis and prior inadequate response or intolerance to a systemic biological treatment.
Source: Reviewer's analysis.

Table 26 shows the results of the tipping point analysis. The tipping analysis indicated that results were tipped from being clinically similar to not being clinically similar under the following assumptions:

- Increase by at least 85% for FYB202 and reduction by at least 85% for EU-approved Stelara,
- Reduction by at least 200% for FYB202 and increase by at least 215% for EU-approved Stelara,
- Reduction by at least 205% for FYB202 and increase by at least 210% for EU-approved Stelara,
- Reduction by at least 210% for FYB202 and increase by at least 200% for EU-approved Stelara,
- Reduction by at least 215% for FYB202 and increase by at least 190% for EU-approved Stelara.

Given the observed data at week 12, the probability of observing as large as or more extreme than 100% of the difference between FYB202 and EU-approved Stelara is almost 0. It can thus be concluded that the tipping points observed did not align with

realistic scenarios based on available data, thereby supporting the robustness of the primary endpoint results.

Table 26. The Percent Improvement in PASI Score from Baseline to Week 12 by Tipping Point Analysis (FAS)

FAS, Tipping point analysis									
Shift for EU-Stelara	**Shift for FYB202**								
	90%	85%	80%	···	-195%	-200%	-205%	-210%	-215%
-90%	**6.22 (2.19, 10.26)**	**6.15 (2.14, 10.17)**	6.09 (2.10, 10.08)						
-85%	**6.11 (2.10, 10.12)**	**6.04 (2.42, 10.03)**	2.41 (2.02, 9.94)						
-80%	6.00 (2.02, 9.98)	5.93 (1.98, 9.89)	5.87 (2.39, 9.80)						
⋮									
185%									-4.14 (-9.91, 1.64)
190%								-4.09 (-9.85, 1.66)	**-4.20 (-10.01, 1.60)**
195%							-4.05 (-9.78, 1.69)	-4.16 (-9.95, 1.63)	**-4.27 (-10.11, 1.57)**
200%						-4.00 (-9.72, 1.72)	-4.11 (-9.89, 1.66)	**-4.22 (-10.05, 1.60)**	**-4.33 (-10.21, 1.54)**
205%						-4.07 (-9.83, 1.69)	-4.18 (-9.99, 1.63)	**-4.29 (-10.15, 1.57)**	**-4.40 (-10.31, 1.51)**
210%						-4.13 (-9.93, 1.66)	**-4.25 (-10.09, 1.60)**	**-4.36 (-10.25, 1.54)**	**-4.47 (-10.42, 1.48)**
215%					-4.09 (-9.87, 1.69)	**-4.20 (-10.03, 1.63)**	**4.31 (-10.20, 1.57)**	**-4.42 (-10.36, 1.51)**	**-4.53 (-10.52, 1.45)**

Estimates and 90% CIs for the treatment difference are displayed.
Source: Reviewer's analysis.

Supplemental analyses were performed using MMRM restricted to data of the PPS, on modified FAS populations (e.g., FAS with complete case analysis) or different handling of intercurrent events. Table 27 summarizes these supplemental analyses. The supplemental analyses supported the result of the primary analysis.

Table 27. Supplemental Analyses for the Primary Efficacy Endpoint

Method	LS Mean (SE)		Difference (FYB202 – Stelara)	
	FYB202	Stelara	Mean (SE)	90% CI
(S10) MMRM [1], PPS	79.58 (2.490)	76.08 (2.451)	3.50 (2.159)	(-0.062, 7.057)
(S11) MMRM [1], FAS (complete case analysis)	79.59 (2.488)	76.16 (2.450)	3.43 (2.137)	(-0.097, 6.950)
(S14) MMRM [1], FAS (excluding all assessments following major protocol deviations)	79.55 (2.494)	76.17 (2.451)	3.37 (2.159)	(-0.189, 6.933)
(S15) ANCOVA [2], PPS	80.38 (4.259)	77.11 (4.152)	3.27 (2.170)	(-0.309, 6.846)

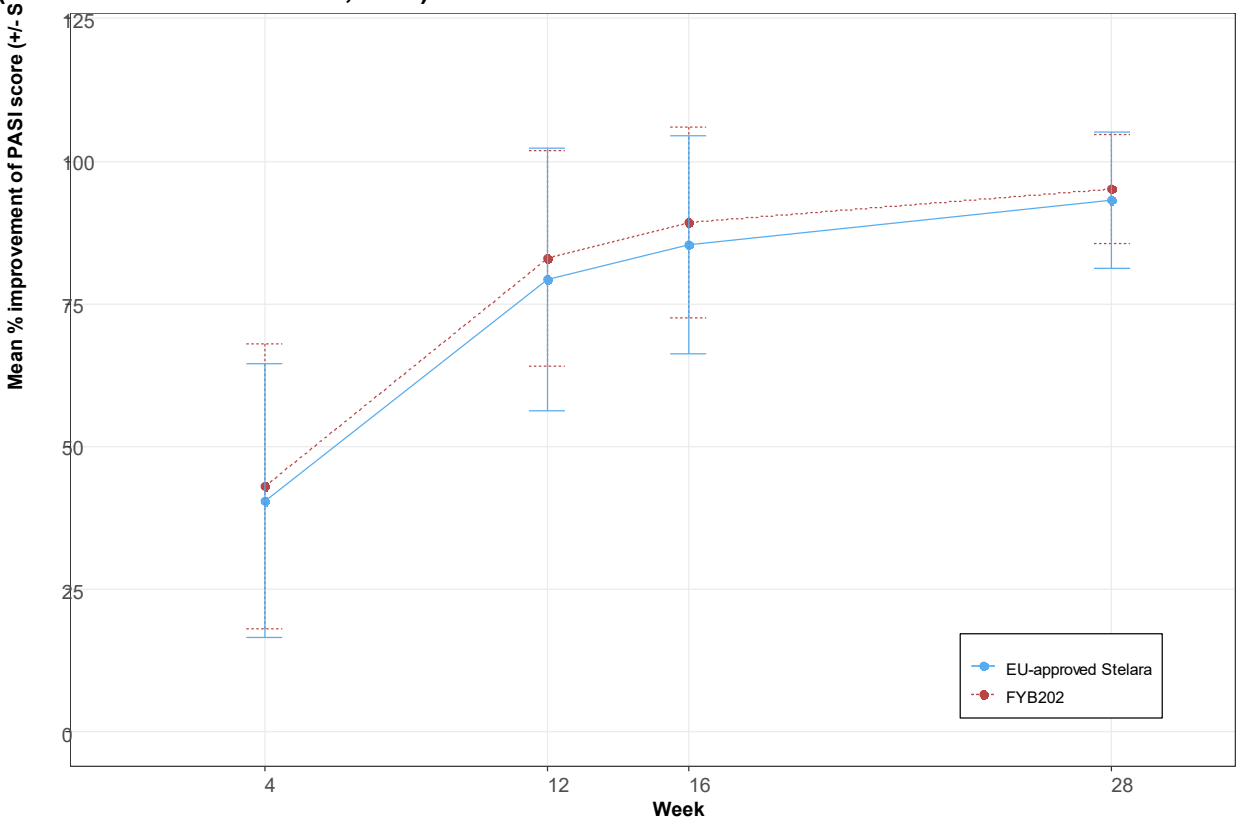
[1] Estimates are adjusted for baseline PASI score, baseline weight, time since onset of psoriasis and prior inadequate response or intolerance to a systemic biological treatment.
[2] Estimates are adjusted for baseline PASI score, baseline weight, time since onset of psoriasis and prior inadequate response or intolerance to a systemic biological treatment.
Source: Reviewer's analysis.

Analysis of Secondary Clinical Endpoint(s)

Percent improvement of PASI score

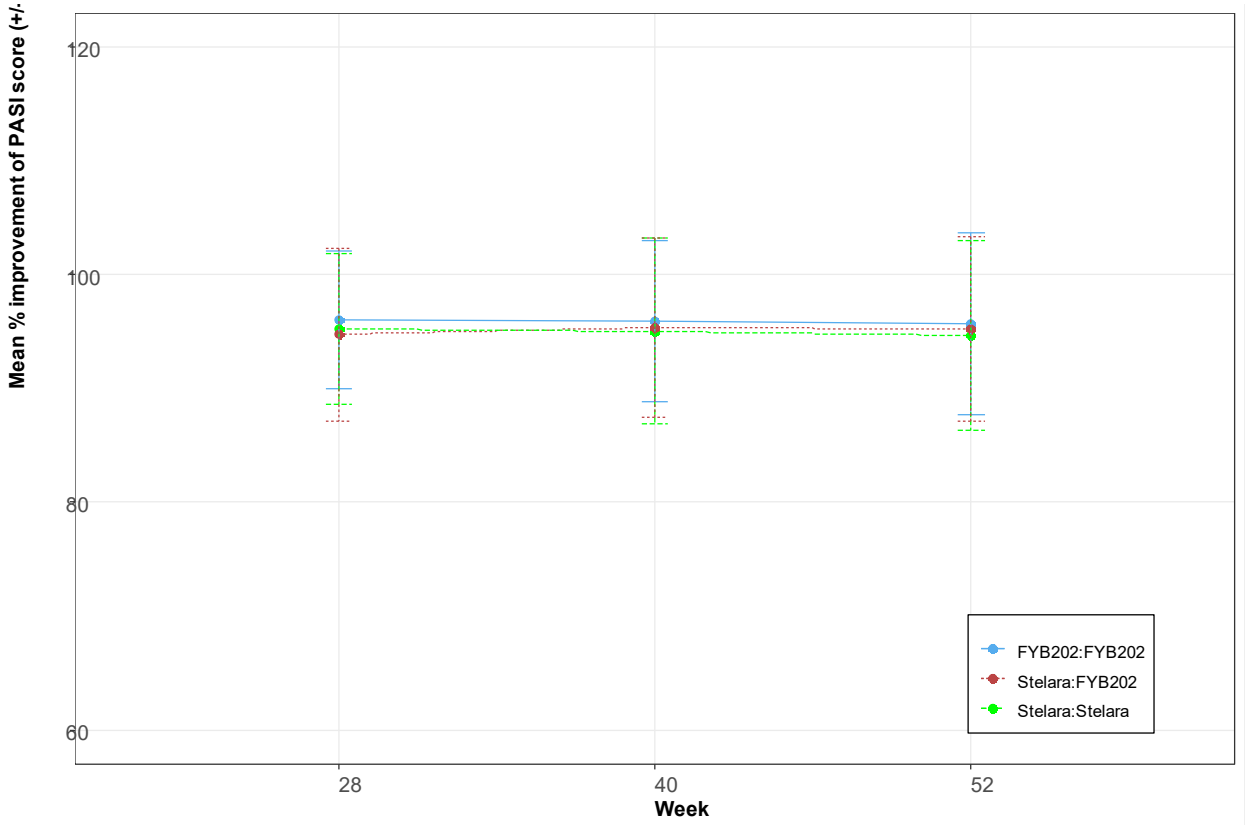
Figures 7 and 8 present the analysis results of percent improvement in PASI score from baseline over time up to week 52. Figure 7 displays the percent improvement in PASI score from baseline over time up to week 28 before rerandomization. In addition, a consistent and significant improvement emerged starting from rerandomization at week 28 in the group transitioning from EU-approved Stelara to FYB202, and very similarly in the groups keeping to their initial randomized treatment. Figure 9 shows the difference (FYB202 – EU-approved Stelara) in adjusted mean percent improvement in PASI score over time up to week 28 with 90% CIs. The two-sided 90% CIs for the differences at weeks 4, 16, and 28 were well comparable to the 90% CI for the difference seen for the primary efficacy endpoint at week 12. Also, all 90% CIs are contained within the similarity margin [-10%, 10%].

Figure 7. Percent Improvement in PASI Score from Baseline to Weeks 4, 16, and 28 (Before Rerandomization, FAS)



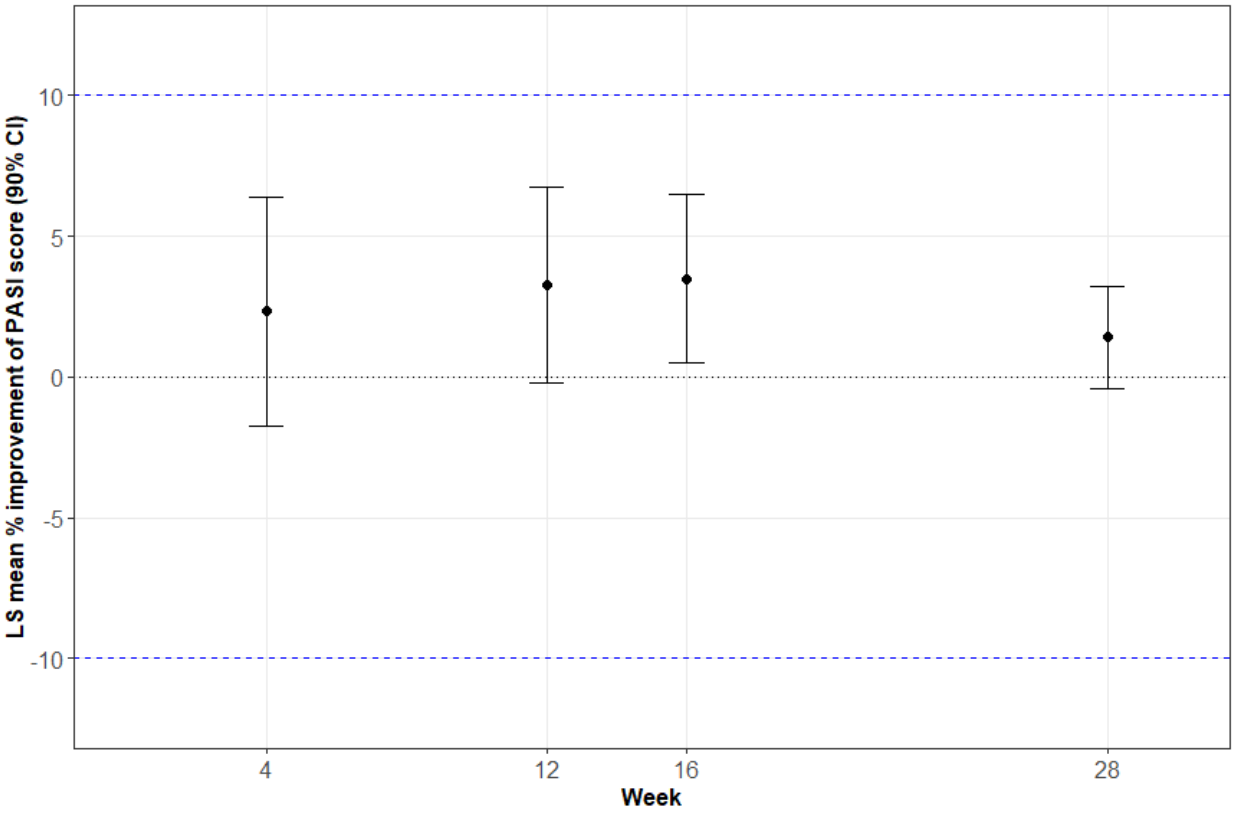
Source: Reviewer's analysis.

Figure 8. Percent Improvement in PASI Score from Baseline to Weeks 28, 40, And 52 (RRAS, FAS)



Source: Reviewer's analysis

Figure 9. Plot for Difference (FYB202 - EU-Stelara) in Mean Percent Improvement in PASI Score with 90% CI Over Time Up to Week 28 (FAS)

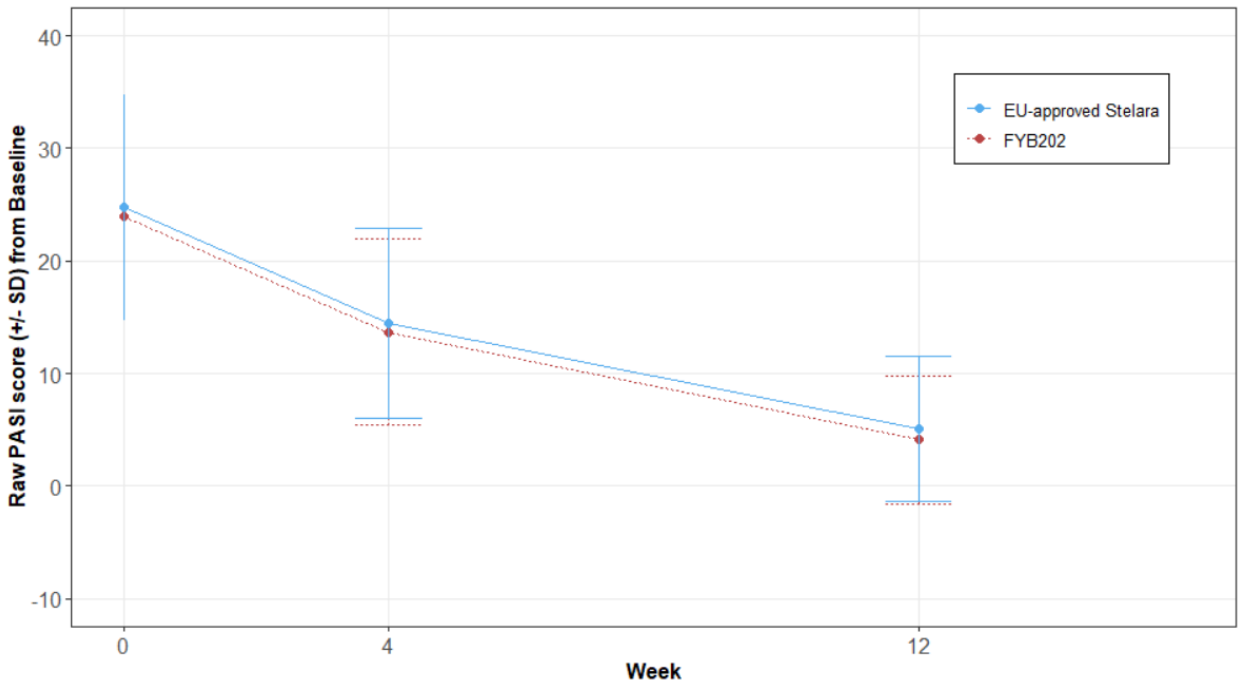


Source: Reviewer's analysis.

Raw PASI scores at baseline, weeks 4 and 12

Figure 10 presents the descriptive statistics for the raw PASI scores at baseline, week 4, and week 12. As seen in Figure 10, raw PASI scores at baseline, week 4, and week 12 appear to be comparable trends in both FYB202 group and the EU-approved Stelara group in the FAS.

Figure 10 Raw PASI Score from Baseline to Week 12 (FAS)

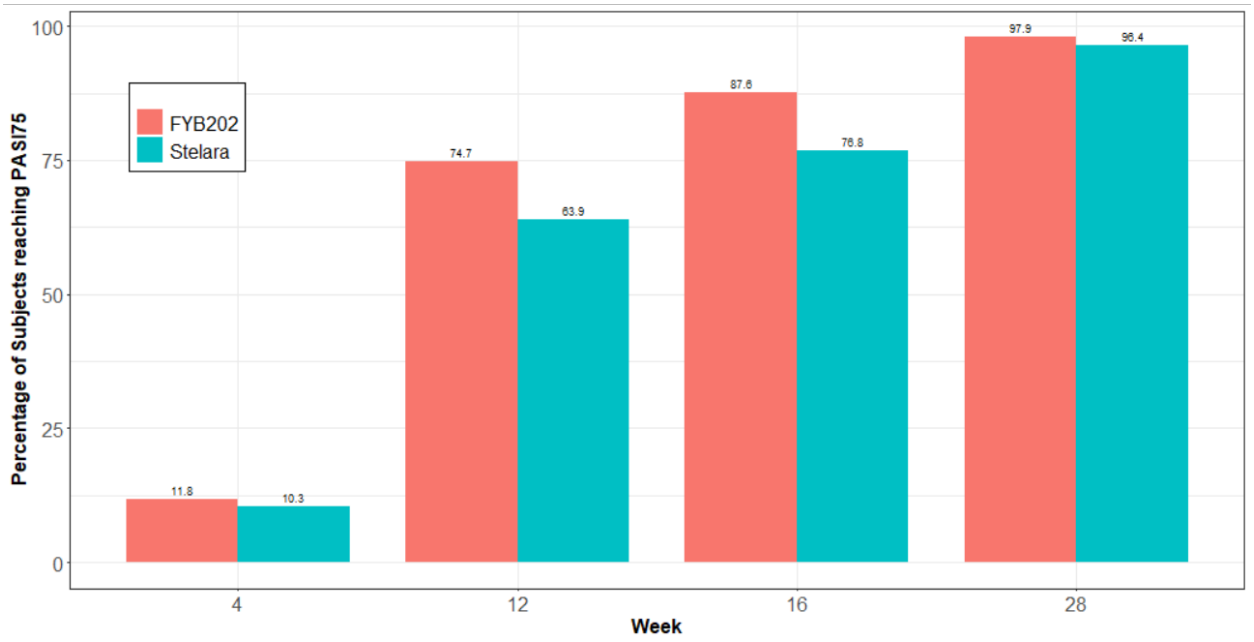


Source: Reviewer's analysis.

Proportion of patients with PASI 75 and PASI 90 responses at weeks 4, 12, 16, 28, 40, and 52

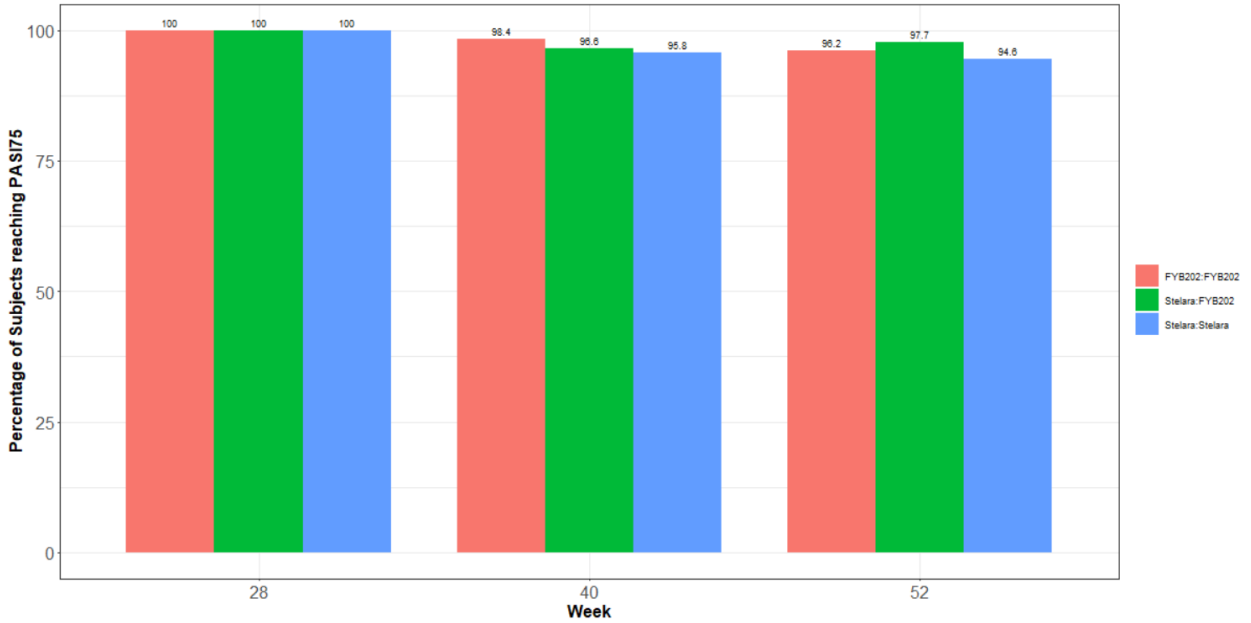
Figures 11 and 12 show the percentages of patients who reached an improvement in PASI score of at least 75% (PASI 75). The trends in PASI 75 response rates were consistent across both groups, showing the most significant uptick between weeks 4 and 12, with nearly all patients attaining a PASI 75 response by week 28. After rerandomization from week 28 onwards, a sustained response was evident in all three groups, indicating that the single transition did not affect the maintenance of response over time.

Figure 11. Proportion of Subjects Reaching PASI 75 Before Re-randomization (FAS)



Source: Reviewer's analysis

Figure 12. Proportion of Subjects Reaching PASI 75 After Re-randomization (RRAS)



Source: Reviewer's analysis.

Table 28 shows the result from the repeated measures logistic regression analysis comparing the PASI 75 response rates between FYB202 and EU-approved Stelara. The odds ratios and their corresponding confidence intervals suggest that, except for at week 16, there are no substantial differences between the two groups. At week 16, an odds ratio of 0.51 with a 95% confidence interval of (0.30, 0.88) seems to indicate a statistically significant association.

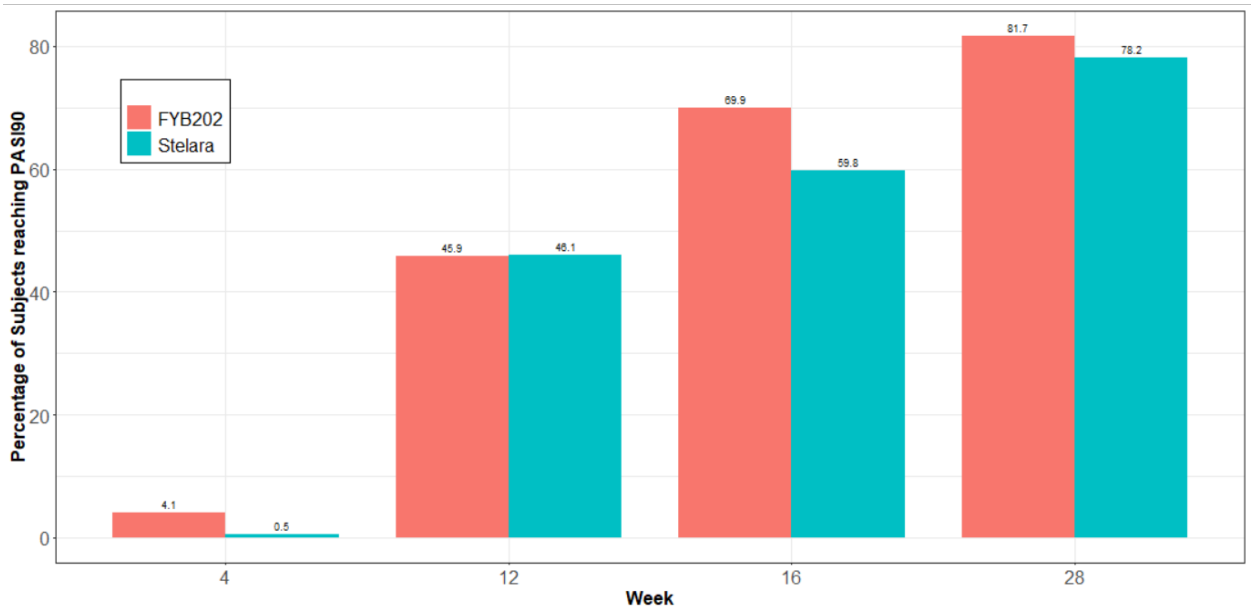
Table 28. Comparison of FYB202 and EU-approved Stelara in PASI 75 Response Rates Before Rerandomization (FAS)

Visit week	FYB202	EU-approved Stelara	Odds ratio (95% CI) [1]
Week 4	0.12	0.10	0.88 (0.47, 1.66)
Week 12	0.75	0.64	0.65 (0.42, 1.01)
Week 16	0.88	0.77	0.51 (0.30, 0.88)
Week 28	0.98	0.96	0.57 (0.17, 1.95)

[1] Odds ratio and 95% confidence intervals are estimated from a logistic regression including baseline PASI score, baseline weight, time since onset of psoriasis and prior inadequate response or intolerance to a systemic biological treatment.
Source: Reviewer's analysis.

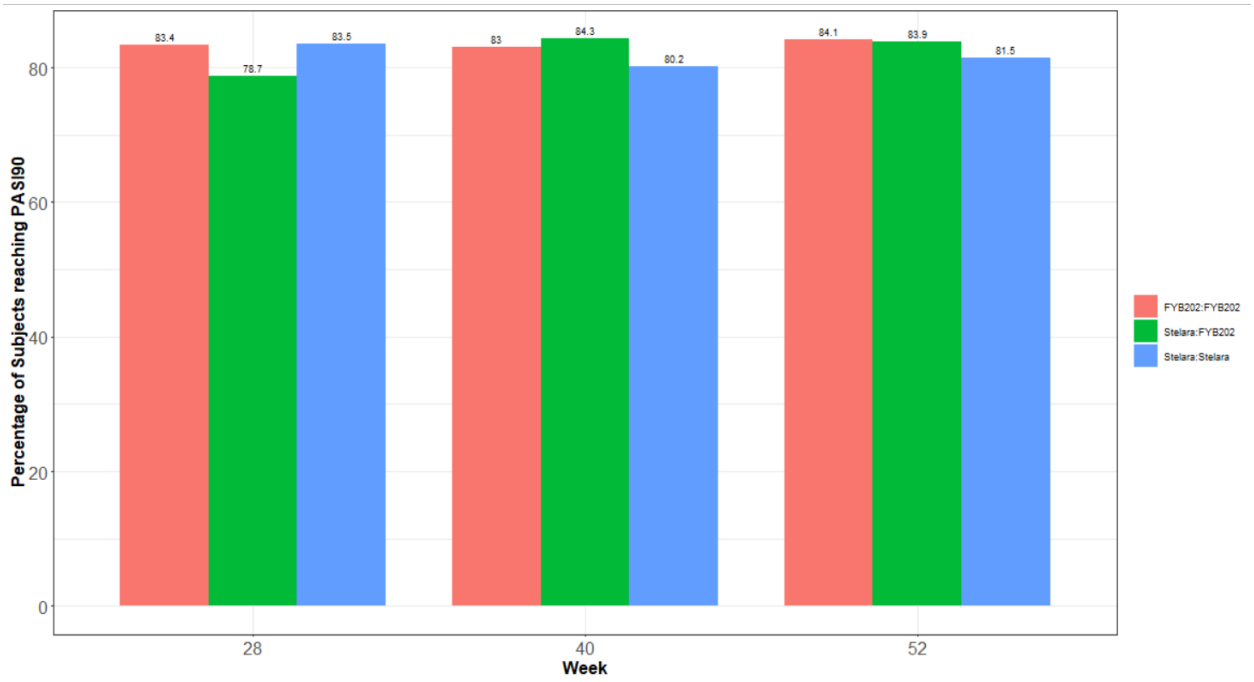
Figures 13 and 14 show the percentages of patients who reached an improvement in PASI score of at least 90% (PASI 90). As for PASI75, the PASI 90 response demonstrated a similar trend throughout the treatment duration for both FYB202 and EU-approved Stelara, with roughly 80% of patients achieving a PASI 90 response by week 28. After rerandomization from week 28 onward, PASI 90 response rates consistently exceeded 80% in the EU-Stelara to FYB202 transition group, as well as in the groups maintaining their originally assigned treatments.

Figure 13. Proportion of Subjects Reaching PASI 90 Before Re-randomization (FAS)



Source: Reviewer's analysis.

Figure 14. Proportion of Subjects Reaching PASI 90 After Re-randomization (RRAS)



Source: Reviewer's analysis.

Table 29 shows the result from the repeated measures logistic regression analysis comparing the PASI 90 response rates between FYB202 and EU-approved Stelara. The odds ratios and their corresponding confidence intervals at weeks 12 and 28 suggest that there are no substantial differences between the two groups; however, the odds ratios and their corresponding confidence intervals at weeks 4 and 16 seems to indicate a statistically significant difference in response rates between the two groups. However, when considered with the PK similarity data, the primary efficacy data, and other supportive secondary endpoints, the observed confidence intervals at weeks 4 and 16 do not preclude a demonstration that FYB202 has no clinically meaningful differences from US-Stelara.

Table 29. Comparison Of FYB202 and EU-Approved Stelara in PASI 90 Response Rates Before Rerandomization (FAS)

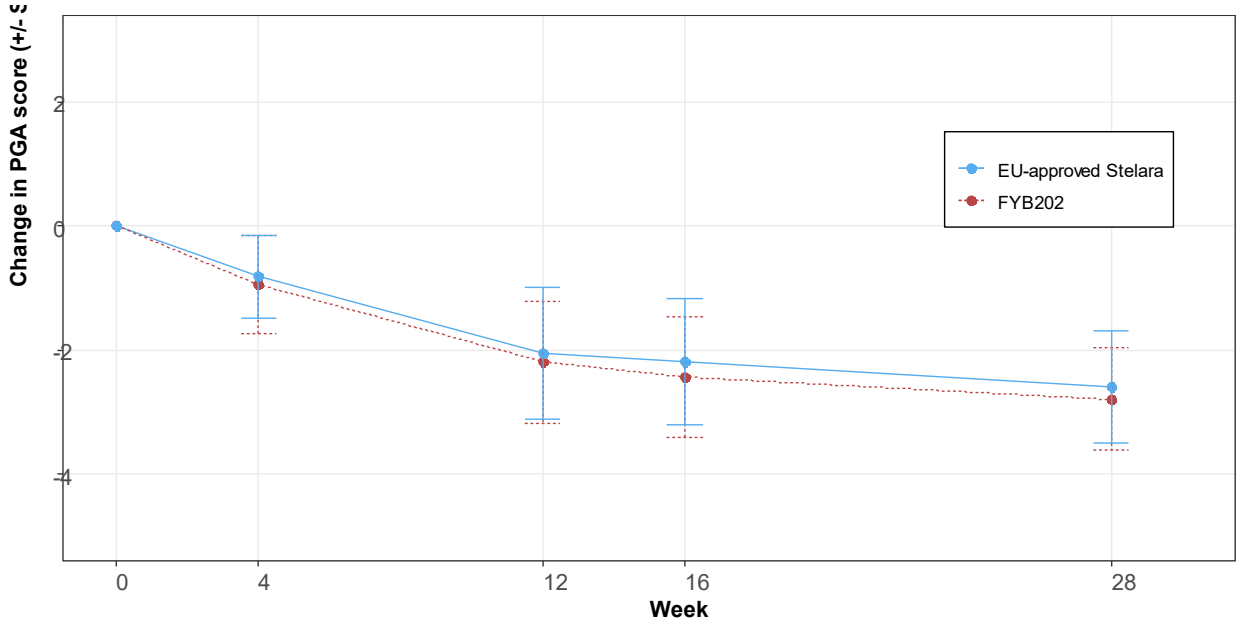
Visit week			
	FYB202	EU-approved Stelara	Odds ratio (95% CI) [1]
Week 4	0.04	0.05	0.14 (0.02, 0.99)
Week 12	0.46	0.46	1.07 (0.71, 1.62)
Week 16	0.70	0.60	0.64 (0.42, 0.99)
Week 28	0.82	0.78	0.81 (0.48, 1.35)

[1] Odds ratio and 95% confidence intervals are estimated from a logistic regression including baseline PASI score, baseline weight, time since onset of psoriasis and prior inadequate response or intolerance to a systemic biological treatment.
Source: Reviewer's analysis.

Change per PGA over time

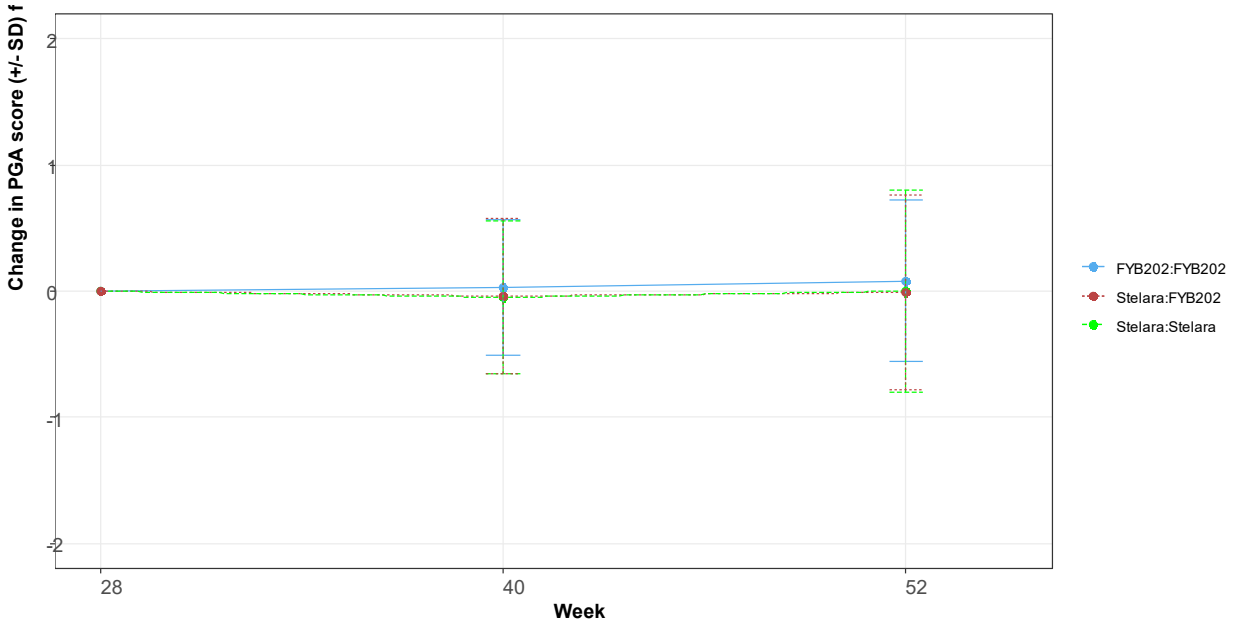
Figure 15 shows the change from baseline in PGA scores throughout at weeks 4, 12, 16, and 28. Figure 16 shows the change from week 28 to weeks 40 and 52 in PGA score after rerandomization from week 28. Changes in PGA scores appear to be comparable trends in all groups.

Figure 15. Change from Baseline in PGA Score up to Week 28 (FAS)



Source: Reviewer's analysis

Figure 16. Change from Week 28 in PGA Score up to Week 52 (RRAS)



Source: Reviewer's analysis

In Table 30, the MMRM analysis for the difference between treatment groups in PGA score change showed similar reductions from baseline to weeks 4, 12, 16, and 28.

Table 30. MMRM: Comparison of Change from Baseline in PGA Score from Baseline to Weeks 4, 12, 16, And 28 (FAS)

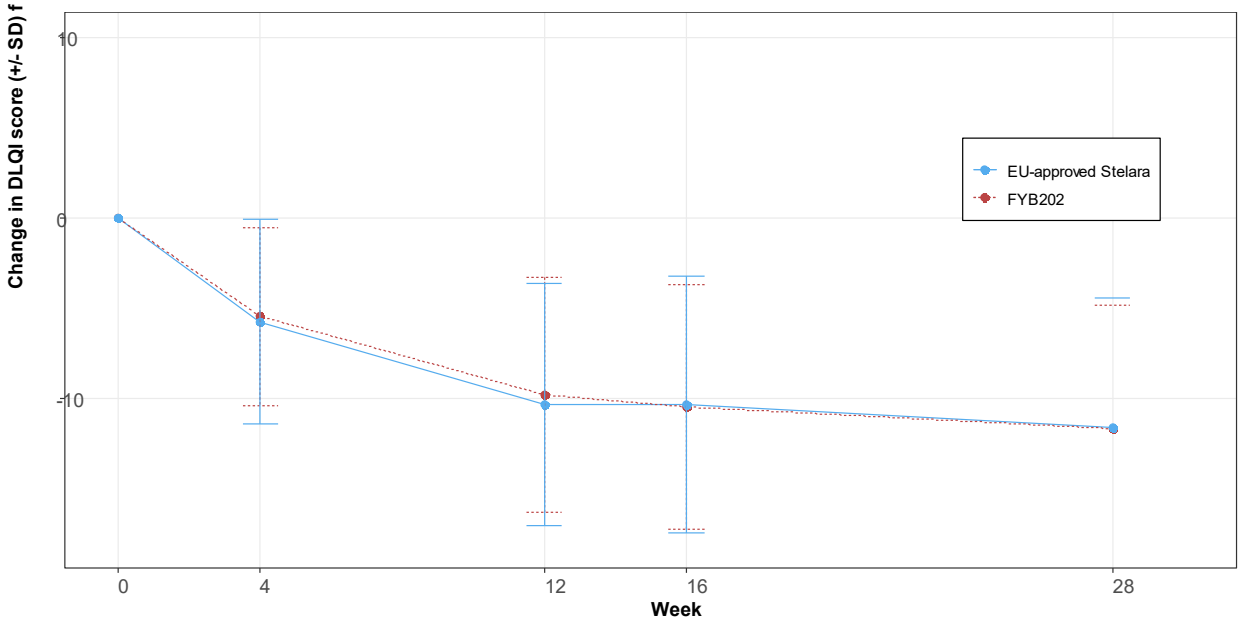
	LS Mean (SE)		Difference (FYB202 – Stelara)	
	FYB202	Stelara	Mean (SE)	95% CI
Week 4	-0.84 (0.117)	-0.76 (0.114)	-0.08 (0.071)	(-0.22, 0.06)
Week 12	-2.09 (0.125)	-1.99 (0.123)	-0.10 (0.094)	(-0.29, 0.08)
Week 16	-2.34 (0.123)	-2.13 (0.121)	-0.20 (0.090)	(-0.38, -0.03)
Week 28	-2.68 (0.119)	-2.53 (0.116)	-0.15 (0.076)	(-0.30, -0.00)

LS means calculation is based on the MMRM; Two-sided 95% confidence interval based on normal approximation. Estimates are adjusted for baseline PASI score, baseline weight, time since onset of psoriasis and prior inadequate response or intolerance to a systemic biological treatment.
Source: Reviewer's analysis.

Improvement of DLQI total score from baseline at weeks 4, 12, 16, 28, 40, and 52

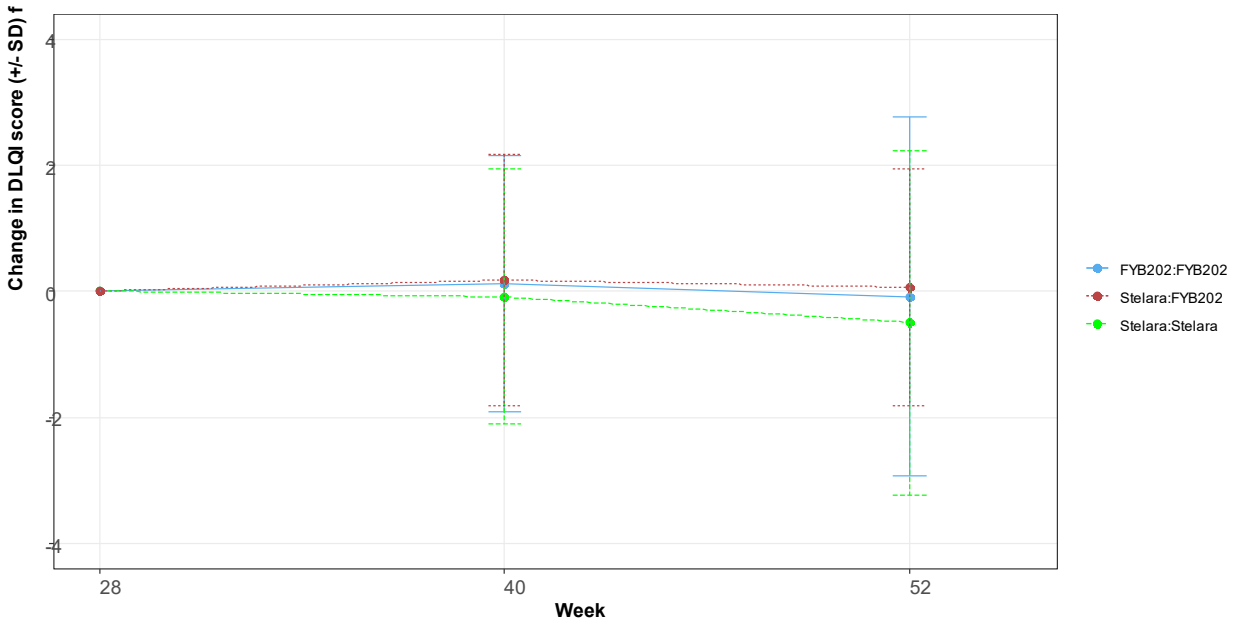
Figure 17 shows the change from baseline in DLQI scores throughout at weeks 4, 12, 16, and 28. Figure 18 shows the change from week 28 to weeks 40 and 52 in DLQI score after rerandomization from week 28. Changes in DLQI scores appear to be comparable trends in all groups.

Figure 17. Change from Baseline in DLQI Score up to Week 28 (FAS)



Source: Reviewer's analysis.

Figure 18. Change from Week 28 in DLQI Score up to Week 52 (RRAS)



Source: Reviewer's analysis.

In Table 31, the MMRM analysis for the difference between treatment groups in DLQI score change showed similar reductions from baseline to weeks 4, 12, 16, and 28.

Table 31. Comparison Of Change from Baseline in DLQI Score from Baseline to Weeks 4, 12, 16, and 28 (FAS)

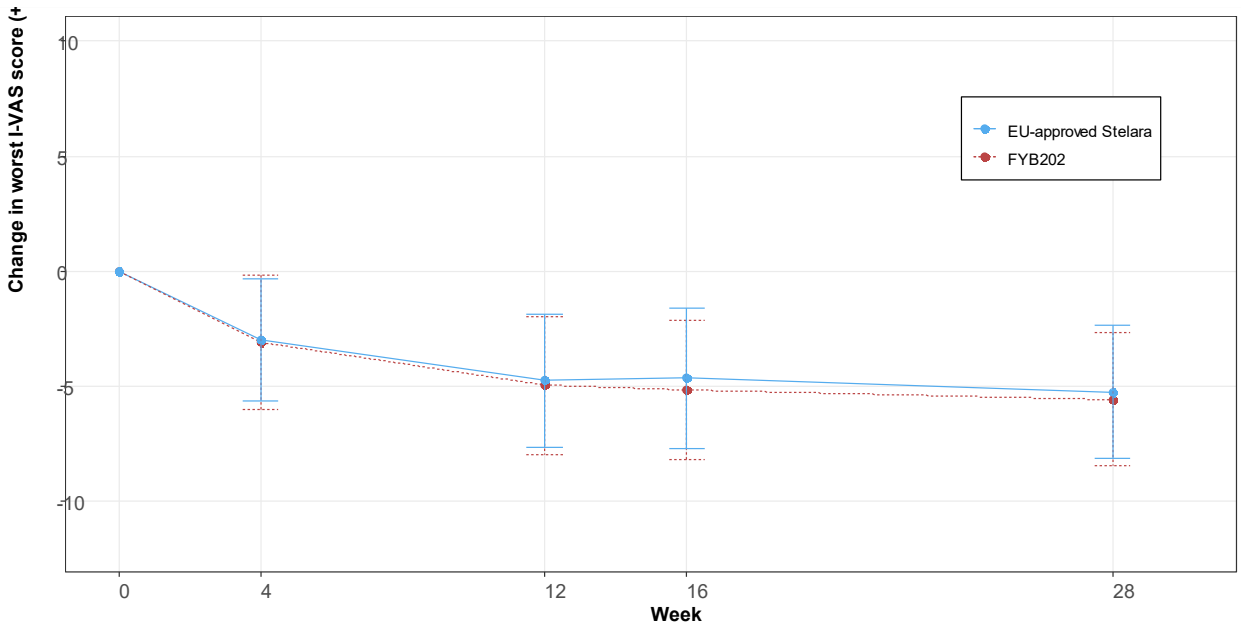
	LS Mean (SE)		Difference (FYB202 – EU-Stelara)	
	FYB202	Stelara	Mean (SE)	95% CI
Week 4	-5.77 (0.700)	-5.73 (0.686)	-0.05 (0.484)	(-1.00, 0.91)
Week 12	-10.12 (0.681)	-10.20 (0.667)	0.07 (0.428)	(-0.77, 0.92)
Week 16	-10.75 (0.684)	-10.36 (0.669)	-0.39 (0.437)	(-1.24, 0.47)
Week 28	-11.93 (0.670)	-11.53 (0.655)	-0.40 (0.390)	(-1.16, 0.37)

LS means calculation is based on the MMRM; Two-sided 95% confidence interval based on normal approximation. Estimates are adjusted for baseline PASI score, baseline weight, time since onset of psoriasis and prior inadequate response or intolerance to a systemic biological treatment.
Source: Reviewer's analysis.

I-VAS at baseline and at weeks 4, 12, 16, 28, 40, and 52

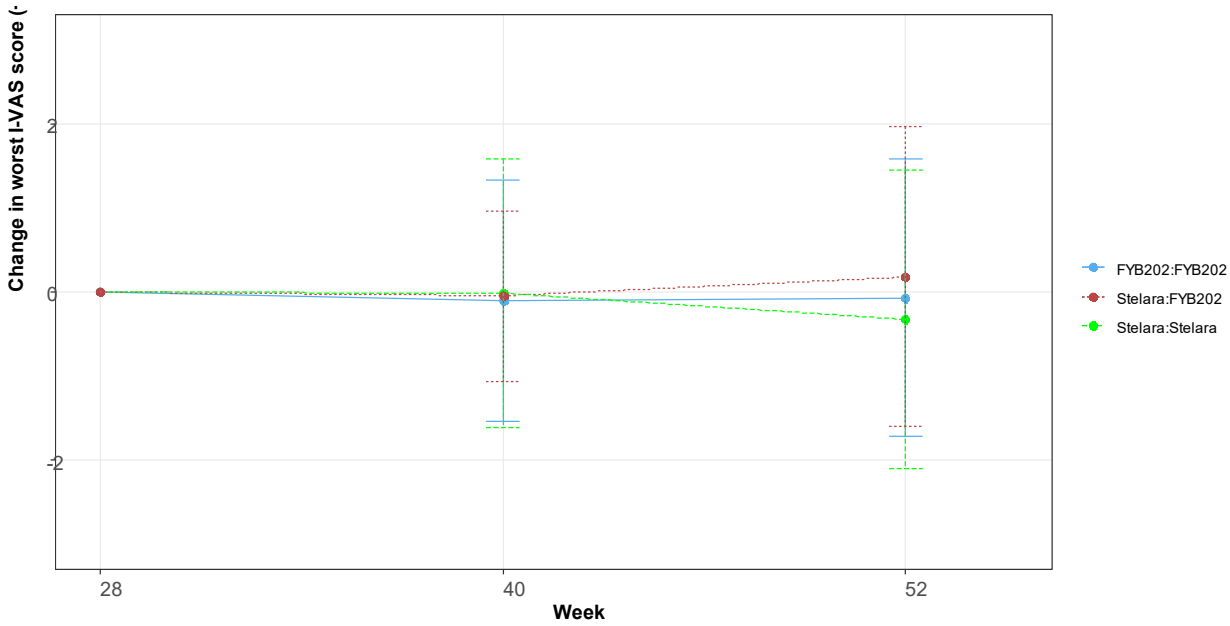
The analysis of the I-VAS is carried out separately for the average itch experience and the worst itch experience (Worst I-VAS: Figures 20 and 21, and Table 32; Average I-VAS: Figures 22 and 23, and Table 33). It appears that both worst and average I-VAS improvements were similar and substantial for both FYB202 and EU- Stelara.

Figure 19. Change from Baseline in Worst I-VAS Score up to Week 28 (FAS)



Source: Reviewer's analysis.

Figure 20. Change from Week 28 in Worst I-VAS Score up to Week 52 (RRAS)



Source: Reviewer's analysis.

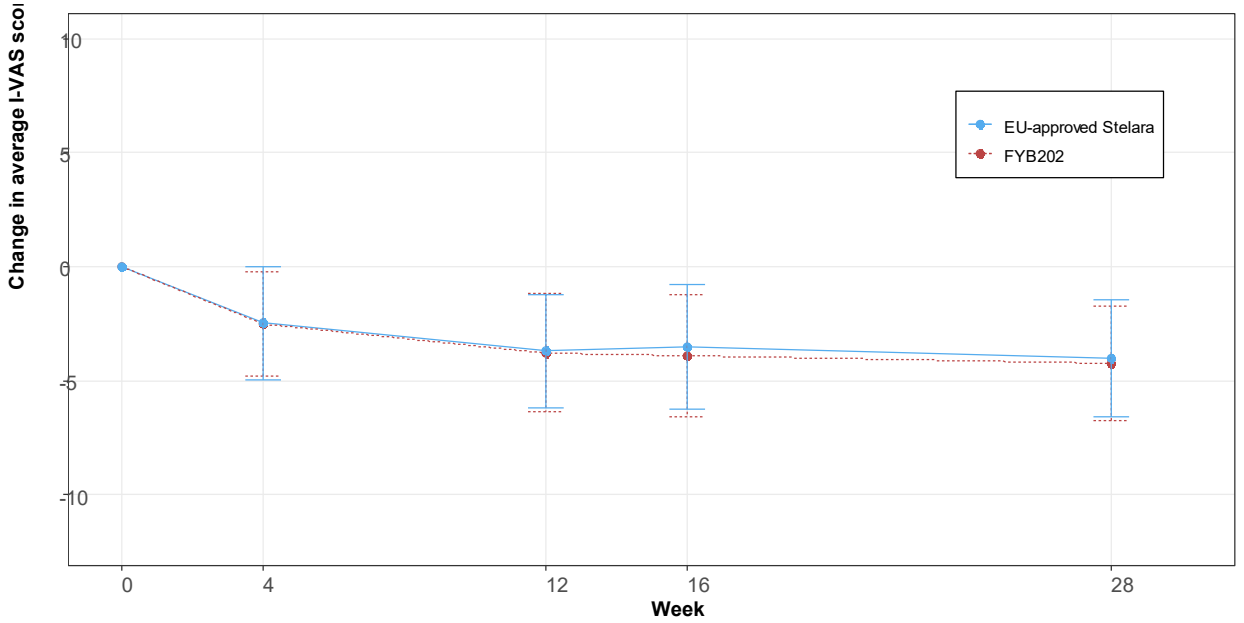
Table 32. Comparison of Change from Baseline in Worst I-VAS Score from Baseline to Weeks 4, 12, 16, And 28 (VAS)

	LS Mean (SE)		Difference (FYB202 – EU-Stelara)	
	FYB202	EU-Stelara	Mean (SE)	95% CI

Week 4	-3.14 (0.339)	-3.18 (0.332)	0.04 (0.245)	(-0.44, 0.52)
Week 12	-5.05 (0.331)	-4.94 (0.324)	-0.11 (0.221)	(-0.55, 0.32)
Week 16	-5.21 (0.333)	-4.88 (0.326)	-0.33 (0.227)	(-0.78, 0.12)
Week 28	-5.61 (0.320)	-5.44 (0.312)	-0.17 (0.185)	(-0.54, 0.19)

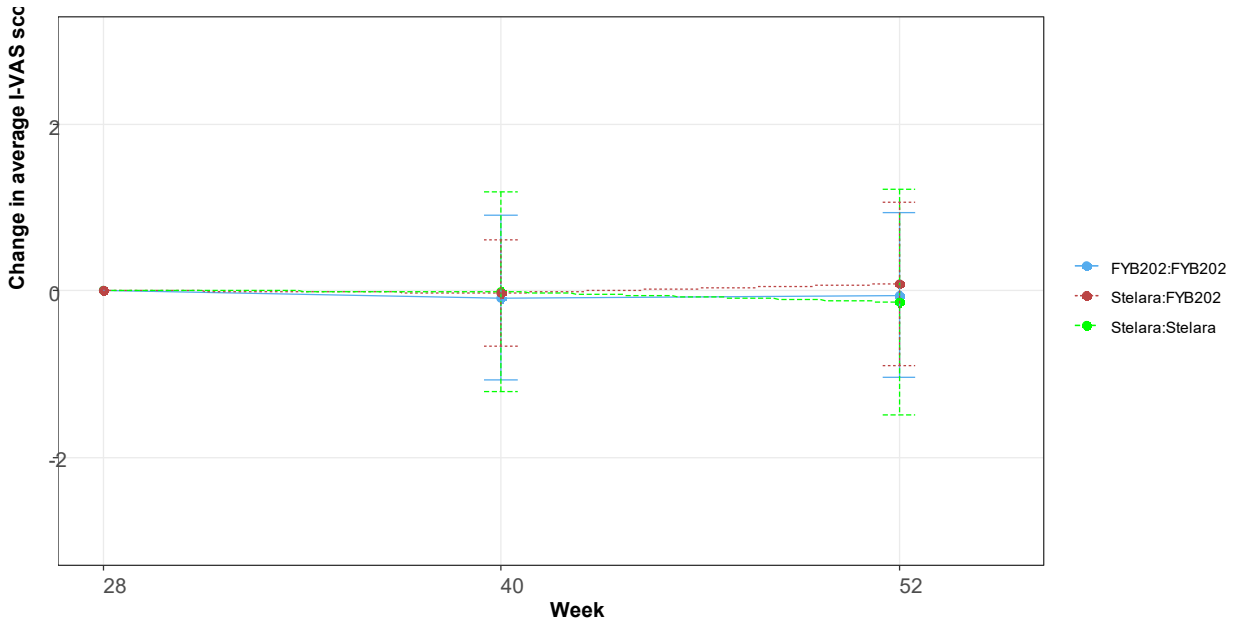
LS means calculation is based on the MMRM; Two-sided 95% confidence interval based on normal approximation. Estimates are adjusted for baseline PASI score, baseline weight, time since onset of psoriasis and prior inadequate response or intolerance to a systemic biological treatment.
Source: Reviewer's analysis.

Figure 21. Change from Baseline in Average I-VAS core up to Week 28 (FAS)



Source: Reviewer's analysis.

Figure 22. Change from Week 28 in Aaverage I-VAS Score up to Week 52 (RRAS)



Source: Reviewer's analysis.

Table 33. Comparison of Change from Baseline in Average I-VAS Score from Baseline to Weeks 4, 12, 16, and 28 (VAS)

	LS Mean (SE)		Difference (FYB202 – EU-Stelara)	
	FYB202	EU-Stelara	Mean (SE)	95% CI
Week 4	-2.50 (0.253)	-2.54 (0.248)	0.04 (0.197)	(-0.35, 0.43)
Week 12	-3.80 (0.241)	-3.75 (0.236)	-0.05 (0.165)	(-0.37, 0.28)
Week 16	-3.88 (0.248)	-3.62 (0.243)	-0.26 (0.184)	(-0.62, 0.10)
Week 28	-4.22 (0.232)	-4.08 (0.226)	-0.14 (0.134)	(-0.40, 0.13)

LS means calculation is based on the MMRM; Two-sided 95% confidence interval based on normal approximation. Estimates are adjusted for baseline PASI score, baseline weight, time since onset of psoriasis and prior inadequate response or intolerance to a systemic biological treatment.
Source: Reviewer's analysis.

Other Clinical Endpoints

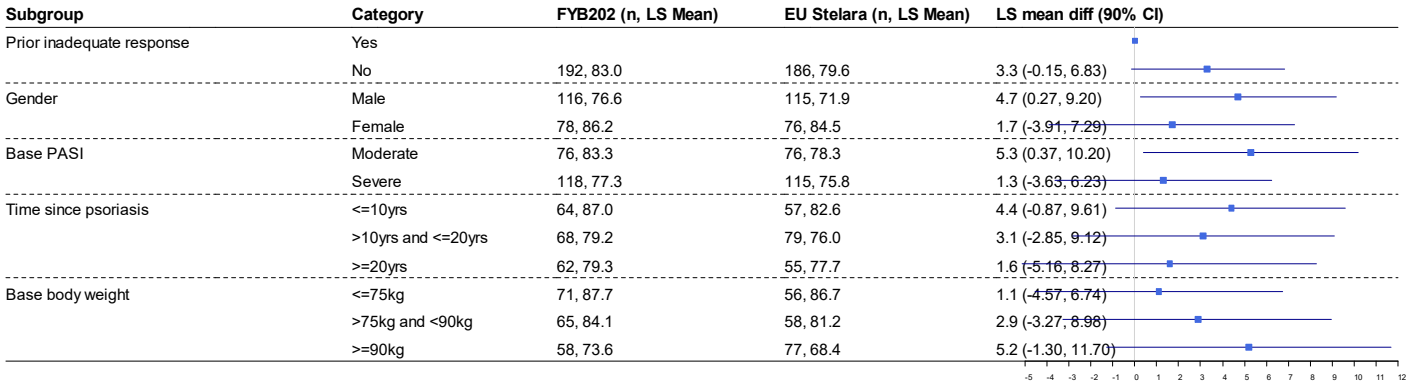
Subgroup Analysis

In this section, the primary efficacy endpoint is analyzed across the subgroups defined by the following factors:

- Prior inadequate response or intolerance to a systemic biological treatment (yes/no)
- Sex (male or female)
- Baseline PASI score (moderate or severe)
- Time since onset of psoriasis (≤ 10 years, > 10 years and ≤ 20 years, and ≥ 20 years)
- Baseline body weight (≤ 75 kg, > 75 kg and < 90 kg, and ≥ 90 kg).

Figure 24 shows the summary of the adjusted mean changes in the percent improvement in PASI score from baseline to week 12 by the subgroup variables. While some numerical variances noted among the subgroups, these variances were derived from relatively small number of the patients and the results did not indicate any clinically significant trend.

Figure 23. Percent Improvement in PASI Score from Baseline to Week 12 by Subgroups (FAS)



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.
Source: Reviewer's analysis.

6.3. Review of Safety Data

6.3.1. Methods

To evaluate comparative safety, adverse events, laboratory examination, vital signs, hypersensitivity, and immunogenicity were reviewed. The primary study used to evaluate comparative safety was the comparative clinical study, FYB202-03-01, as it provided comparisons between EU-Stelara and FYB202 in subjects with moderate to severe plaque psoriasis for up to 12 weeks. Additionally, a portion of subjects with PASI 75 or better in FYB202-03-01 who received EU-Stelara were transitioned to FYB202 at Week 28 in order to assess for potential safety issues after transitioning from EU-Stelara to FYB202 for an additional 24 weeks. Safety data from the PK similarity study FYB202-01-02 in healthy volunteers was reviewed as supportive of the primary safety assessment.

Clinical Studies Used to Evaluate Safety

The Applicant collected safety data from three clinical studies, as listed in Section 2.2 and summarized below.

In the PK similarity study FYB202-01-02, 491 subjects received a single dose of 45 mg SC of either FYB202 (164 subjects), US-Stelara (164 subjects) or EU-Stelara (163 subjects) with a follow-up period of 16 weeks (112 days). This study had limited follow-up.

The primary safety data was derived from the comparative clinical study (FYB202-03-01), which was conducted in two stages. See Figure 1 for the study schema. In the first stage, 392 subjects were randomized in 1:1 ratio to either FYB202 (197 subjects) or EU-Stelara (195 subjects). All subjects weighed less than 100kg and were dosed according to the standard dosing schedule for US-Stelara: 45mg initially and 4 weeks later, followed by 45mg at Week 16. The primary efficacy endpoint was the percent improvement in PASI score from baseline to Week 12.

At Week 28, subjects with less than PASI 75 response were discontinued. Of the 375 subjects remaining, those in the FYB202 arm stayed on FYB202 (189 subjects) and those remaining in the EU-Stelara arm were re-randomized in a 1:1 ratio to continue EU-Stelara (EU-Stelara/EU-Stelara, 97 subjects) or switch to FYB202 (EU-Stelara/FYB202, 89 subjects). These subjects were dosed at Week 28 and Week 40 and followed to Week 52.

Categorization of Adverse Events

A serious AE (SAE) was defined as any untoward medical occurrence that met at any dose:

- Results in death (fatal)

- Life-threatening (places the subject at immediate risk of death)
- Requires inpatient hospitalization or prolongation of existing hospitalization, unless hospitalization is for elective or pre-planned treatment of a pre-existing condition that is not related to the study indication and did not worsen from baseline (week 0)
- Results in persistent or significant disability/incapacity
- Congenital anomaly/birth defect
- Is an important medical event (e.g., intensive treatment in an emergency room or at home for allergic bronchospasm; blood dyscrasias, or convulsions that do not result in hospitalization; development of drug dependency or drug abuse; or malignancy tumors [histologically different from primary tumor])

Life-threatening: The term "life-threatening" in the definition of "seriousness" refers to an event in which the subject was at risk of death at the time of the event. It does not refer to an event, which hypothetically might have caused death, if it were more severe.

Other medically important serious event: Medical or scientific judgment is to be exercised in deciding whether SAE reporting is appropriate in other situations such as important medical events that may not be immediately life-threatening or result in death or hospitalization but may jeopardize the subject or may require medical or surgical intervention to prevent 1 of the other outcomes listed in the above definition.

An adverse event (AE) was recorded if it occurred from the time the subject signed the informed consent form (ICF) until the last study event. Treatment-emergent adverse events (TEAEs) were defined as AEs that first occurred or worsened in severity after the first administration of study intervention. TEAEs were assigned to the last treatment that was administered prior to onset of the TEAE. TEAEs were also analyzed separately for the time period after rerandomization.

Adverse events in the clinical studies are coded to the appropriate system organ class (SOC) and preferred term according to the Medical Dictionary for Regulatory Activities (MedDRA) version 24 for Study FYB202-03-01.

Adverse events of special interest (AESI) were defined as follows:

- Serious infections
- All malignancies, in particular non-melanoma skin cancer
- Systemic and respiratory hypersensitivity reactions
- Serious skin conditions
- Injection site reactions (ISRs)

Safety Analyses

The Applicant's safety analysis set (SAS) consists of all randomized subjects with at least 1 dose of investigational product, with treatment assignment based on actual treatment received, and was used for analysis of safety endpoints, immunogenicity data, and PK concentration data. The re-randomized SAS is a subset of the SAS

consisting of subjects who were re-randomized with at least 1 dose of investigational product after re-randomization, with data analyzed according to actual treatment sequence received prior to and post week 28, and was used for summaries of safety, immunogenicity, and PK data post week 28 and for the entire study period.

6.3.2. Major Safety Results

Relevant Characteristics of the Population Evaluated for Safety

Table 34. Population Demographics of Study FYB202-03-01

Characteristic	FYB202 N=197	EU-Stelara N=195	Total Population N=392
Sex, n (%)			
Male	117 (59.4)	117 (60)	234 (59.7)
Female	80 (40.6)	78 (40)	158 (40.3)
Age, range (years)	19-74	18-77	18-77
Mean (SD)	41.3 (12.9)	42.1 (13.2)	41.7 (13.02)
Median	39	42	41
Age groups, n (%)			
18-64	186 (94.4)	182 (93.3)	368 (93.9)
65+	11 (5.6)	13 (6.7)	24 (6.1)
Race, n (%)			
White	197 (100)	195 (100)	392 (100)
Ethnicity, n (%)			
Non-Hispanic	197 (100)	195 (100)	392 (100)
Country of participation, n (%)			
Poland	103 (26.3)	109 (27.8)	212 (54.1)
Ukraine	55 (14)	53 (13.5)	108 (27.6)
Georgia	26 (6.6)	23 (5.9)	49 (12.5)
Estonia	13 (3.3)	10 (2.6)	23 (5.9)

Source: Reviewer. ADSL.

Deaths

There were no deaths in Study FYB202-03-01.

Treatment Emergent Adverse Events (TEAEs)

Serious Adverse Events (SAEs)

Table 35. SAEs in Subjects with PsO up to Week 28 (Treatment Period 1)(TP01)

Subjects, n (%)	FYB202 N=197	EU-Stelara N=195
Total SAEs	5	6
Subjects with an SAE	4 (2.0)	3 (1.5)
COVID-19/COVID-19 pneumonia	2 (1.0)	0 (0)
Pulmonary embolism	1 (0.5)	0 (0)
Pneumothorax spontaneous	1 (0.5)	0 (0)
Ureterolithiasis	1 (0.5)	0 (0)
Accident automobile/multiple injuries	0 (0)	1 (0.5)
Acute pancreatitis	0 (0)	1 (0.5)
Cholecystolithiasis	0 (0)	1 (0.5)
Choledocholithiasis	0 (0)	1 (0.5)
Renal cancer metastatic	0 (0)	1 (0.5)

Source: Reviewer, ADAE.

Selective narratives for subjects taking FYB202 in TP01:

- **Spontaneous pneumothorax** – Subject (b) (6) is a 25 yo white male with plaque psoriasis. On SD 187, the subject was hospitalized for a right-sided spontaneous pneumothorax. The last dose of study medication was administered on SD 113 (Week 16). The pneumothorax resolved about a week after pleural cavity drainage. The subject continued in the study.
- **COVID-19 pneumonia/pulmonary embolism** – Subject (b) (6) is a 55 yo white male with plaque psoriasis. On Study Day (SD) 17 (17 days after the first dose of FYB202 on SD 0), the subject was admitted to the hospital due to worsening dyspnea, weakness, and non-productive cough. Due to the probability of COVID-19 infection, blood was collected for the COVID-19 IgM antibodies, which yielded a positive result of 37.69. A computed tomography (CT) of the pulmonary arteries showed signs of pulmonary embolism with the presence of embolic material in the superior lobar artery to the left lung and in the numerous and segmentary arteries of both lungs. Treatment included use of dexamethasone, heparin, and anticoagulant therapy with enoxaparin. Additional treatment for the event of pneumonia after COVID-19 infection included empirical antibiotic therapy with ceftriaxone plus clarithromycin, dexamethasone, and passive oxygen. The Applicant assessed the SAE as unlikely related to FYB202. The study drug was withdrawn in response to the events.

  Reviewer Comment: *With the onset of the SAE of COVID-19 pneumonia approximately 2 weeks after the introduction of an immunosuppressive drug such as FYB202, this SAE is possibly related to FYB202 given the known increased risk of infections with US-Stelara and the temporal sequence from administration of the study intervention. This SAE, although considered serious, was rare with comparable rates of serious infection across the treatment groups.*

Table 36. SAEs in Subjects with PsO and q12wk dosing, Weeks 28-52 (Treatment Period 2)(TP02)

Subjects, n (%)	FYB202/ FYB202 N = 189	EU-Stelara/ FYB202 N = 97	EU-Stelara/ EU-Stelara N = 89
Total SAEs	3	1	1
Subjects with an SAE	3 (1.6)	1 (1)	1 (1.1)
COVID-19	1 (0.5)	0 (0)	0 (0)
Appendicitis perforated	1 (0.5)	0 (0)	0 (0)
Carpal tunnel syndrome	1 (0.5)	0 (0)	0 (0)
Anomaly congenital	0 (0)	1 (1)	0 (0)
Respiratory failure	0 (0)	0 (0)	(1.1)

Source: Reviewer, ADAE.

Selective narratives for subjects taking FYB202 in TP02:

- **Appendicitis perforated** – Subject (b) (6) is a 44 yo white, non-Hispanic female with moderate to severe plaque psoriasis, vitiligo, hypertension, and insulin resistance in the FYB202/FYB202 arm. Her first dose of FYB202 was administered on (b) (6). Her last dose (#5) prior to the SAE was on Study Day 286. During the study follow-up period, the subject was hospitalized with acute appendicitis with peritoneal abscess on Study Day 300 (b) (6). She had an appendectomy with peritoneal drainage with subsequent diagnosis of gangrenous appendicitis. She was discharged on (b) (6) (Study Day 304) with ciprofloxacin and the SAE resolved on (b) (6). There were no changes in the IP as the subject had already completed all the study doses, and the subject completed the study. The Applicant assessed the appendicitis as not related to FYB202.
- **Pregnancy, Congenital anomaly in offspring** – Subject (b) (6) is a 29 yo white female with moderate to severe plaque psoriasis in the EU-Stelara/FYB202 arm. Her first dose of EU-Stelara was on (b) (6) Although the subject was on oral contraceptives at screening, the subject stopped the contraceptive in (b) (6) and switched to a condom/emergency contraceptive pills but did not report it to the site. At the end of (b) (6), the subject took an emergency contraception pill and continued to have menses. Between (b) (6) (Week 28, first dose of FYB202) and (b) (6) (the last dose of FYB202, Week 40), the subject had 2 negative urine pregnancy tests and a menstrual period. At the end of (b) (6), the subject conducted a self-pregnancy test that was positive (unreported). On (b) (6) (Study Day 333, approx Week 47), the subject was admitted to the maternity hospital and pregnancy with twins was confirmed. The pregnancy had not been followed by a gynecologist, and the subject reported smoking five cigarettes per day during the pregnancy. The infants were delivered the next day (at 26 weeks gestation) by caesarean section. Both infants were diagnosed with congenital malformation (hypertelorism, slight exophthalmos, cranium developmental anomaly, and anomalies in the toes). Both infants survived, self-breathing, and with no gene defects noted. The subject completed the study treatments but discontinued the study early due to

concerns about the infants. The Applicant assessed the SAE as unexpected and unlikely related to FYB202, but the temporal relationship between the study drug and the event can't be ruled out. In addition, the Applicant listed the subject's smoking habits as a confounding factor.

Reviewer Comment: *I agree with the Applicant's assessment that the congenital anomalies are possibly, but unlikely, related to FYB202. Several factors that are known to lead to high-risk pregnancies including smoking and lack of pregnancy supervision by a provider are present. In addition, there are irregularities in the medical history (negative pregnancy tests while pregnant based on gestation) and subject failure to adhere to study requirements (maintaining reliable contraception, having unprotected intercourse) that further confound accurate causality determination.*

Dropouts and/or Discontinuations

Table 37. Discontinuations in Subjects with PsO up to Week 28 (TP01)

Subjects, n (%)	FYB202 N=197	EU-Stelara N=195
Total Discontinuations	4 (2)	5 (2.6)
Death	0 (0)	0 (0)
Adverse Event	1 (0.5)	3 (1.5)
Lost to Follow Up	0 (0)	1 (0.5)
Protocol Deviation	1 (0.5)	0 (0)
Withdrawal by Subject	2 (1)	1 (0.5)

Source: Reviewer, ADSL.

Table 38. Discontinuations in Subjects with PsO, Weeks 28-52 (TP02)

Subjects, n (%)	FYB202/ FYB202 N = 189	EU-Stelara/ FYB202 N = 97	EU-Stelara/ EU-Stelara N = 89
Total Discontinuations	2 (1.1)	1 (1)	0 (0)
Adverse Event	0 (0)	1 (1)	0 (0)
Withdrawal by Subject	1 (0.5)	0 (0)	0 (0)
Lost to Follow Up	1 (0.5)	0 (0)	0 (0)

Source: Reviewer, ADSL.

There were less than 3% of discontinuations at any point during the study in any arm. In the arms receiving FYB202, there were fewer discontinuations than those receiving EU-Stelara. A total of 11 subjects (approx. 2.8%) over the course of the study discontinued due to AEs.

Common Adverse Events

Table 39. TEAEs >1% in Subjects with PsO up to Week 28 (TP01)

Subjects, n (%)	FYB202 N=197	EU-Stelara N=195
Subjects with any TEAE	78 (39.6)	79 (40.5)
Injection site reaction[a]	29 (14.7)	21 (10.8)
Nasopharyngitis[b]	15 (7.6)	10 (5.1)
COVID-19/pneumonia[c]	7 (3.6)	5 (2.6)
Headache	4 (2)	8 (4.1)
Arthralgia	4 (2)	0 (0)
C-reactive protein increased	3 (1.5)	4 (2.1)
Vaccination site pain	3 (1.5)	0 (0)
Food poisoning	2 (1)	0 (0)
Pruritus	2 (1)	0 (0)

Source: Reviewer, ADAE.
[a] Injection site reaction includes injection site pain, injection site reaction, injection site erythema, injection site induration, and injection site swelling
[b] Nasopharyngitis includes nasopharyngitis, upper respiratory tract infection (RTI), and pharyngitis
[c] COVID-19 includes COVID, COVID pneumonia

During the first 28 weeks (TP01) of Study FYB202-03-01, 39.6% of subjects receiving FYB202 had at least one TEAE, compared to 40.5% of subjects in the EU-Stelara arm. Specific AEs that were ≥1% and had a ≥1% difference between FYB202 and EU-Stelara were injection site reaction (14.7% vs 10.8%), nasopharyngitis (7.6% vs 5.1%), and COVID-19/pneumonia (3.6% vs 2.6%).

Table 40. TEAEs >1% in Subjects with PsO, Weeks 28-52 (TP02)

Subjects, n (%)	FYB202/ FYB202 N = 189	EU-Stelara/ FYB202 N = 97	EU-Stelara/ EU-Stelara N = 89
Subjects with any TEAE	33 (17.5)	18 (9.5)	16 (8.5)
COVID-19	13 (6.9)	5 (5.2)	6 (6.7)
Nasopharyngitis [a]	9 (4.8)	7 (7.2)	6 (6.7)
Injection site reaction[b]	2 (1.1)	1 (1)	0 (0)
Toothache	2 (1.1)	0 (0)	0 (0)

Source: Reviewer, ADAE.
[a] Nasopharyngitis includes nasopharyngitis, pharyngitis, upper respiratory tract infection, rhinorrhea
[b] Injection site reaction includes injection site pain, injection site induration, injection site reaction

After re-randomization at Week 28 during TP02, more subjects in the FYB202/FYB202 arm (17.5%) experienced a TEAE; however, incidence rates for each AE were similar or less than the EU-Stelara/FYB202 and EU-Stelara/EU-Stelara arms.

Adverse Reactions (ARs)

Table 41. Adverse Reactions in Subjects with PsO up to Week 28 (TP01)

Subjects, n (%)	FYB202 N=197	EU-Stelara N=195
Total ARs	48	32
Subjects with any AR	32 (16.2)	32 (16.4)
Injection site reaction[a]	29 (14.7)	20 (10.3)
Headache	2 (1)	1 (0.5)
Cystitis	1 (0.5)	0 (0)
Dizziness	1 (0.5)	1 (0.5)
Rash	1 (0.5)	0 (0)
White blood cell count increased	1 (0.5)	0 (0)
Cheilosis	0 (0)	1 (0.5)
Cholestasis	0 (0)	1 (0.5)
Hepatitis toxic	0 (0)	1 (0.5)
Laryngitis	0 (0)	1 (0.5)
Upper respiratory tract infection	0 (0)	1 (0.5)

Source: Reviewer, ADAE
[a] Injection site reaction includes injection site pain, injection site reaction, injection site erythema, injection site induration, injection site swelling, and induration

Although the incidence of ARs in subjects administered FYB202 was numerically higher than in subjects administered EU-Stelara (48 vs 32), the incidence rates between the two arms are very similar. However, there was a notable difference in the incidence of injection site reactions in the FYB202 arm compared to the EU-Stelara arm (14.7% vs 10.3%). However, when considered with the other available data, this difference does not preclude a demonstration that FYB202 has no clinically meaningful differences from US-Stelara.

Table 42. Adverse Reactions in Subjects with PsO, Weeks 28-52 (TP02)

Subjects, n (%)	FYB202/ FYB202 N = 189	EU-Stelara/ FYB202 N = 97	EU-Stelara/ EU-Stelara N = 89
Total ARs	2	3	0
Subjects with any AR	2 (1)	2 (2)	0 (0)
Injection site reaction[a]	2 (1)	1 (1)	0 (0)
Nasopharyngitis	0 (0)	1 (1)	0 (0)

Source: Reviewer, ADAE
[a] Injection site reaction includes injection site pain and injection site reaction

Adverse Events of Special Interest (AESIs)

The prescribing information for US-Stelara carries the following warnings and precautions: infections (including cellulitis, pneumonia, sepsis, zoster, abscess, and

tuberculosis), malignancies, hypersensitivity reactions, posterior reversible encephalopathy syndrome (PRES), and noninfectious pneumonia.

The Applicant identified the following AEs as Events of Interest: systemic and respiratory hypersensitivity reactions, serious infections, malignancy, serious skin conditions, and injection site reactions.

Overall, the proportion of subjects experiencing AESIs were similar across all arms for the entire duration of the study (before and after re-randomization), with the exception of more injection site reactions in the FYB202 arm in TP01.

Table 43. AESIs in Subjects with PsO up to Week 28 (TP01)

Subjects, n (%)	FYB202 N=197	EU-Stelara N=195
Serious infections		
COVID-19	7 (3.6)	5 (2.6)
COVID-19 pneumonia	1 (0.5)	0 (0)
Erysipelas	1 (0.5)	0 (0)
Blastocystis infection	1 (0.5)	0 (0)
Influenza	0 (0)	2 (1)
Urinary tract infection	0 (0)	2 (1)
Pancreatitis acute	0 (0)	1 (0.5)
Bacteriuria	0 (0)	1 (0.5)
Injection site reactions		
Injection site pain	22 (11.2)	15 (7.7)
Injection site reaction	4 (2)	4 (2)
Injection site erythema	2 (1)	2 (1)
Injection site induration	2 (1)	0 (0)
Injection site swelling	1 (0.5)	0 (0)
Induration	1 (0.5)	0 (0)
Malignancy		
Renal cancer metastatic	0 (0)	1 (0.5)

Source: Reviewer, ADAE.

Table 44. AESIs in Subjects with PsO, Weeks 28-52 (TP02)

Subjects, n (%)	FYB202/ FYB202 N = 189	EU-Stelara/ FYB202 N = 97	EU-Stelara/ EU-Stelara N = 89
Serious infections			
COVID-19	13 (6.9)	5 (5.2)	6 (6.7)
Influenza	0 (0)	1 (1)	0 (0)
Injection site reactions			
Injection site induration	1 (0.5)	0 (0)	0 (0)
Injection site pain	1 (0.5)	1 (1)	0 (0)

Injection site reaction	0 (0)	1 (1)	0 (0)

Source: Reviewer, ADAE.

Laboratory Evaluations

No clinically relevant changes over time or differences between treatment groups were observed for hematology or clinical chemistry parameters (including liver function tests and creatinine) in Study FYB202-03-01. Across treatment periods, the proportions of patients with newly occurring clinically notable values of clinical chemistry parameters were low and there were no relevant differences among groups.

Vital Signs

No clinically relevant changes were observed in any of the vital signs variables in any of the clinical studies.

ECGs

For the comparative clinical study (Study FYB202-03-01), ECGs were assessed. There were 2 subjects who experienced arrhythmias: Subject (b) (6) at Week 4 and Week 52 (atrial fibrillation, 2 episodes, FYB202 arm) and Subject (b) (6) at V7/Week 52 (tachycardia, FYB202-FYB202 arm). The causality for these 2 subjects were assessed by the Applicant as unlikely due to FYB202.

6.4. Clinical Conclusions on Immunogenicity

The immunogenicity evaluation included qualitative and quantitative measurement of anti-drug antibody (ADA) and neutralizing antibody (NAb) in healthy subjects (from single dose PK studies) and in patients with plaque psoriasis (multiple doses up to 54 weeks), and an assessment of the impact of ADA on PK, efficacy and safety. In particular, there were no meaningful differences between the frequency of treatment-emergent AEs in the FYB202/FYB202 group versus the other treatment groups (EU-Stelara/FYB202 and EU-Stelara/EU-Stelara, respectively), regardless of NAb status. It is concluded that FYB202 was similar to EU-Stelara in the production of ADA/NAb and their impact on PK, efficacy and safety. Refer to Section 5.4 (Clinical Immunogenicity Studies) for results of the immunogenicity assessments.

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6.5. Risk in Terms of Safety or Diminished Efficacy of Switching Between Products and the Any Given Patient Evaluation (to Support a Demonstration of Interchangeability)

The Applicant has developed FYB202 as a proposed interchangeable biosimilar to US-Stelara and is seeking licensure of FYB202 for the same indications, same dosage form, strengths and routes of administration as US-Stelara. The Applicant provided sufficient justification that FYB202 can be expected to produce the same clinical results as US-licensed Stelara in any given patient. The scientific justification considered the factors that are described in the FDA guidance for industry, *Considerations in Demonstrating Interchangeability with a Reference Product* (refer also to Section 6.6 Extrapolation).

The Applicant also provided sufficient scientific justification that the risk in terms of safety or diminished efficacy of alternating or switching between use of FYB202 and US-licensed Stelara is not greater than the risk of using US-licensed Stelara without such alteration or switch. The Applicant referenced the comparative analytical data provided in their application that evaluated and compared critical quality attributes of FYB202 and US-Stelara and the results from the comparative clinical study (Study FYB202-03-01) to support their justification. The Applicant also described that the results from the single transition included in Study FYB202-03-01 provided supportive evidence of a low immunogenic risk and no safety concerns with switching between FYB202 and US-Stelara. FDA considers the risk of a clinically impactful immunogenic response when alternating or switching between FYB202 and US-licensed Stelara to be low. Thus, a switching study that compares immunogenicity and PK and/or PD to assess whether the risk in terms of safety or diminished efficacy of alternating or switching between use of FYB202 and US-licensed Stelara is not greater than using US-licensed Stelara without such alternation or switch was considered unnecessary to support a demonstration of interchangeability for FYB202.

The data and information provided by the Applicant are sufficient to demonstrate that FYB202 can be expected to produce the same clinical result as US-Stelara in any given patient and that the risk in terms of safety or diminished efficacy of alternating or switching between use of FYB202 and US-Stelara is not greater than the risk of using US-Stelara without such alternation or switch.

6.6. Extrapolation

The Applicant submitted data and information in support of a demonstration that FYB202 is highly similar to US-Stelara notwithstanding minor differences in clinically inactive components, and that there are no clinically meaningful differences between FYB202 and US-Stelara in terms of safety, purity and potency in patients with plaque psoriasis (Study FYB202-03-01). In addition, the totality of evidence submitted in the application sufficiently demonstrates that FYB202 can be expected to produce the same clinical results as US-licensed Stelara in any given patient and that, the risk in terms of

safety or diminished efficacy of alternating or switching between use of FYB202 and US-licensed Stelara is not greater than the risk of using US-licensed Stelara without such alteration or switch.

The Applicant is seeking licensure of FYB202 for the following indication(s) for which US-Stelara has been previously licensed and for which FYB202 has not been directly studied:

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

The Applicant provided a justification for extrapolating data and information submitted in the application to support licensure of FYB202 as an interchangeable biosimilar for each such indication for which licensure is sought and for which US-Stelara has been previously approved. This Applicant's justification was evaluated and considered adequate and is summarized below.

Therefore, the totality of the evidence provided by the Applicant supports licensure of FYB202 for each of the following indication(s) for which US-Stelara has been previously licensed and for which the Applicant is seeking licensure of FYB202:

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

The Applicant is not seeking licensure of FYB202 in a 45 mg/0.5 mL single-dose vial for subcutaneous use. US-Stelara is available in a 45 mg/0.5 mL single-dose vial for subcutaneous use for weight-based dosing of pediatric patients with a body weight of less than 60 kg. Section 2 of the labeling for FYB202 will note that there is no dosage form of the product that allows weight-based dosing for pediatric patients below 60 kg. Please see Section 10 below for more information on the Applicant's plans to develop the 45 mg/0.5 mL vial.

6.6.1. Division of Rheumatology and Transplant Medicine (DRTM)

In addition to the plaque psoriasis indication, the Applicant is seeking licensure of FYB202 for the following indication under the purview of DRTM: active psoriatic arthritis (PsA) in adults and pediatric patients (6 years or older).

In their application, the Applicant has provided justification for extrapolation of data and relevant supportive information for licensure of FYB202 as an interchangeable

biosimilar for the above indication for which licensure is sought and for which US-Stelara has been previously licensed and FYB202 has not been directly studied.

First, as summarized above, the Applicant submitted data and information to demonstrate that FYB202 is highly similar to US-Stelara and/or EU-Stelara and that there are no clinically meaningful differences in PK between FYB202 and US-Stelara, FYB202 and EU-Stelara, and between EU-Stelara and US-Stelara in healthy subjects (FYB202-01-02), and that there are no clinically meaningful differences in terms of efficacy, safety, and immunogenicity between FYB202 and EU-Stelara in patients with plaque psoriasis (PsO) (FYB202-03-01). In addition, the totality of evidence submitted in the application sufficiently demonstrates that FYB202 can be expected to produce the same clinical results as US-licensed Stelara in any given patient and that, the risk in terms of safety or diminished efficacy of alternating or switching between use of FYB202 and US-licensed Stelara is not greater than the risk of using US-licensed Stelara without such alteration or switch.

The additional points considered in the scientific justification for extrapolation of data and information to support licensure of FYB202 for the treatment of PsA are described below.

Mechanism of Action (MOA)

In comprehensive in vitro comparative testing, FYB202 has been shown to be functionally similar to US-Stelara. These data demonstrate that the biologic activity and potency of FYB202 have a high degree of similarity to US-Stelara and provide additional evidence that the MOA of the two products, binding to the p40 subunit of the IL-23 and IL-12 and, subsequently, preventing the interaction of IL-23 and IL-12 with IL-12Rb1, is the same.

The Applicant adequately addressed each of the known and potential mechanisms of action of Stelara and submitted data to support the conclusion that FYB202 and US-Stelara have the same mechanisms for the sought indication of PsA to the extent that the mechanisms of action are known or can reasonably be determined.

Pharmacokinetics (PK)

FYB202 was demonstrated to be highly similar to US-Stelara, as discussed in the section on CMC/Product Quality; therefore, there are no product-related attributes that would increase the uncertainty that the PK/biodistribution may differ between FYB202 and US-Stelara in the rheumatology indication for licensure (PsA). Thus, a similar PK profile would be expected between FYB202 and US-Stelara in patients with PsA.

The Applicant provided adequate justification that a similar PK profile is expected between FYB202 and US-Stelara for PsA.

Immunogenicity

Immunogenicity of FYB202 was examined in the PK similarity study in healthy subjects (FYB202-01-02) and comparative clinical study in subjects with PSO (Study FYB202-03-01). The impact of immunogenicity on PK, efficacy, and safety between FYB202 and US/EU-Stelara was generally comparable and there were no meaningful differences in anti-drug antibodies (ADA) in subjects that underwent a single transition from EU-Stelara to FYB202.

The Applicant provided adequate justification that there are no clinically significant differences in immunogenicity is expected between FYB202 and US-Stelara for PsA.

Toxicity

The Applicant demonstrated that there are no clinically meaningful differences in safety between FYB202 and EU-Stelara in patients with PsO and between FYB202, EU-Stelara, and US-Stelara following single doses in healthy subjects. Additionally, in controlled clinical studies of US-Stelara submitted to support its approval, as described in the approved labeling, the types of adverse events and their rates were similar across indications. Coupled with the demonstration of analytical and PK similarity between FYB202, US-Stelara, and EU-Stelara, a similar safety profile would be expected between FYB202 and US-Stelara in patients with PsA.

The Applicant provided adequate justification that a similar safety profile would be expected between FYB202 and US-Stelara for PsA.

Conclusions

Based on the above considerations, DRTM concludes that the Applicant has provided sufficient scientific justification (based on the mechanism of action, pharmacokinetics, immunogenicity, and safety profile) for extrapolation of the data and information to support licensure of FYB202 for the rheumatologic indication of psoriatic arthritis for which US-Stelara has been previously licensed and for which the Applicant is seeking licensure.

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6.6.2. Division of Gastroenterology (DG)

Executive Summary: Consistent with the principles of the FDA guidance for industry *Scientific Considerations in Demonstrating Biosimilarity to a Reference Product* (April 2015),[5] the Division of Gastroenterology (DG) concludes that the Applicant has provided sufficient scientific justification to support extrapolation of data submitted in the application to support licensure of FYB202 as an interchangeable biosimilar to US-licensed Stelara, under section 351(k) of the PHS Act, for the non-studied indications of

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

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

Mechanism of Action: The mechanisms of action of ustekinumab that are relevant to moderate to severe active plaque psoriasis (PsO; the studied clinical study population) are also relevant to inflammatory bowel disease (IBD) (i.e., CD and UC). The Applicant provided data to support that FYB202 has the same known and potential mechanisms of action as US-Stelara, which supports extrapolation to indications not directly studied in the FYB202 clinical program. Ustekinumab belongs to the pharmacologic class of interleukin (IL)-23 and IL-12 antagonists. It is a human IgG1κ monoclonal antibody that binds with specificity to the p40 protein subunit used by both the IL-12 and IL-23 cytokines that are involved in inflammatory and immune responses, such as natural killer cell activation and CD4+ T-cell differentiation and activation. In the *in vitro* models, ustekinumab was shown to disrupt IL-12 and IL-23 mediated signaling and cytokine cascades by disrupting the interaction of these cytokines with a shared cell-surface receptor chain, IL-12Rβ1. The cytokines IL-12 and IL-23 have been implicated as important contributors to the chronic inflammation that is a hallmark of CD and UC.[6] The biological activities of FYB202 and US-Stelara were evaluated by a comprehensive set of comparative functional and binding assays. The product quality reviewers concluded the acceptability of the comparative analytical assessments. Biological activities relevant to the primary mode of action i.e., IL-12 and IL-23 binding and neutralization, were similar across FYB202 and US-Stelara. Furthermore, inhibition of cytokine release and STAT3/STAT4 signaling, Fc mediated functions, as well as absence of effector functions were similar across FYB202 vs. US-Stelara. Overall, these data support the determination that FYB202 and US-Stelara are highly similar. Data support the conclusion that FYB202 and US-Stelara utilize the same mechanism(s) of action, to the extent such mechanism(s) are known.

Pharmacokinetics (PK): Study FYB202-01-02 was a randomized, double-blind, parallel group, single dose, 3-way, PK similarity study conducted in healthy male and female volunteers. The clinical pharmacology reviewers concluded that the data from this study support a demonstration of PK similarity between FYB202 vs. US-Stelara, FYB202 vs. EU-Stelara, and US-Stelara vs. EU-Stelara in healthy volunteers (refer to Section 5 Clinical Pharmacology Evaluation and Recommendations). Available data on US-Stelara do not indicate any major differences in PK based on disease state. It is reasonable to conclude that PK for FYB202 is expected to be similar between the studied populations and those with IBD.

Immunogenicity: In the FYB202 development program, immunogenicity was evaluated in populations that were considered sensitive for detecting meaningful differences (healthy subjects and PsO). While some differences were noted in the ADA incidence across the treatment groups in both study populations, per the Clinical Pharmacology reviewers, the impact of immunogenicity on PK, efficacy, and/or safety

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

between FYB202 and US-/EU-Stelara was generally comparable and not considered to be clinically meaningful. Additionally, there were no meaningful differences in the rates of ADA in those subjects that underwent a single transition from EU-Stelara to FYB202 in Study FYB202-03-01 compared to those that remained on EU-Stelara. Therefore, it is reasonable to conclude that the impact of immunogenicity in patients with IBD receiving FYB202 would be similar to that observed in patients with PsO receiving US-Stelara. Refer to Section 5 (Clinical Pharmacology Evaluation and Recommendations) of this review for further details.

Safety: The safety of FYB202 compared to EU-Stelara was assessed in the comparative clinical study FYB202-03-01 conducted in patients with PsO. Safety assessments included adverse events (AEs), physical examinations, vital signs, 12-lead ECGs, clinical laboratory testing, and immunogenicity assessments. The frequency of TEAEs, SAEs and discontinuations due to AEs were generally comparable between the FYB202 and EU-Stelara groups in the clinical study. In addition, as previously noted, a single transition from EU-Stelara to FYB202 was assessed as part of the study. No meaningful differences in the incidence of adverse events, were observed in patients with PsO that underwent a single transition, compared to those that remained on their randomized treatment (FYB202 or EU-Stelara). Refer to the Section 6.3. Review of Safety Data, for further details. In controlled clinical studies of US-licensed Stelara, as described in the approved labeling, the types of adverse events and their rates were similar across indications. The safety profile of FYB202 has been shown to be similar to that of EU-Stelara in patients with PsO. When combined with the adequate PK bridging between US-Stelara and EU-Stelara from the healthy volunteer study FYB202-01-02 as well as similar product quality attributes, PK, and immunogenicity, the safety profile in the IBD population is expected to be generally comparable to that observed in patients with PsO, and overall, the data support extrapolation to the non-studied IBD population.

Regulatory Recommendations: DG concludes that sufficient scientific justification was provided to support licensure of FYB202 for the following indications:

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

Authors:

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

7. Labeling Recommendations

7.1. Nonproprietary Name

The Applicant's nonproprietary name, ustekinumab-aauz, was found to be conditionally accepted by the Agency (DMEPA review dated July 17, 2024).

7.2. Proprietary Name

The Applicant's proposed proprietary name for FYB202, Otulfi, has been conditionally approved. This name has been reviewed by the Division of Medication Error Prevention and Analysis (DMEPA), who concluded that the name is acceptable (DMEPA review dated January 10, 2024).

7.3. Other Labeling Recommendations

It was determined that the proposed labeling is compliant with Physician Labeling Rule (PLR) and Pregnancy and Lactation Labeling Rule (PLLR), is clinically meaningful and scientifically accurate, and conveys the essential scientific information needed for safe and effective use of the product.

Authors:

Felisa Lewis, MD, MPH
Clinical Reviewer

Snezana Trajkovic, MD
Clinical Team Leader

8. Human Subjects Protections/Clinical Site and other Good Clinical Practice (GCP) Inspections/Financial Disclosure

The data quality and integrity of the studies were acceptable. The BLA submission was in electronic common technical document (eCTD) format and was adequately organized.

Documented approval was obtained from institutional review boards (IRBs) and independent ethics committees (IECs) prior to study initiation. All protocol modifications were made after IRB/IEC approval. The studies were conducted in accordance with good clinical practice (GCP), code of federal regulations (CFR), and the Declaration of Helsinki.

The Applicant has adequately disclosed financial interests and arrangements with the investigators. Form 3454 is noted in Section 14.2 and verifies that no compensation is linked to study outcome. The Principal Investigators (PIs) did not disclose any proprietary interest to the sponsor.

Authors:

Felisa Lewis, MD, MPH
Clinical Reviewer

Snezana Trajkovic, MD
Clinical Team Leader

9. Advisory Committee Meeting and Other External Consultations

No advisory committee was held for this biosimilar application as it was determined that there were no issues where the Agency needed input from the committee.

Author:
Snezana Trajkovic, MD
Cross Discipline Team Leader

10. Pediatrics

This application included the July 31, 2020, agreed iPSP.

In this application, the Applicant included assessment via extrapolation for pediatric patients ages 6-17 years with plaque psoriasis and psoriatic arthritis. See Section 6.6 for review of the assessments. However, because the Applicant has not submitted a 45 mg/0.5 mL single-dose vial presentation in this application, weight-based dosing of plaque psoriasis and psoriatic arthritis patients 6 years and older is limited to 60 kg and above.

Under the Pediatric Research Equity Act (PREA) (section 505B of the FD&C Act), all applications for new active ingredients, new indications, new dosage forms, new dosing regimens, or new routes of administration are required to contain a pediatric assessment to support dosing, safety, and effectiveness of the product for the claimed indication unless this requirement is waived, deferred, or inapplicable. Section 505B(l) of the FD&C Act provides that a biosimilar product that has not been determined to be interchangeable with the reference product is considered to have a "new active ingredient" for purposes of PREA, and a pediatric assessment is generally required unless waived or deferred or inapplicable. Under the statute, an interchangeable product is not considered to have a "new active ingredient" for purposes of PREA.

At the time of this review, another ustekinumab product, Wezlana, has been approved as an interchangeable biosimilar and has qualified for a period of FIE. FDA has previously determined that FIE for the Wezlana products will expire on April 30, 2025.[7] Therefore, because FYB202 will be approved first as a biosimilar (and not as interchangeable), this biologic will be considered to have a new active ingredient.

[7] https://purplebooksearch.fda.gov/

Therefore, the Applicant is required to develop an age-appropriate formulation (presentation) that can be accurately administered to pediatric patients who weigh less than 60 kg. This BLA was discussed at the PeRC meeting on September 17, 2024. PeRC recommended that a PREA post-marketing requirement (PMR) be issued for the development of an age-appropriate presentation for weight-based dosing of the product for patients with plaque psoriasis and/or psoriatic arthritis as young as 6 years of age and weighing less than 60 kg.

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

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

Authors:

Felisa Lewis, MD, MPH
Clinical Reviewer

Snezana Trajkovic, MD
Clinical Team Leader

11. REMS and Postmarketing Requirements and Commitments

11.1. Recommendations for Risk Evaluation and Mitigation Strategies

None.

11.2. Recommendations for Postmarket Requirements (PMRs) and Commitments (PMCs)

The current FYB202 presentations are not designed to allow for accurate administration of doses less than 45 mg, which impacts children who weigh less than 60 kg. For accurate weight-based dosing, an age-appropriate formulation (presentation) is required by PREA. Therefore, a PREA PMR is necessary for the development of a formulation (presentation) that can be used to administer FYB202 in patients who weigh less than 60 kg.

PMR-1: Develop a presentation that can be used to accurately administer FYB202 to pediatric patients who weigh less than 60kg.
Final Report Submission:03/2025

Fresenius Kabi USA, LLC agreed to the following PMCs developed by OPQ:

PMC-1: Perform a real-world commercial shipping validation study to confirm the suitability of shipping container and transportation method with respect to maintaining intended product temperature, package integrity, and product quality of the Otulfi drug product, stored in a vial 130 mg/26 mL (5 mg/mL) and pre-filled syringe (90 mg/mL), based on the worst-case scenario. The study design and results will be provided in the final study report to the BLA.

Final report submission date: 09/2025

PMC-2: Perform an additional study(ies) to support the control limits for (b) (4) FYB202 90 mg/mL pre-filled syringe drug product batch. The study should be designed to support (b) (4) using FYB202 DS batches (b) (4) Submit the results in a final study report to the BLA.

Final report submission date: 09/2025

PMC-3: Implement pressure monitoring during sterilizing filtration of FYB202 (b) (4) 5 mg/mL) vial drug product (DP) and update Sections 3.2.P.3.3 and 3.2.P.3.4 of the BLA (b) (4) validated by a bacterial retention study.

Final report submission date: 06/2025

PMC-4: Validate and implement a container closure integrity test (CCIT) method (b) (4)

Final report submission date: 12/2024

PMC-5: Conduct a minimum load sterilization validation study with three runs (b) (4)

Final report submission date: 12/2024

PMC-6: Validate and implement an alternative quantitative bacterial endotoxin method not subject to low endotoxin recovery to replace the USP <151> pyrogen test for FYB202 130 mg/26 mL (5 mg/mL) vial DP release.

Final report submission date: 09/2025

PMC-7: Revalidate the blue dye ingress CCIT method to demonstrate the CCIT method is reliable for use (i.e., all positive controls show positive results) for FYB202 drug product pre-filled syringe (PFS) 45 mg in 0.5 mL and FYB202 DP PFS 90 mg in 1.0 mL.

Final report submission date: 12/2024

Authors:

Felisa Lewis, MD, MPH
Clinical Reviewer

Snezana Trajkovic, MD
Clinical Team Leader

12. Comments to Applicant

None.

13. Division Director Comments

13.1. Division Director (OND – Clinical) Comments

I concur with the team's assessment of the data and information submitted in this BLA. The data and information submitted by the Applicant, including adequate justification for extrapolation of data and information, demonstrate that FYB202 is biosimilar to US-Stelara. I also concur with the team's recommendation to provisionally determine that the following FYB202 products would be interchangeable with US-Stelara products as follows:

- FYB202, 45 mg/0.5 mL PFS for subcutaneous use with US-Stelara 45 mg/0.5 mL PFS for subcutaneous use,
- FYB202, 90 mg/mL PFS for subcutaneous use with US-Stelara 90 mg/mL PFS for subcutaneous use, and
- FYB202, 130 mg/26 mL single-dose vial for intravenous (IV) use with US-Stelara 130 mg/26 mL single-dose vial for IV use.

These FYB202 products have met the statutory interchangeability requirements for the following indications for which US-Stelara has previously been approved:

Treatment of:

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

The Applicant is not seeking licensure of FYB202 in a 45 mg/0.5 mL single-dose vial for subcutaneous use. US-Stelara is available in a 45 mg/0.5 mL single-dose vial for subcutaneous use for weight-based dosing of pediatric patients with a body weight of less than 60 kg. Section 2 of the final approved labeling for FYB202 notes that there is no dosage form of the product that allows weight-based dosing for pediatric patients below 60 kg. Please see BMER Section 10 above for more information on the Applicant's plans to develop the 45 mg/0.5 mL vial.

When action is taken for this BLA, it will be administratively split to facilitate an approval action for FYB202 as a biosimilar product ("Original 1") and a provisional determination that FYB202 is an interchangeable biosimilar product, as described in Section 1.1 above ("Original 2").

This provisional determination is appropriate because at this time, FDA is unable to approve FYB202 injection 45 mg/0.5 mL PFS for subcutaneous use as interchangeable with US-Stelara injection 45 mg/0.5 mL PFS for subcutaneous use, FYB202 injection 90 mg/mL PFS for subcutaneous use as interchangeable with US-Stelara injection 90 mg/mL PFS for subcutaneous use, or FYB202 injection 130 mg/26 mL single-dose vial for intravenous use as interchangeable with US-Stelara injection 130 mg/26 mL single-dose vial for intravenous use, because of unexpired FIE for the Wezlana products. FDA has previously determined that FIE for the Wezlana products will expire on April 30, 2025.[8] As described in the provisional determination letter, Fresenius is expected to submit an amendment seeking approval of its FYB202 45 mg/0.5 mL injection for subcutaneous use, FYB202 90mg/mL injection for subcutaneous use, and 130 mg/26 mL injection for intravenous use products as interchangeable no more than six months prior to the expiration of FIE for the Wezlana products.

Author:
Tatiana Oussova, MD, MPH
Deputy Director for Safety

14. Appendices

14.1. Financial Disclosure

Covered Clinical Study: FYB202-01-01

Was a list of clinical investigators provided:	Yes ☒	No ☐ (Request list from Applicant)
Total number of investigators identified: 8		
Number of investigators who are Sponsor employees (including both full-time and part-time employees): 0		
Number of investigators with disclosable financial interests/arrangements (Form FDA 3455): 0		
If there are investigators with disclosable financial interests/arrangements, identify the number of investigators with interests/arrangements in each category (as defined in 21 CFR 54.2(a), (b), (c) and (f)):		

[8] https://purplebooksearch.fda.gov/

Compensation to the investigator for conducting the study where the value could be influenced by the outcome of the study: _____ Significant payments of other sorts: _____ Proprietary interest in the product tested held by investigator: _____ Significant equity interest held by investigator in S Sponsor of covered study: _____		
Is an attachment provided with details of the disclosable financial interests/arrangements:	Yes ☐	No ☐ (Request details from Applicant)
Is a description of the steps taken to minimize potential bias provided:	Yes ☐	No ☐ (Request information from Applicant)
Number of investigators with certification of due diligence (Form FDA 3454, box 3) 0		
Is an attachment provided with the reason:	Yes ☐	No ☐ (Request explanation from Applicant)

Covered Clinical Study: FYB202-01-02

Was a list of clinical investigators provided:	Yes ☒	No ☐ (Request list from Applicant)
Total number of investigators identified: 29		
Number of investigators who are Sponsor employees (including both full-time and part-time employees): 0		
Number of investigators with disclosable financial interests/arrangements (Form FDA 3455): 0		
If there are investigators with disclosable financial interests/arrangements, identify the number of investigators with interests/arrangements in each category (as defined in 21 CFR 54.2(a), (b), (c) and (f)): Compensation to the investigator for conducting the study where the value could be influenced by the outcome of the study: _____ Significant payments of other sorts: _____ Proprietary interest in the product tested held by investigator: _____ Significant equity interest held by investigator in S Sponsor of covered study: _____		
Is an attachment provided with details of the disclosable financial interests/arrangements:	Yes ☐	No ☐ (Request details from Applicant)
Is a description of the steps taken to	Yes ☐	No ☐ (Request information

minimize potential bias provided:		from Applicant)
Number of investigators with certification of due diligence (Form FDA 3454, box 3) 0		
Is an attachment provided with the reason:	Yes ☐	No ☐ (Request explanation from Applicant)

Covered Clinical Study: FYB202-03-01

Was a list of clinical investigators provided:	Yes ☒	No ☐ (Request list from Applicant)
Total number of investigators (primary and sub-investigators identified: 92		
Number of investigators who are Sponsor employees (including both full-time and part-time employees): 0		
Number of investigators with disclosable financial interests/arrangements (Form FDA 3455): 0		
If there are investigators with disclosable financial interests/arrangements, identify the number of investigators with interests/arrangements in each category (as defined in 21 CFR 54.2(a), (b), (c) and (f)): Compensation to the investigator for conducting the study where the value could be influenced by the outcome of the study: _____ Significant payments of other sorts: _____ Proprietary interest in the product tested held by investigator: _____ Significant equity interest held by investigator in S Sponsor of covered study: _____		
Is an attachment provided with details of the disclosable financial interests/arrangements:	Yes ☐	No ☐ (Request details from Applicant)
Is a description of the steps taken to minimize potential bias provided:	Yes ☐	No ☐ (Request information from Applicant)
Number of investigators with certification of due diligence (Form FDA 3454, box 3) 0		
Is an attachment provided with the reason:	Yes ☐	No ☐ (Request explanation from Applicant)

14.2. Nonclinical Appendices

14.2.1. Nonclinical Pharmacology

In Vivo Pharmacology

There were no in vivo pharmacology studies.

14.2.2. Nonclinical Pharmacokinetics

The Applicant conducted in minipigs a comparative PK study of the current product versus US-Stelara; however, the study was deemed unnecessary to support this 351(k) BLA application and therefore not reviewed.

14.2.3. General Toxicology

There were no general toxicology studies.

14.2.4. Other Toxicology Studies

The sponsor conducted extractables studies for the two container closure systems (CCSs) of the drug product. The first one is a 1-mL (b) (4) glass syringe with a rubber plunger stopper used for packaging of the 90 mg/mL solution for subcutaneous injection. The second one is a 30-mL glass vial (26-mL fill volume) with a rubber stopper used for packaging of the 130 mg/26 mL (5 mg/mL) solution for intravenous infusion.

The 90 mg/mL solution for subcutaneous injection has the maximum daily dose (MDD) of 90 mg (1 syringe, once every 8 weeks), when the drug is used in the maintenance treatment of Crohn's disease and ulcerative colitis. The 130 mg/26 mL (5 mg/mL) solution is used as a single intravenous infusion in the initial treatment of Crohn's disease and ulcerative colitis. It has the MDD of 260 mg (2 vials) for the body weight of ≤ 55 kg, 390 mg (3 vials) for the body weight of 55-85 kg, and 520 mg (4 vials) for the body weight ≥ 100 kg. For the purpose of toxicological assessment of the CCSs, the worst-case scenario is one syringe per day for the 90 mg/mL solution or three vials per day for the 130 mg/26 mL (5 mg/mL) solution, based on a body weight of 60 kg.

For the (b) (4) syringe, the sponsor set the safety concern threshold (SCT) at (b) (4) μg/day and assumed the maximum daily use of one syringe. For the 30-mL glass vial, the sponsor set the SCT at (b) (4) μg/day and assumed the maximum daily use of four vials. The extractable studies were conducted by using the placebo buffer (clinical formulation without the drug substance) or (b) (4) extraction solvent

under harsh conditions, i.e., 55 °C x 56 days for the syringe or 55 °C x 42 days for the vials. The only organic extractable above the SCT was (b) (4) which had the maximum daily exposure (MDE) of (b) (4) μg for the syringe and (b) (4) μg for the vials (calculated based on the use of three vials). Elemental impurities were all below the parenteral permitted daily exposure (PDE) values summarized in the ICH Q3D guidance.

A recent review by the European Food Safety Authority (EFSA) for (b) (4) as a food additive established an acceptable daily intake (ADI) of (b) (4) mg/day. Oral absorption of (b) (4) was approximately 2-4% as assessed in a monkey study summarized in the review. Therefore, the ADI of (b) (4) mg/day translates to the absorbed amount of approximately (b) (4) mg/day, which is much higher than the MDE value of (b) (4) μg detected in the glass vials. The amount of (b) (4) present in the extractables is acceptable from a nonclinical perspective.

Overall, the levels of extractables and potential leachables from the two CCSs of the drug product are acceptable from a nonclinical perspective.

14.3. Clinical Pharmacology Appendices

14.3.1. Study FYB202-01-01

Study FYB202-01-01 was the first PK similarity study conducted to demonstrate pairwise PK similarity between FYB202, EU-Stelara, and US-Stelara following the administration of a single SC dose of 45 mg in 0.5 mL solution. Study FYB202-01-01 was similar to the PK similarity Study FYB202-01-02, randomized, double-blind, single-dose, three-arm, parallel-group study in healthy subjects.

This study failed to show PK similarity between FYB202 vs EU-Stelara and FYB202 vs US-Stelara because the upper limit of the 90% CIs for the GMR of AUC0-inf exceeded 125% (Table 45). Analysis of retained samples of the respective clinical batches administered in the comparative PK Study FYB202-01-01 indicated difference in the amount of protein contents, which introduced a between-treatment group bias in the amount of ustekinumab that was actually dosed.

Table 45. Summary of Statistical Analyses for Assessment of Pairwise Pharmacokinetic Similarity between FYB202, EU-Stelara and US-Stelara (Study FYB202-01-01)

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)
Source: Study FYB202-01-01 Report, Table 21.

The Applicant conducted post-hoc statistical analysis following dose correction to adjust for different protein contents of clinical batches used in Study FYB202-01-01 and respective 90% CI for the pairwise comparison of $AUC_{0\text{-}inf}$ were contained within the no boundary effect of 80-125% (Table 46). The results from this post-hoc analysis suggest that the protein content difference may have impacted the PK comparisons between FYB202 and US-/EU-Stelara products.

Table 46. Summary of the Statistical Analysis for the Protein Content Calculated Dose Adjusted (mg) Primary PK Endpoints in Study FYB202-01-01

Parameter	Ratio (%)	90% Confidence interval
	FYB202 \ Stelara EU	
AUC_{0-inf}[a]	111.96	103.27;121.38
C_{max}[b]	103.46	95.80;110.23
	FYB202 \ Stelara US	
AUC_{0-inf}[a]	113.89	105.09;123.42
C_{max}[b]	107.17	99.24;115.74
	Stelara EU \ Stelara US	
AUC_{0-inf}[a]	101.72	93.86;111.73
C_{max}[b]	103.59	95.91;111.90
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)
Source: IND 141478, SDN 0008, Module 1.6.2, BPD Type 3 Meeting-Briefing Book, Table 44.

14.3.2. Summary of Bioanalytical Method Validation and Performance

The bioanalytical studies were developed and validated by [redacted] (b) (4) to determine the concentration of FYB202 / Ustekinumab in human serum samples by enzyme-linked immunosorbent assay (ELISA). The samples were collected in the clinical trials FYB202-01-02 and FYB202-03-01. The lower limit of quantification of the ELISA method was 40 ng/mL in neat human plasma (Table 47). The bioanalytical method was developed based on the FDA Bioanalytical Method Validation Guidance for Industry (2018).

Table 47. Summary of [redacted] (b) (4) Bioanalytical Validation Method

Validation parameters	Method validation summary	
Reference standard used for calibration curve and QCs		FYB202: 91.8 mg/mL (for Calibration Standards and QC/DQC)) EU-Stelara: 87.0 mg/mL (for QC/DQC) US-Stelara: 86.3 mg/mL (used for method validation) and 89.5 mg/mL (for QC/DQC)
Standard calibration curve performance	Range and Calibration Standards (FYB202)	Range: 40 (LLOQ) to 1400 (ULOQ) ng/mL Concentration levels: 40, 100, 250, 400, 600, 800, 1150, 1400 ng/ml
	Quality control (QC) and dilution quality control (DQC) samples	Concentration levels: 40 (LLQC), 120 (LQC), 650 (MQC), 1000 (HQC), 1400 (ULQC), 25000 (DQC) ng/mL
	Cumulative accuracy (%bias) from LLOQ to ULOQ	FYB202: -5.8 to -0.3 EU-Stelara: -11.5 to -1.7

<table>
<tr><td></td><td></td><td colspan="3">US-Stelara: -4.3 to 2.2</td></tr>
<tr><td></td><td>Cumulative precision (%CV) from LLOQ to ULOQ</td><td colspan="3">FYB202: 5.9 to 14.4
EU-Stelara: 6.6 to 11
US-Stelara: 6.8 to 10.1</td></tr>
<tr><td></td><td>Total error (%) from LLOQ to ULOQ</td><td colspan="3">FYB202: 6.2 to 20.2
EU-Stelara: 12.7 to 10.9
US-Stelara: 7.2 to 14.4</td></tr>
<tr><td>Minimum required dilutions (MRDs)</td><td colspan="4">1:30</td></tr>
<tr><td>Regression Model</td><td colspan="4">4-Parameter Logistic (4PL) fit with weighting factor 1/Y</td></tr>
<tr><td>Carryover</td><td colspan="4">Not applicable</td></tr>
<tr><td>Selectivity

Healthy
Psoriatic
Lipemic
Hemolyzed</td><td colspan="4">– 10 individual healthy human sera and healthy human serum pool, 10 individual disease (psoriatic) human sera and disease human serum pool, were tested. Testing was done unspiked (blank) and spiked LLOQ and high QC level, separately for each reference item. In addition, three healthy lipemic sera and three healthy hemolyzed sera (prepared from individuals with 3% whole blood added) were tested.
– The accuracy of spiked matrices should be within 20% of the expected concentration for both levels.
– The blanks should be below LLOQ. In at least 80% of the standard matrices evaluated each criterion should be met separately, for each experiment.
– The same criteria apply for lipemic and hemolyzed matrices, but only need to be met in 2/3 of the matrices.
– Criteria were met

FYB202 | EU-Stelara | US-Stelara
10/10 individual and pool | 10/10 individual and pool | 9/10 individual and pool
9/10 individual and pool | 10/10 individual and pool | 9/10 individual and pool
3/3 individuals | 3/3 individuals | 3/3 individuals
3/3 individuals | 3/3 individuals | 2/3 individuals</td></tr>
<tr><td colspan="2" rowspan="2">Biosimilarity comparison</td><td rowspan="2">FYB202 versus EU-Stelara</td><td colspan="2">FYB202 versus</td><td rowspan="2">EU-Stelara versus US-Stelara</td></tr>
<tr><td>US-Stelara lot A</td><td>US-Stelara lot B</td></tr>
<tr><td rowspan="5">Difference % mean relative error</td><td>LLOQ-QC</td><td>-7.8</td><td>3.7</td><td>-5.2</td><td>-8.9</td></tr>
<tr><td>LQC</td><td>-4.7</td><td>3.9</td><td>-2</td><td>-8.2</td></tr>
<tr><td>MQC</td><td>-9.3</td><td>3</td><td>-2.3</td><td>-8.6</td></tr>
<tr><td>HQC</td><td>-10.5</td><td>6.3</td><td>-1.5</td><td>-11.7</td></tr>
<tr><td>ULOQ-QC</td><td>-10.4</td><td>1</td><td>-0.2</td><td>-11.7</td></tr>
<tr><td>Dilution linearity</td><td colspan="4">Demonstrated up to 335-fold for FYB202, Stelara EU, Stelara US in healthy and psoriatic matrix
No hook effect up to 25 µg/mL</td></tr>
<tr><td>Stabilities</td><td colspan="4">– The stability of FYB202 in healthy human serum was evaluated at 120 ng/mL (LQC), 1000 ng/mL (HQC) and 25000 ng/ml (DQC, diluted 25-fold to 1000 ng/mL).
– The stability samples were stored at -20°C and -80°C.
– FYB202, Stelara EU and Stelara US tested with comparable performance, within specification.
• Benchtop stability: at least 42 hours at room temperature
• Freeze-thaw stability: samples were frozen for at least 12 hours before they are thawed for at least 3 hours for a total of 6 cycles
• Long-term stability: at least 1188 days</td></tr>
<tr><td>Storage conditions of calibration standards, QC and DQC samples</td><td colspan="4">At -20°C and -80°C (for use as stability samples)</td></tr>
<tr><td>Parallelism</td><td colspan="4">Details obtained from bioanalytical studies.
12 study samples at a high concentration are diluted into the quantitation range, selecting samples near ULOQ. As a default dilution, 2-fold serial dilution (2-, 4-, 8-, 16-fold) with blank matrix are applied. At least all dilutions that fall into range between 80 ng/mL (2×LLOQ) and 1400 ng/mL (ULOQ) are subjected to analysis (single replicate per dilution factor).
Acceptance (below) criteria were met for all individual samples thus demonstrating parallelism:
– at least 3 dilutions fall into the analytical range and are valid data points
– per treatment arm (drug product), precision ≤ 30% between samples in a dilution series
– at least 80% of the tested samples (per dilution series) meet the CV criterion</td></tr>
<tr><td>Incurred sample reproducibility</td><td colspan="4">If the %Difference between re-assay and original result is less than or equal to ±30.0%, a pair of results is considered a passing match. The analytical method is considered reproducible if at least 67% of the result pairs match. If less than 67% of the pairs match, an event investigation is required.
• Study FYB202-01-02: The method for the determination of FYB202 / Ustekinumab in human serum was considered reproducible, 98% out of 702 repeat analyses to evaluate incurred sample reproducibility met acceptance criteria.
• Study FYB202-03-01: The method for the determination of Ustekinumab in human serum was considered reproducible, 176 (96%) out of 184 repeat analyses to evaluate incurred sample reproducibility met the acceptance criteria.</td></tr>
</table>

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U.S. Department of Health and Human Services
Food and Drug Administration
Center for Drug Evaluation and Research
Office of Translational Sciences
Office of Biostatistics

STATISTICAL REVIEW AND EVALUATION

CLINICAL STUDIES

NDA/BLA #:	BLA 761379
Supplement #:	NA
Drug Name:	FYB202, Proposed biosimilar of ustekinumab
Indication(s):	Moderate-to-severe plaque psoriasis
Applicant:	Bioeq GmbH
Date(s):	Date Submitted: September 28, 2023 Primary Review Due Date: May 28, 2024 BsUFA Goal Date: September 28, 2024
Review Priority:	Standard
Biometrics Division:	Division of Biometrics VIII
Statistical Reviewer:	Sungwoo Choi, Ph.D., DB VIII
Concurring Reviewers:	Jessica Kim, Ph.D., DB VIII
Medical Division:	Division of Dermatology and Dentistry
Clinical Team:	Felisa Lewis, MD
Project Manager:	Kimberle Searcy

Keywords: Biosimilar

Table of Contents

LIST OF TABLES

LIST OF FIGURES

1 EXECUTIVE SUMMARY

The applicant (Bioeq GmbH) submitted Biologic License Application (BLA) 761379 to demonstrate similarity of the proposed biosimilar product FYB202 to US-licensed Stelara (ustekinumab), based on the totality of evidence from the analytical, nonclinical, and clinical data. The clinical program includes clinical comparative efficacy and safety study FYB202-03-01 in patients with moderate-to-severe Plaque Psoriasis. The study FYB202-03-01 was a multi-center, randomized, double-masked, 2-arm parallel group, comparative Phase 3 clinical study with a duration of 56 weeks to demonstrate that there is no clinically meaningful difference between FYB202 and EU-approved Stelara in subjects with moderate-to-severe Plaque Psoriasis.

Patients were randomized into one of the two treatment groups in a 1:1 ratio to FYB202 arm or EU-approved Stelara arm. Randomization before the first study intervention was stratified by prior inadequate response or intolerance to a systemic biological treatment in the opinion of the investigator. A total of 392 subjects were randomized to FYB202 arm (N = 197) or EU-approved Stelara arm (N = 195).

The primary efficacy endpoint was the percent improvement in PASI score from baseline to week 12. The primary efficacy analysis was conducted to assess whether there is no clinically meaningful difference between FYB202 and EU-approved Stelara in the primary efficacy endpoint based on the full analysis set (FAS). The pre-specified similarity margin was set as [-10%, 10%].

In terms of the primary efficacy endpoint, the adjusted mean percent improvement in PASI score from baseline to week 12 were comparable between the two treatment groups (79.51% for FYB202 and 76.24% for EU-approved Stelara). In addition, the adjusted mean difference was 3.27% with 90% CIs of (-0.2249%, 6.7699%), which was contained within the similarity margin of [-10%, 10%]. Thus, the study FYB202-03-01 demonstrated the similarity of FYB202 and EU-licensed Stelara for the primary efficacy endpoint.

In summary, the reviewer concludes that this application provides adequate statistical evidence that there is no clinically meaningful difference between FYB202 and EU-approved Stelara in the primary efficacy endpoint according to the prespecified biosimilar margin.

2 INTRODUCTION

This section provides an overview of the application, a summary of the clinical studies, and information on data sources submitted in BLA 761379.

2.1 Overview

The applicant seeks approval of FYB202 as a proposed biosimilar to US-licensed Stelara (ustekinumab). The proposed indication and usage for FYB202 are identical to those of US-licensed Stelara except for children weighing less than 60 kg.

US-licensed Stelara's indications are:

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

The clinical development program for FYB202 included three studies: Study FYB202-01-01, Study FYB202-01-02, and Study FYB202-03-01. Both Study FYB202-01-01 and Study FYB202-01-02 were three-arm bridging studies aimed at demonstrating pharmacokinetic (PK) equivalence of FYB202, EU-approved Stelara, and US-licensed Stelara. Study FYB202-03-01, which is hereafter referred to as Study 0301, evaluated the clinical similarity of FYB202 and EU-approved Stelara regarding efficacy, safety, and immunogenicity in the treatment of subjects with moderate-to-sever Ps.

This statistical review pertains to Study 0301, and Table 1 shows the summary of Study 0301.

Table 1: Summary of specific study reviewed.

Study ID	Design	Duration	Treatment, Sample Size (n)	Study Population
FYB202-03-01 (0301)	Multicenter, double-blind, parallel-group, randomized phase 3 study	56 weeks: Screening (4 weeks), Treatment (40 weeks), and follow-up (12 weeks)	• FYB202 90 mg/mL, n=197 • EU-approved Stelara 90 mg/mL, n=195	Subjects with moderate-to-sever Ps

Source: reviewer's summary based on the clinical study report.

2.2 Data Sources

The data sources for this review include protocol, statistical analysis plans (SAP), clinical study report (CSR), and the datasets.

The protocol, SAP and CSR can be found at the following location:

- \\CDSESUB1\evsprod\BLA761379\0001\m5\53-clin-stud-rep\535-rep-effic-safety-stud\psoriasis\5351-stud-rep-contr\fyb202-03-01.

The datasets were submitted in the formats of Study Data Tabulation Model (SDTM) and Analysis Data Model (ADaM) in electronic submission. The datasets can be located at

- \\CDSESUB1\evsprod\BLA761379\0001\m5\datasets\fyb202-03-01.

3 STATISTICAL EVALUATION

3.1 Data and Analysis Quality

No major issues were identified regarding the quality and integrity of the submitted SDTM and ADaM datasets under BLA 761379. The data quality control/assurance procedures are properly documented in the CSRs. The Applicant's primary efficacy results are reproducible using the ADaM datasets.

3.2 Evaluation of Efficacy

This section evaluates the efficacy results of Study 0301.

3.2.1 Study Design and Endpoints

Study design

Study 0301 was a multi-center, double-blind, parallel-group, active control, randomized phase 3 study to demonstrate that there is no clinically meaningful difference between FYB202 and EU-approved Stelara in subjects with moderate-to-severe Ps regarding efficacy, safety, and immunogenicity.

Patients were randomized 1:1 to receive subcutaneous (SC) injections of either FYB202 or EU-approved Stelara 45 mg at weeks 0, 4, 16, 28, and 40. Randomization before the first study intervention was stratified by prior inadequate response or intolerance to a systemic biological treatment in the opinion of the investigator (yes/no).

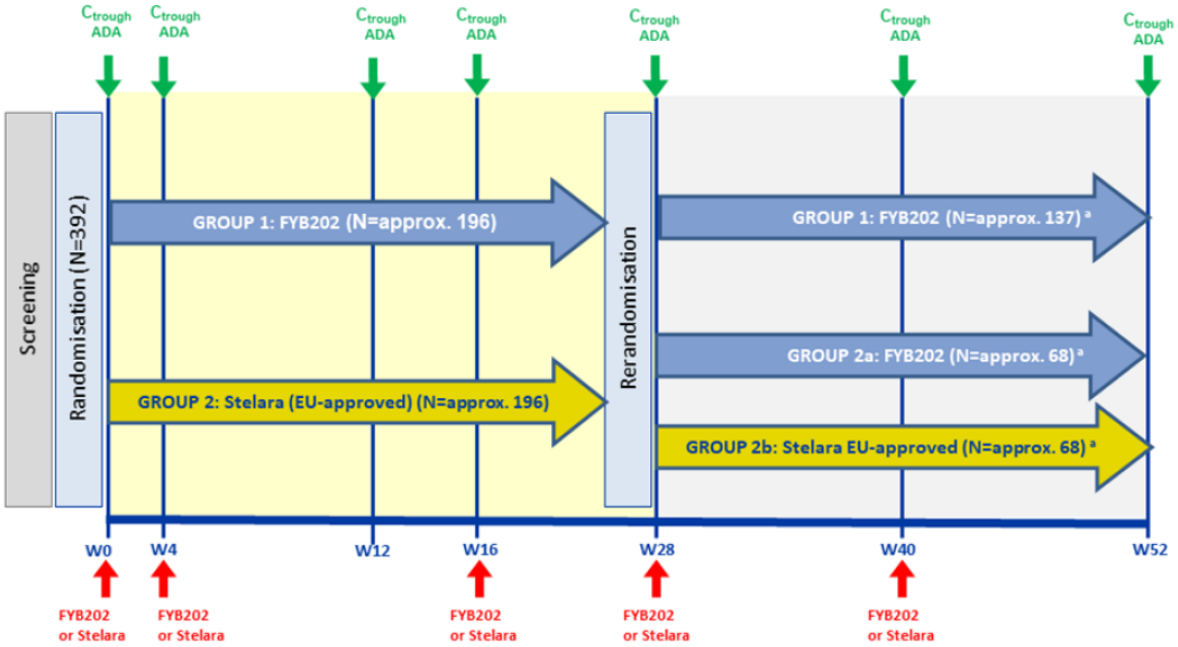
Patients failing to attain a ≥75% improvement in Psoriasis Area and Severity Index (PASI) score (PASI 75) from baseline at week 28 (estimated approximately 30% of patients) would be categorized as non-responders. These patients would cease the study intervention but would be followed until the study's completion at week 52.

At week 28, patients would be re-randomized in a blinded manner. Those initially assigned to treatment arm EU-approved Stelara would be re-randomized at a 1:1 ratio, with 50%

transitioning to FYB202 while the remaining 50% would maintain EU-approved Stelara. Patients originally assigned to FYB202 would continue receiving it without change.

The schedule of activities is presented in Figure 1. The week 12 assessment corresponds to the primary efficacy endpoint evaluation time.

Figure 1: Schematic of the study design



[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.
Source: Figure 9-1 of the Clinical Study Report (CSR)

Study endpoints

The primary efficacy endpoint was the percent improvement in PASI score from baseline (week 0) to week 12.

Table 2: Efficacy endpoints in Study 0301

Primary	• **Percent improvement in PASI score from baseline (week 0) to week 12**
Secondary	• 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 • Change per Physician's Global Assessment (PGA) over time. • Improvement of Dermatology Life Quality Index (DLQI) total score from baseline (week 0) at weeks 4, 12, 16, 28, 50, and 52 • Itching Visual Analogue Scale (I-VAS) at baseline and at weeks 4, 12, 16, 28, 40, and 52 • Changes in PASI 75 and PASI 90 response from week 28 through week 52 in patients following a single transition from EU-approved Stelara to FYB202

Source: reviewer's summary based on the clinical study report.

Estimand

According to SAP, the primary estimand is the mean difference between the randomized treatment groups, FYB202 and EU-approved Stelara, for the primary endpoint, regardless of treatment adherence and usage of concomitant medications, using data of all patients in the full analysis set (FAS).

The attributes as defined in the ICH E9 addendum of this estimand are described as follows:

1. Treatment condition: FYB202 or EU-approved Stelara administered according to planned schedule.
2. Population: patients with moderate-to-severe plaque psoriasis fulfilling the in- and exclusion criteria in the FAS.
3. Endpoint: percent improvement in PASI score from baseline to week 12.
4. Intercurrent event and strategies: all intercurrent events are handled according to the treatment policy strategy, i.e., all values of interest are analyzed whether or not the intercurrent event occurred. The following intercurrent events are considered for this estimand.
    a. Use of prohibited medication as rescue medication.
    b. No assessment of PASI until analysis visit week 12.
    c. Poor compliance to study intervention prior to week 12: less than two study interventions were applied prior to Visit 3 / Week 12.
    d. Questionable/spurious data: any efficacy data that was not assessed according to protocol by time window.

e. Patient received study intervention from a treatment group the patient was not randomized to.

5. Population level summary: mean difference between treatment groups.

3.2.2 Statistical Methodologies

In this section we primarily focus on describing statistical methodologies for analyzing the primary efficacy endpoint. Hypothesis testing was conducted only for the primary endpoint, and no formal analysis based on statistical hypothesis was intended for the other endpoints.

Analysis populations

The SAP defines the following analysis sets:

- Full analysis set (FAS): all patient randomized and treated with study intervention at least once. Patients are analyzed according to the study intervention they have been randomized to prior to the first study intervention.
- Safety analysis set: all patients treated with study intervention at least once. Patients are generally analyzed according to the study intervention they actually received at week 0 and/or at week 28.
- Per-protocol set (PPS): all patients from the FAS who are solely treated with study intervention from the randomized treatment group until week 28 and have no major protocol deviation that might interfere with the interpretation of the PASI assessment at baseline (week 0) or at week 12. Also, intercurrent events that affected either the availability or the interpretation of the PASI assessment at Week 12 led to the exclusion of a patient from the PPS.
- Re-randomized analysis set (RRAS): all patients who are re-randomized and treated with study intervention at least once at week 28 or later. Patients are analyzed according to the study interventions they actually received at week 0 and at week 28 or later.

The FAS is used as the primary basis for all efficacy evaluations up to and including week 28. After re-randomization, efficacy data are analyzed using the RRAS.

Similarity margin justification

According to the CSR, the similarity margin (-10%, +10%) was determined based on findings from prior studies. In addition, the margin was further investigated by calculating the retained treatment effect of Stelara® in trials PHOENIX 1 & 2 (Leonardi et al., 2008; Papp et al., 2008). The results from both studies were combined using meta-analyses. The estimated treatment effect of Stelara was approximately 70%, with the lower limit of the associated 95% confidence interval being 67%. The retained treatment effect was approximately 85.7%, calculated using the provided formula:

$$Retained\ treatment\ effect = \frac{Stelara\ treatment\ effect - similarity\ margin}{Stelara\ treatment\ effect}.$$

***Reviewer's comments**: The similarity margin was discussed in Biosimilar Biological Product Development (BPD) Type 2 meeting under pre-IND 141478 on February 13, 2019. The applicant's proposal for the margin was* (b) (4) *Regarding this proposal, the FDA stated, "For your study design and expected percent improvement in PASI values, we recommend using margins of ± 10%, rather than* (b) (4) *%" (see the DARRTS entry on March 15, 2019).*

Sample size determination

The sample size calculation was based on the following assumptions in Table 3.

Table 3: Assumptions for sample size calculations

Confidence level	90%
Power	90%
Similarity margin	± 10%
Treatment difference	0%
Standard deviation	30%
Drop-out rate	20%

Source: This table was produced by the reviewer using the information in Table 9-8 of the CSR

The applicant provided the parameters used in sample size calculation, as outlined in Table 3. Using the assumptions, approximately 196 patients per treatment group are required to achieve 90% power (not included 20% drop-out rate). This calculation assumes similarity testing procedures and a normal distribution of the primary efficacy parameter, with no anticipated difference between the two treatment groups.

***Reviewer's comments**: The reviewer verified that the study size of 196 was reproducible using the listed assumptions. However, the applicant' assumption regarding the standard deviation of 30% lacks clarity regarding its source.*

Analysis of primary efficacy endpoint

The hypotheses to be tested are

$$H_0: |\mu_F - \mu_S| \geq \delta \quad \text{versus} \quad H_A: |\mu_F - \mu_S| < \delta,$$

where μ_F and μ_S are the mean percentage change from baseline to week 12 in PASI score for FYB202 and EU-approved Stelara respectively; δ is the similarity margin ($\delta = 10\%$). To establish the similarity between FYB202 and EU-approved Stelara, the 90% confidence interval (CI) for the mean difference $\mu_F - \mu_S$ is calculated. The null hypothesis H_0 is rejected with a type I error probability $\alpha = 0.05$ if the 90% CI for $\mu_F - \mu_S$ is contained within the interval [-10%, 10%]. Rejecting the null hypothesis H_0 supports the conclusion of similarity between FYB202 and EU-approved Stelara.

The 90% CI for the mean difference $\mu_F - \mu_S$ is constructed using the least-squares mean and error estimates derived from a mixed model repeated measures (MMRM). The MMRM includes

baseline variables such as PASI score, weight, duration of psoriasis, prior inadequate response or intolerance to a systemic biological treatment and visit as factors. According to the SAP, the MMRM includes interaction terms between treatment group and visit, as well as between baseline PASI score and visit. Correlations within patients are accounted for using an unstructured variance-covariance matrix. Additionally, the Kenward-Roger degrees of freedom approximation is applied.

Handling of missing data

Per SAP, MMRM is used for the efficacy analyses. Missing data regarding the primary or secondary efficacy endpoints are not explicitly imputed. Nevertheless, the model is operated under the assumption that the missing data for a patient are similar to the observed values of other patients sharing identical baseline characteristics and experiencing a similar progression from baseline to the relevant visit/week.

Due to the definition of baseline values and the definition of inclusion and exclusion criteria in the protocol, all randomized patients are expected to possess baseline data for the primary and secondary efficacy endpoints. Thus, there should be no necessity to exclude any patient from the MMRM analysis due to missing baseline values. For patients who does not exhibit any post-baseline values until week 28, no course of change from baseline could be assumed, and therefore, these patients are excluded from the primary analysis. The applicant further stated that due to the clinical status of patients it is regarded as very unlikely that no post-baseline assessment of the PASI exists.

***Reviewer's comments**: Two patients (Subject IDs: (b) (6)) did not exhibit any post baseline values until week 28, and they were excluded from the primary analysis. Note that the primary efficacy analysis is based on data of all patients in the FAS.*

Sensitivity analyses for the primary efficacy endpoint

To assess robustness of the primary analysis results of the primary endpoint, the following sensitivity analyses are performed as planned in the SAP.

(S1) MMRM including only data until week 12 under the assumption that patients exhibiting comparable post-treatment values up to Week 28 will demonstrate similar behavior.

(S2) Analysis of covariance (ANCOVA) model including the baseline PASI score, baseline weight, duration of psoriasis as covariates, and prior inadequate response or intolerance to a systemic biological treatment and treatment group as fixed effects; based on observed cases.

(S3) ANCOVA model with using multiple imputation.

(S4) MMRM including patients discontinued study status prior to week 16 as a fixed effect.

(S5) MMRM including patients discontinued study status prior to week 12 as a fixed effect.

(S6) MMRM including patients discontinued study intervention status prior to week 16 as a fixed effect.

(S7) MMRM including patients with any major protocol deviation status as a fixed effect.

(S8) MMRM including patients with any major protocol deviation category as a fixed effect.

(S9) Tipping point analysis; sensitivity parameter $\theta = 0$ as a starting point and increments of 2% in both directions to increase the difference between the treatment groups.

Supplemental analyses for the primary efficacy endpoint

According to SAP, the supplemental estimands outlined below are evaluated using the same statistical methods (MMRM) as those for the primary analysis if at least 10 patients meet the relevant criteria described below:

(S10) Comparison of % improvement in PASI score from baseline to week 12 including data up to and including week 28 - excluding patients with major protocol deviations, which is the analysis based on the PPS at the same time,

(S11) Comparison of % improvement in PASI score from baseline to week 12 including data up to and including week 28 excluding patients from the FAS who discontinue study intervention before week 16 or do not have a week 12 PASI assessment (complete case analysis),

(S12) Comparison of % improvement in PASI score from baseline to week 12 including data up to and including week 28 excluding all assessments following discontinuation of study intervention (while on treatment strategy),

(S13) Comparison of % improvement in PASI score from baseline to week 12 including data up to and including week 28 excluding assessments following a missed study intervention,

(S14) Comparison of % improvement in PASI score from baseline to week 12 including data up to and including week 28 excluding all assessments following major protocol deviations.

***Reviewer's comments**:*

- *Note that only 4 and 3 patients met the criteria on (S12) and (S13), respectively.*

In addition, the reviewer conducts the following supportive analysis:

(S15) ANCOVA using the PPS: the ANCOVA model in this supportive analysis is the same as that in the sensitivity analysis.

Analysis of secondary efficacy endpoints

Recall that there were four secondary efficacy endpoints based on the PASI score.

1) Percent improvement in PASI score from baseline to weeks 4, 16, 28, 40, and 52.
2) Raw PASI scores at baseline and weeks 4 and 12.
3) Proportion of patients with PASI 75 and PASI 90 responses at weeks 4, 12, 16, 28, 40, and 52.
4) Changes in PASI 75 and PASI 90 response from week 28 through week 52 in patients following a single transition from EU-approved Stelara to FYB202.

The secondary efficacy endpoints based on the PASI score are analyzed as follows:

- The raw PASI scores and the percent improvement in PASI score were summarized. descriptively.
- The percent improvement in PASI score at the analysis visits Week 4, Week 16 and Week 28 was statistically analyzed using the same MMRM as the one for the primary efficacy endpoint.
- The time course of the PASI 75 and PASI 90 response was presented using bar plots.
- The difference between treatment groups in the response rates of PASI 75 and PASI 90 at each analysis visit from Week 4 to Week 28 were analyzed via a repeated measures logistic regression model.
- The change in PASI 75/PASI 90 response from week 28 to week 40 and week 52 were presented in the terms of shift tables by treatment group for the RRAS.

Recall that the secondary efficacy endpoints, excluding those determined by the PASI score, are as follows:

5) Change per PGA over time,
6) Improvement of DLQI total score from baseline at weeks 4, 12, 16, 28, 50, and 52
7) I-VAS at baseline and at weeks 4, 12, 16, 28, 40, and 52

Change per PGA over time is analyzed as follows:

- The changes in PGA score from baseline are descriptively summarized.
- The same MMRM as one for the primary endpoint was used to analyze the difference in treatment groups with respect to the absolute change from baseline in PGA score at week 4, week 12, week 16, and week 28.

The secondary efficacy endpoint based on the DLQI, and I-VAS were analyzed in an analogous manner as explained in the method for PGA. In addition, the analysis of the I-VAS is carried out separately for the average itch experience and the worst itch experience.

Subgroup analysis

According to SAP, the primary endpoint was analyzed across the subgroups defined by the following factors:

- Prior inadequate response or intolerance to a systemic biological treatment (yes/no)
- Sex (male or female)
- Baseline PASI score (moderate or severe)
- Time since onset of psoriasis ($\leq$ 10 years, > 10 years and $\leq$ 20 years, and $\geq$ 20 years)
- Baseline body weight ($\leq$ 75 kg, > 75 kg and < 90 kg, and $\geq$ 90 kg)

The primary efficacy endpoint analysis using the MMRM was repeated for subgroups of the FAS if the subgroup size allowed the calculation of meaningful confidence intervals.

3.2.3 Patient Disposition, Demographic and Baseline Characteristics

Analysis populations, subject disposition and primary reasons for study discontinuation are summarized in Table 4. A total of 507 subjects were screened. Of these, 392 subjects were randomized to receive study treatment: 197 patients were randomized to receive FYB202 and 195 patients to receive EU-approved Stelara.

No patients were excluded from the FAS or SAF. Thus, both sets comprised a total of 392 patients. There were 13 patients who had a major protocol deviation, these patients were excluded from the PPS. There were 9 (2.3%) patients who were excluded from RRAS because they were non-responders, 5 (1.3%) because they discontinued the study before week 28, and 3 (0.8%) patients because they were not rerandomized due to other reasons.

By week 28, 387 patients completed the study, while 5 patients discontinued the study prematurely. Among those who completed the study, 9 patients were non-responders, and 3 patients were not eligible for rerandomization due to other reasons such as discontinuation due to adverse events or non-attendance at week 28 due to patient non-compliance. Consequently, 375 patients were rerandomized at week 28. Of these, 189 patients originally on FYB202 stayed on FYB202 as per study design (FYB202: FYB202), 97 patients initially on EU-approved Stelara were rerandomized to EU-approved Stelara (EU-approved Stelara: EU-approved Stelara), and 89 patients on EU-approved Stelara were rerandomized to FYB202 (EU-approved Stelara: FYB202).

Following initial randomization, 380 patients completed the study until week 52. Following rerandomization of 375 patients, 372 patients completed the study until week 52; 187 patients on FYB202: FYB202 group, 97 patients on EU-approved Stelara: EU-approved Stelara group, and 88 patients on EU-approved Stelara: FYB202 group.

Table 4: Analysis population and subject disposition

	FYB202	EU-approved Stelara	Overall
Screened			507
Screening failure			115
Randomized	197	195	392
Safety	197 (100.0)	195 (100.0)	392 (100.0)
FAS	197 (100.0)	195 (100.0)	392 (100.0)
PPS	191 (97.0)	188 (96.4)	379 (96.7)
Excluded from PPS			
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	2 (1.0)	5 (2.6)	7 (1.8)
RRAS	189 (95.9)	186 (95.4)	375 (95.7)
Excluded from RRAS			
Non-responder	4 (2.0)	5 (2.6)	9 (2.3)
Discontinued study before week 28	4 (2.0)	1 (0.5)	5 (1.3)
Not rerandomized for other reason	0 (0.0)	3 (1.5)	3 (0.8)
Completed study up to week 28	193 (98.0)	194 (99.5)	387 (98.7)
Discontinued study			
Withdrew consent	2 (1.0)	0 (0.0)	2 (0.5)
Adverse event	1 (0.5)	1 (0.5)	2 (0.5)
Protocol deviation	1 (0.5)	0 (0.0)	1 (0.3)
Not re-randomized at week 28	4 (2.0)	8 (4.1)	12 (3.1)
Non-responders	4 (2.0)	5 (2.6)	9 (2.3)
Other reason	0 (0.0)	3 (1.5)	3 (0.8)
Re-randomized at week 28	189 (95.9)	186 (95.4)	375 (95.7)
Completed study up to week 52	191 (97.0)	189 (96.9)	380 (96.9)
Discontinued the study after re-randomization	2 (1.0)	1 (0.5)	3 (0.8)
Adverse event	0 (0.0)	1 (0.5)	1 (0.3)
Withdrew consent	1 (0.5)	0 (0.0)	1 (0.3)
Other	1 (0.5)	0 (0.0)	1 (0.3)

* The total number may add up to more than this number of subjects because a subject may have multiple reasons
Source: This table was produced by the reviewer using Tables 10-2 and 14.1.2.1.1 of CSR.

Demographic and baseline characteristics are summarized in Tables 5, 6 and 7. In general, demographic and baseline characteristics appear to be balanced between the two treatment groups among subjects in the FAS.

Table 5: Demographic characteristics (FAS)

	FYB202	EU-approved Stelara	Overall
FAS	N = 197	N = 195	N = 392
Demographics			
Age (years)			
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
Gender, n (%)			
Male	117 (59.4%)	117 (60.0%)	234 (59.7%)
Female	80 (40.6%)	78 (40.0%)	158 (40.3%)
Race, n (%)			
White	197 (100.0%)	195 (100.0%)	392 (100.0%)
Ethnicity, n (%)			
Not Hispanic/Latino	197 (100.0%)	195 (100.0%)	392 (100.0%)
BMI (kg/m^2)			
Mean (SD)	26.6 (4.21)	27.4 (4.36)	27.0 (4.30)
Median	26.6	27.2	26.80
Min, Max	18.2, 38.9	16.9, 39.3	16.9, 39.3

Source: This table was produced by the reviewer using the Table 10-3 of CSR.

Table 6: Baseline psoriasis characteristics (FAS)

	FYB202	EU-approved Stelara	Overall
FAS	N = 197	N = 195	N = 392
Baseline characteristic			
Time since onset of psoriasis [years]			
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
Time since onset of psoriasis [years] in female patients			
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
Time since onset of psoriasis [years] in male patients			
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
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%)

Source: This table was produced by the reviewer using the Table 10-4 of CSR.

Table 7: Baseline efficacy parameter characteristics

	FYB202	EU-approved Stelara	Overall
FAS	N = 197	N = 195	N = 392
Baseline characteristic			
Baseline PASI Score			
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
Baseline PGA [n (%)]			
3 = moderate	133 (67.5%)	139 (71.3%)	272 (69.4%)
4 = severe	64 (32.5%)	56 (28.7%)	120 (30.6%)
Baseline DLQI			
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
Baseline average itching VAS			
Mean (SD)	4.67 (2.385)	4.64 (2.551)	4.65 (2.466)
Median	4.80	4.70	4.70
Min, Max	0.0, 9.9	0.0, 10.0	0.0, 10.0
Baseline worst itching VAS			
Mean (SD)	6.34 (2.528)	6.21 (2.605)	6.28 (2.564)
Median	6.90	7.00	7.00
Min, Max	4.80, 8.20	4.50, 8.20	4.65, 8.20

Source: This table was produced by the reviewer using the Table 10-5 of CSR.

3.2.4 Results and Conclusions

This section provides efficacy results of the primary, secondary endpoints in Study 0301.

3.2.4.1 Primary Efficacy Endpoint

The objective of the primary efficacy analysis was to demonstrate the similarity of FYB202 and EU-approved Stelara in the primary efficacy endpoint: the percent improvement in PASI score from baseline to week 12 with a similarity margin of ± 10%.

Table 8 presents the primary efficacy analysis results. As shown in Table 8, the adjusted mean percent improvement in PASI score from baseline to week 12 were comparable for the two treatment groups (79.51% for FYB202 and 76.24% for EU-approved Stelara). In addition, the mean difference was 3.27% with 90% CIs of (-0.2249%, 6.7699%), which was contained within the similarity margin of [-10%, 10%]. Thus, the similarity was demonstrated for the primary efficacy endpoint.

Table 8: Primary analysis results for the percent improvement in PASI score from baseline to week 12 (FAS)

FAS	FYB202 (N = 197)	EU-approved Stelara (N = 195)
Baseline PASI		
n	197	195
Mean (SD)	24.07 (8.484)	24.75 (9.999)
Median (Range)	21.60 (12.3, 52.8)	21.80 (12.0, 63.3)
PASI at Week 12		
n	194	191
Mean (SD)	4.13 (5.684)	5.04 (6.435)
Median (Range)	2.40 (0.0, 39.2)	2.40 (0.0, 38.2)
% improvement of PASI at Week 12		
Mean (SD)	83.00 (18.882)	79.29 (23.037)
Median (Range)	88.11 (17.4, 100.0)	86.67 (0.0, 100.0)
Adjusted % improvement of PASI at Week 12[1]		
LS mean (SE)	79.51 (2.48)	76.24 (2.44)
LS mean difference (SE)	3.27 (2.121)	
90% CI for the mean difference	**(-0.225, 6.770)**	

[1] MMRM used all available percent improvements in PASI score from baseline until week 28 for all patients in the FAS for model estimation.
[1] Estimates are adjusted for baseline PASI score, baseline weight, time since onset of psoriasis and prior inadequate response or intolerance to a systemic biological treatment.
Source: Reviewer's analysis

Sensitivity and supplementary analyses

The study evaluated robustness of the primary analysis results by conducting different sensitivity analyses. Table 9 shows the summary of sensitivity analysis result. As shown in Table 9, the sensitivity analysis results were consistent with the primary analysis results, leading to the same conclusion for a robust interpretation of the similarity finding.

Reviewer's comments*: The reviewer included MMRM including patient discontinued study intervention prior to week 16 as additional fixed effect in sensitivity analysis as outlined in the SAP. However, the applicant did not include this sensitivity analysis in their evaluation.*

Table 9: Sensitivity analyses for the primary efficacy endpoint (FAS)

Method	LS Mean (SE)		Difference (FYB202 - Stelara)	
	FYB202	Stelara	Mean (SE)	90% CI
(S1) MMRM [1] using data up to week 12	81.16 (4.096)	78.04 (4.000)	3.12 (2.149)	(-0.431, 6.656)
(S2) ANCOVA [2]	80.31 (4.241)	77.16 (4.140)	3.15 (2.147)	(-0.394, 6.685)
(S3) ANCOVA [2] using MI	80.30 (4.241)	77.14 (4.142)	3.16 (2.153)	(-0.381, 6.702)
(S4) MMRM [1] including patient discontinuation of study status prior to week 16 as additional fixed effect	67.67 (12.445)	64.34 (12.495)	3.33 (2.122)	(-0.169, 6.829)
(S5) MMRM [1] including patient discontinuation of study status prior to week 12 as additional fixed effect	67.67 (12.445)	64.34 (12.495)	3.33 (2.122)	(-0.169, 6.829)
(S6) MMRM [1] including patient discontinuation of study treatment status prior to week 16 as additional fixed effect	79.51 (2.479)	76.24 (2.437)	3.27 (2.121)	(-0.225, 6.770)
(S7) MMRM [1] including patient any major protocol deviation status as additional fixed effect	77.87 (3.046)	74.67 (2.967)	3.20 (2.125)	(-0.301, 6.705)
(S8) MMRM [1] including major protocol deviation category as additional fixed effect	78.45 (4.069)	75.18 (3.975)	3.27 (2.129)	(-0.239, 6.782)

[1] Estimates are adjusted for baseline PASI score, baseline weight, time since onset of psoriasis and prior inadequate response or intolerance to a systemic biological treatment.
[2] Estimates are adjusted for baseline PASI score, baseline weight, time since onset of psoriasis and prior inadequate response or intolerance to a systemic biological treatment.
Source: Reviewer's analysis

Table 10 shows the result of the tipping point analysis. As shown in Table 10, the tipping analysis indicated that results were tipped from being clinically similar to not being clinically similar under the following assumptions:

- Increase by at least 85% for FYB202 and reduction by at least 85% for EU-approved Stelara,
- Reduction by at least 200% for FYB202 and increase by at least 215% for EU-approved Stelara,
- Reduction by at least 205% for FYB202 and increase by at least 210% for EU-approved Stelara,
- Reduction by at least 210% for FYB202 and increase by at least 200% for EU-approved Stelara,
- Reduction by at least 215% for FYB202 and increase by at least 190% for EU-approved Stelara.

Given the observed data at week 12, the probability of observing as large as or more extreme than 100% of the difference between FYB202 and EU-approved Stelara is almost 0. It can thus be concluded that the tipping points observed did not align with realistic scenarios based on available data, thereby supporting the robustness of the primary endpoint results.

Table 10: The percent improvement in PASI score from baseline to week 12 by tipping point analysis (FAS)

FAS, Tipping point analysis									
Shift for Stelara	**Shift for FYB202**								
	90%	85%	80%	···	-195%	-200%	-205%	-210%	-215%
-90%	**6.22 (2.19, 10.26)**	**6.15 (2.14, 10.17)**	6.09 (2.10, 10.08)						
-85%	**6.11 (2.10, 10.12)**	**6.04 (2.42, 10.03)**	2.41 (2.02, 9.94)						
-80%	6.00 (2.02, 9.98)	5.93 (1.98, 9.89)	5.87 (2.39, 9.80)						
⋮									
185%									-4.14 (-9.91, 1.64)
190%								-4.09 (-9.85, 1.66)	**-4.20 (-10.01, 1.60)**
195%							-4.05 (-9.78, 1.69)	-4.16 (-9.95, 1.63)	**-4.27 (-10.11, 1.57)**
200%						-4.00 (-9.72, 1.72)	-4.11 (-9.89, 1.66)	**-4.22 (-10.05, 1.60)**	**-4.33 (-10.21, 1.54)**
205%						-4.07 (-9.83, 1.69)	-4.18 (-9.99, 1.63)	**-4.29 (-10.15, 1.57)**	**-4.40 (-10.31, 1.51)**
210%						-4.13 (-9.93, 1.66)	**-4.25 (-10.09, 1.60)**	**-4.36 (-10.25, 1.54)**	**-4.47 (-10.42, 1.48)**
215%					-4.09 (-9.87, 1.69)	**-4.20 (-10.03, 1.63)**	**4.31 (-10.20, 1.57)**	**-4.42 (-10.36, 1.51)**	**-4.53 (-10.52, 1.45)**

Estimates and 90% CIs for the treatment difference are displayed.
Source: Reviewer's analysis

Supplemental analyses were performed using MMRM restricted to data of the PPS, on modified FAS populations (e.g., FAS with complete case analysis) or different handling of intercurrent events. Table 11 summarizes these supplemental analyses. As shown in Table 11, the supplemental analyses supported the result of the primary analysis.

Table 11: Supplemental analyses for the primary efficacy endpoint

Method	LS Mean (SE)		Difference (FYB202 - Stelara)	
	FYB202	Stelara	Mean (SE)	90% CI
(S10) MMRM [1], PPS	79.58 (2.490)	76.08 (2.451)	3.50 (2.159)	(-0.062, 7.057)
(S11) MMRM [1], FAS (complete case analysis)	79.59 (2.488)	76.16 (2.450)	3.43 (2.137)	(-0.097, 6.950)
(S14) MMRM [1], FAS (excluding all assessments following major protocol deviations)	79.55 (2.494)	76.17 (2.451)	3.37 (2.159)	(-0.189, 6.933)
(S15) ANCOVA [2], PPS	80.38 (4.259)	77.11 (4.152)	3.27 (2.170)	(-0.309, 6.846)

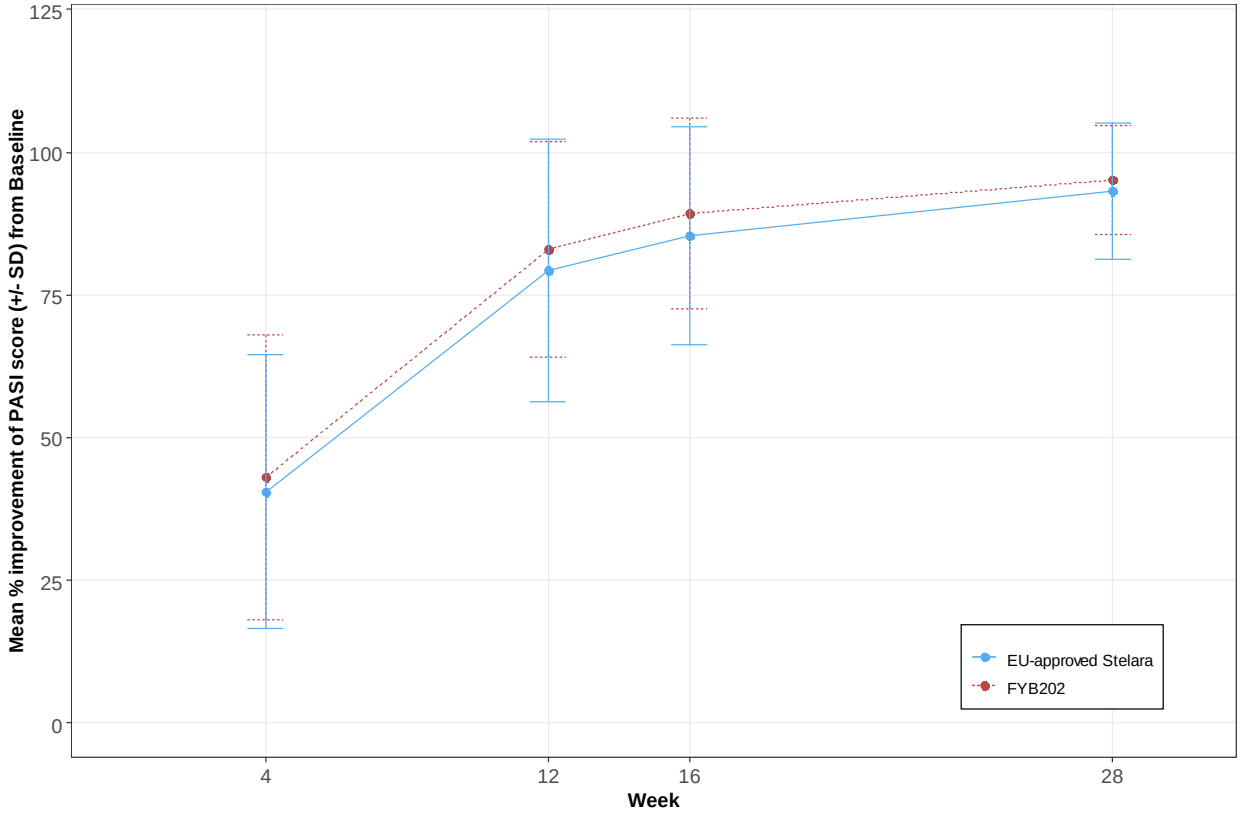
[1] Estimates are adjusted for baseline PASI score, baseline weight, time since onset of psoriasis and prior inadequate response or intolerance to a systemic biological treatment.
[2] Estimates are adjusted for baseline PASI score, baseline weight, time since onset of psoriasis and prior inadequate response or intolerance to a systemic biological treatment.
Source: Reviewer's analysis

3.2.4.2 Secondary Efficacy Endpoints

Percent improvement of PASI score

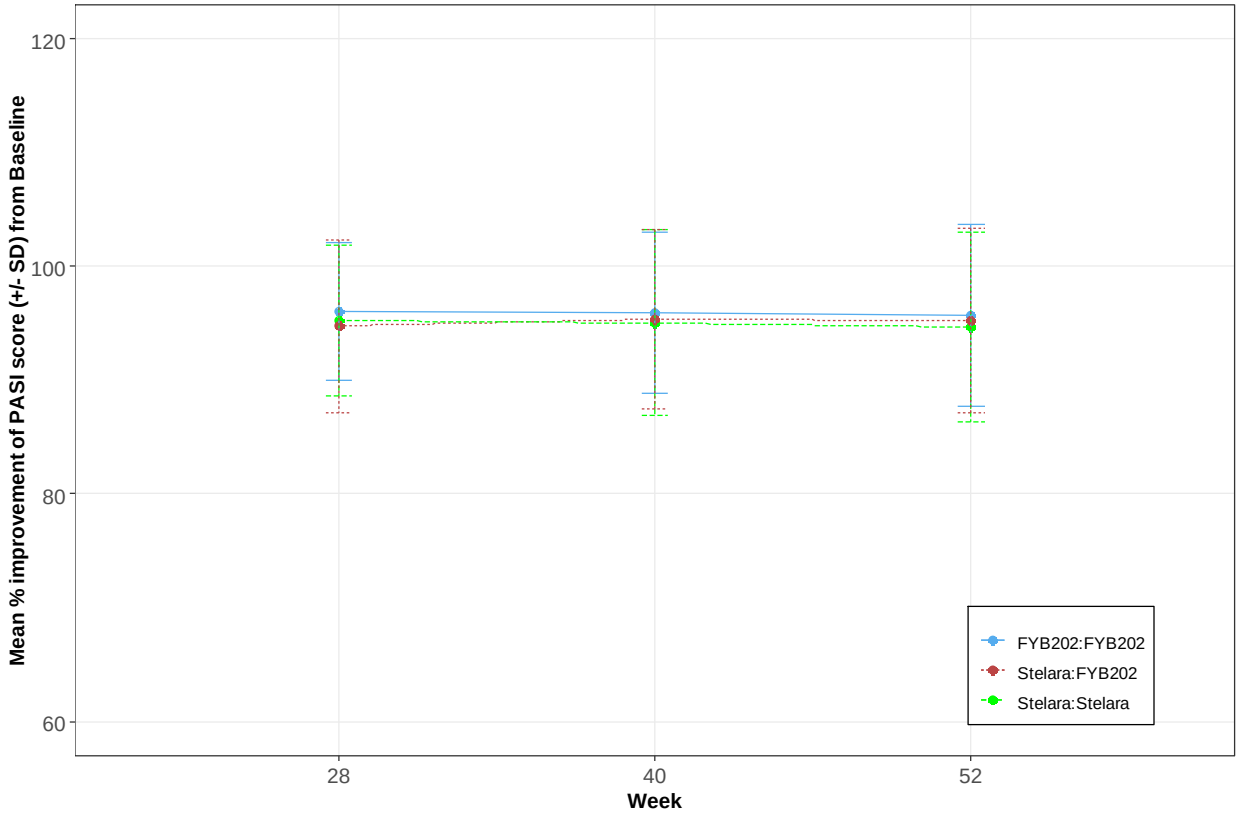
Figures 2 and 3 present the analysis results of percent improvement in PASI score from baseline over time up to week 52. Figure 2 displays the percent improvement in PASI score from baseline over time up to week 28 before rerandomization. In addition, a consistent and significant improvement emerged starting from rerandomization at week 28 in the group transitioning from EU-approved Stelara to FYB202, and very similarly in the groups keeping to their initial randomized treatment. Figure 4 shows the difference (FYB202 – EU-approved Stelara) in adjusted mean percent improvement in PASI score over time up to week 28 with 90% CIs. The two-sided 90% CIs for the differences at weeks 4, 16, and 28 were well comparable to the 90% CI for the difference seen for the primary efficacy endpoint at week 12. Also, all 90% CIs are contained within the similarity margin [-10%, 10%].

Figure 2: Percent improvement in PASI score from baseline to weeks 4, 16, and 28 (before rerandomization, FAS)



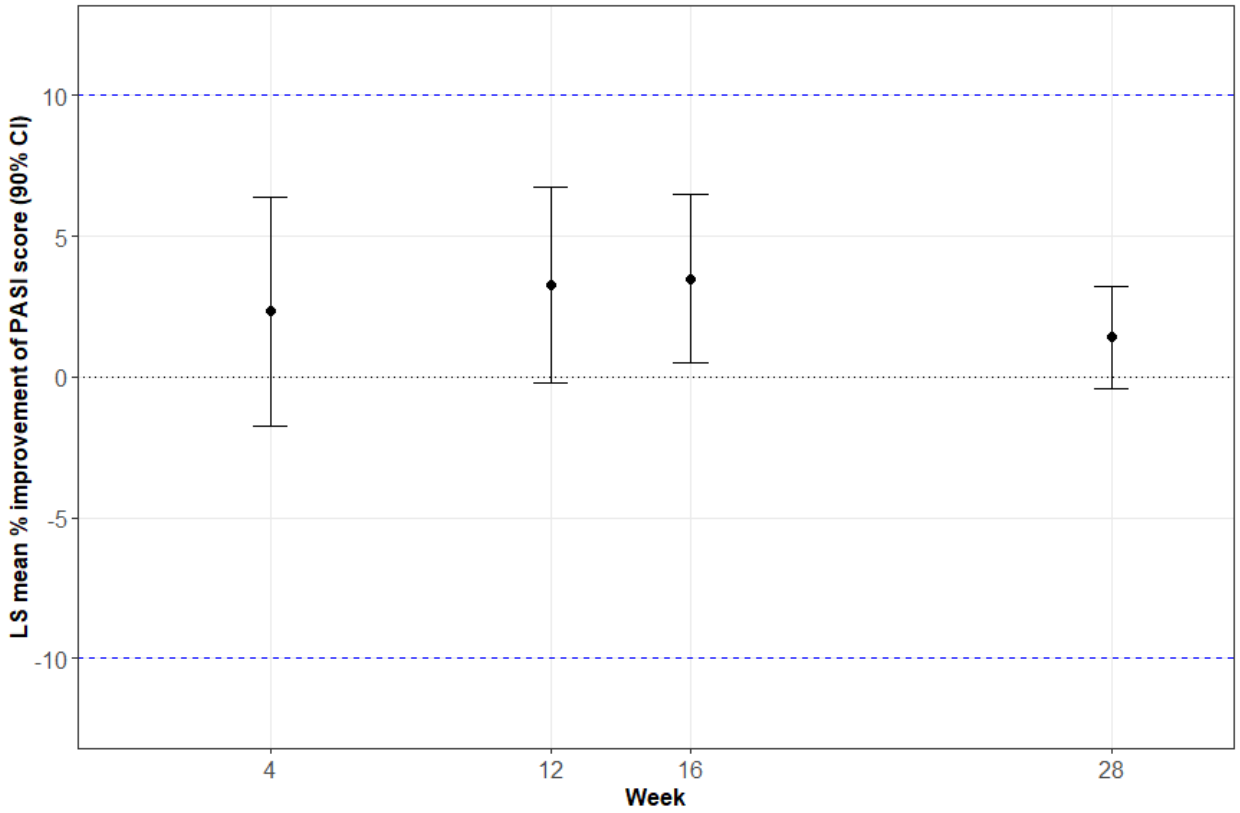
Source: Reviewer's analysis

Figure 3: Percent improvement in PASI score from baseline to weeks 28, 40, and 52 (RRAS, FAS)



Source: Reviewer's analysis

Figure 4: Plot for difference (FYB202-EU - approved Stelara) in mean percent improvement in PASI score with 90% CI over time up to week 28 (FAS)

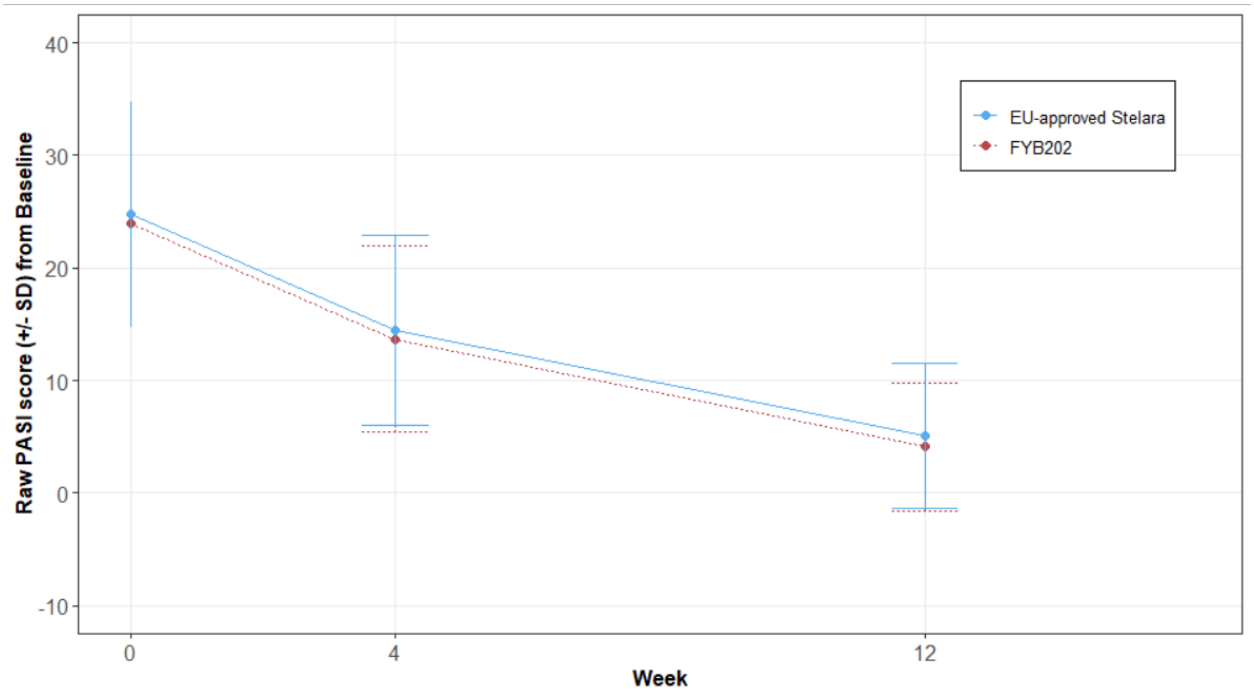


Source: Reviewer's analysis

Raw PASI scores at baseline, weeks 4 and 12

Figures 5 presents the descriptive statistics for the raw PASI scores at baseline, week 4, and week 12. As seen in Figure 5, raw PASI scores at baseline, week 4, and week 12 appear to be comparable trends in both FYB202 group and the EU-approved Stelara group in the FAS.

Figure 5: Raw PASI score from baseline to week 12 (FAS)



Source: Reviewer's analysis

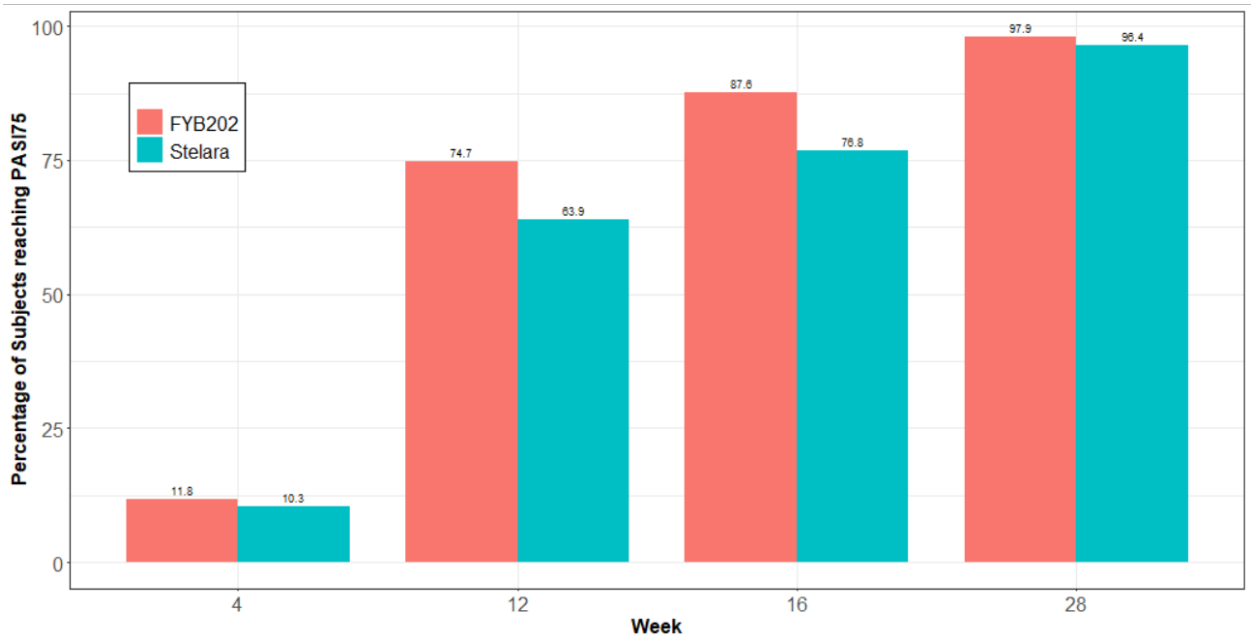
Proportion of patients with PASI 75 and PASI 90 responses at weeks 4, 12, 16, 28, 40, and 52

Figures 6 and 7 show the percentages of patients who reached an improvement in PASI score of at least 75% (PASI 75). The trends in PASI 75 response rates were consistent across both groups, showing the most significant uptick between weeks 4 and 12, with nearly all patients attaining a PASI 75 response by week 28. After rerandomization from week 28 onwards, a sustained response was evident in all three groups, indicating that the single transition did not affect the maintenance of response over time. Table 12 shows the result from the repeated measures logistic regression analysis comparing the PASI 75 response rates between FYB202 and EU-approved Stelara. The odds ratios and their corresponding confidence intervals suggest that, except for at week 16, there are no substantial differences between the two groups. At week 16, an odds ratio of 0.51 with a 95% confidence interval of (0.30, 0.88) seems to indicate a statistically significant association.

Figures 8 and 9 show the percentages of patients who reached an improvement in PASI score of at least 90% (PASI 90). As for PASI75, the PASI 90 response demonstrated a similar trend throughout the treatment duration for both FYB202 and EU-approved Stelara, with roughly 80% of patients achieving a PASI 90 response by week 28. After rerandomization from week 28 onward, PASI 90 response rates consistently exceeded 80% in the EU-Stelara to FYB202 transition group, as well as in the groups maintaining their originally assigned treatments. Table 13 shows the result from the repeated measures logistic regression analysis comparing the PASI 90 response rates between FYB202 and EU-approved Stelara. The odds ratios and their

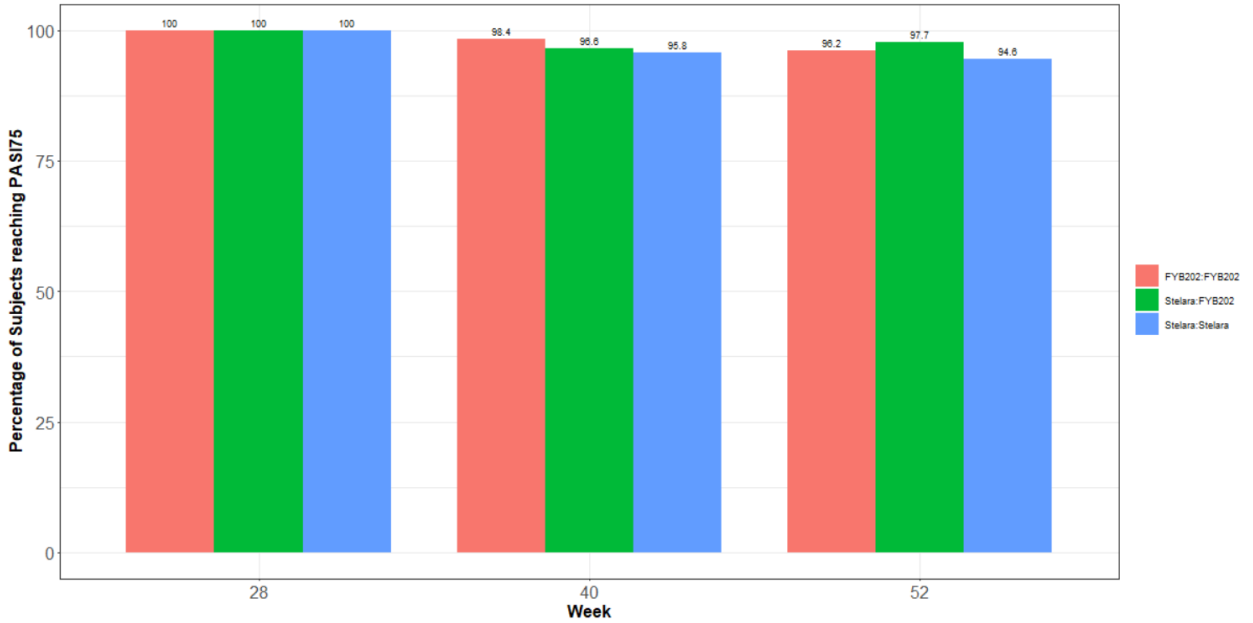
corresponding confidence intervals at weeks 12 and 28 suggest that there are no substantial differences between the two groups; however, the odds ratios and their corresponding confidence intervals at weeks 4 and 16 seems to indicate a statistically significant difference in response rates between the two groups.

Figure 6: Bar chart for the proportion of subjects reaching PASI 75 before re-randomization (FAS)



Source: Reviewer's analysis

Figure 7: Bar chart for the proportion of subjects reaching PASI 75 after re-randomization (RRAS)



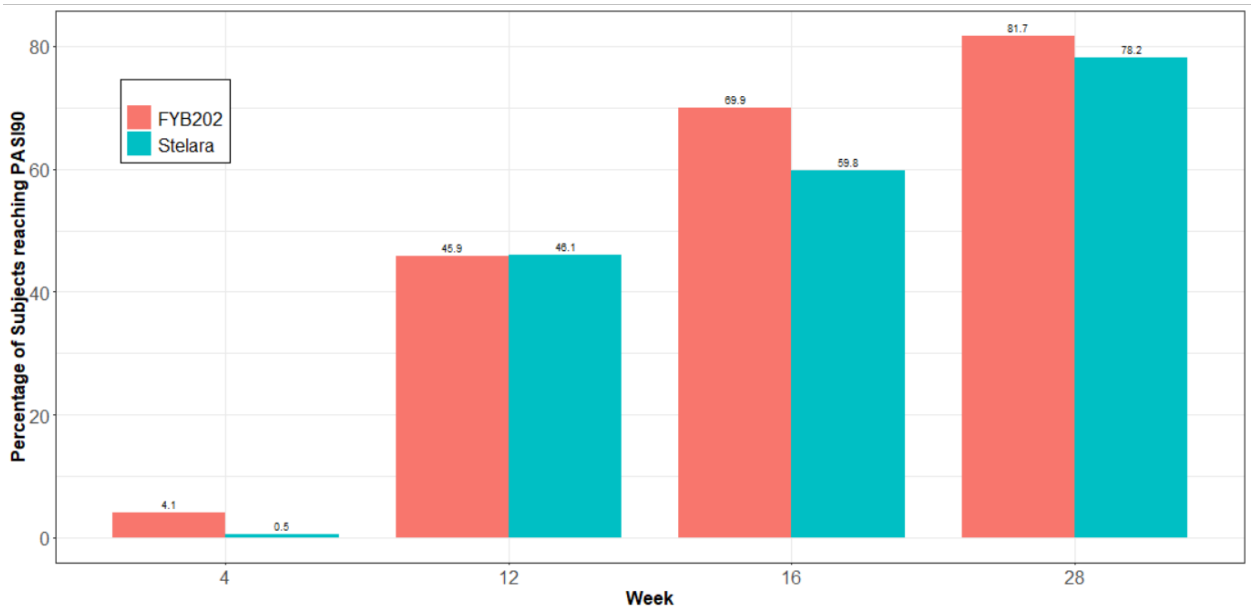
Source: Reviewer's analysis

Table 12: Comparison of FYB202 and EU-approved Stelara in PASI 75 response rates before rerandomization (FAS)

Visit week			
	FYB202	EU-approved Stelara	Odds ratio (95% CI) [1]
Week 4	0.12	0.10	0.88 (0.47, 1.66)
Week 12	0.75	0.64	0.65 (0.42, 1.01)
Week 16	0.88	0.77	0.51 (0.30, 0.88)
Week 28	0.98	0.96	0.57 (0.17, 1.95)

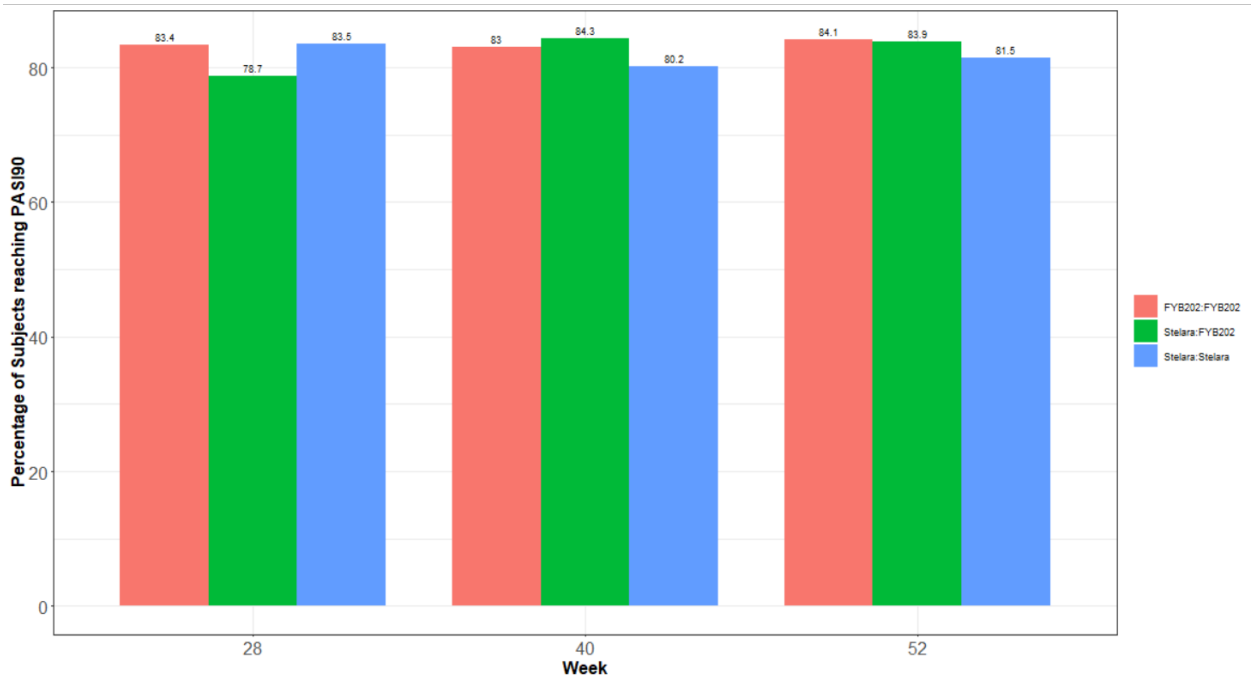
[1] Odds ratio and 95% confidence intervals are estimated from a logistic regression including baseline PASI score, baseline weight, time since onset of psoriasis and prior inadequate response or intolerance to a systemic biological treatment.
Source: Reviewer's analysis

Figure 8: Bar chart for the proportion of subjects reaching PASI 90 before re-randomization (FAS)



Source: Reviewer's analysis

Figure 9: Bar chart for the proportion of subjects reaching PASI 90 after re-randomization (RRAS)



Source: Reviewer's analysis

Table 13: Comparison of FYB202 and EU-approved Stelara in PASI 90 response rates before rerandomization (FAS)

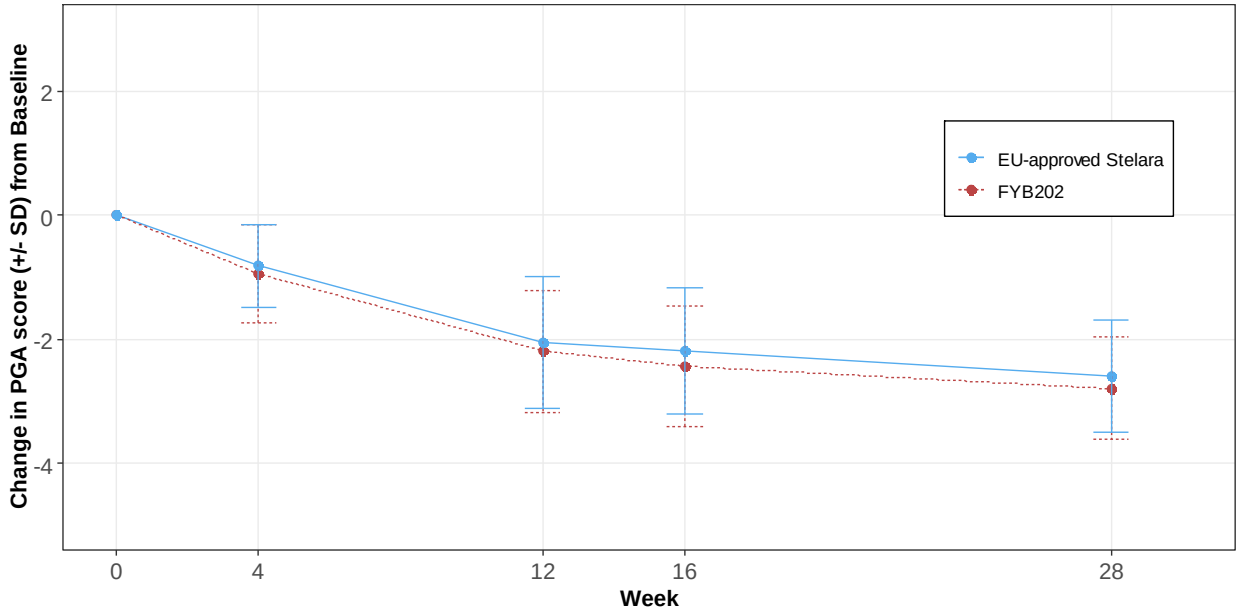
Visit week			
	FYB202	EU-approved Stelara	Odds ratio (95% CI) [1]
Week 4	0.04	0.05	0.14 (0.02, 0.99)
Week 12	0.46	0.46	1.07 (0.71, 1.62)
Week 16	0.70	0.60	0.64 (0.42, 0.99)
Week 28	0.82	0.78	0.81 (0.48, 1.35)

[1] Odds ratio and 95% confidence intervals are estimated from a logistic regression including baseline PASI score, baseline weight, time since onset of psoriasis and prior inadequate response or intolerance to a systemic biological treatment.
Source: Reviewer's analysis

Change per PGA over time

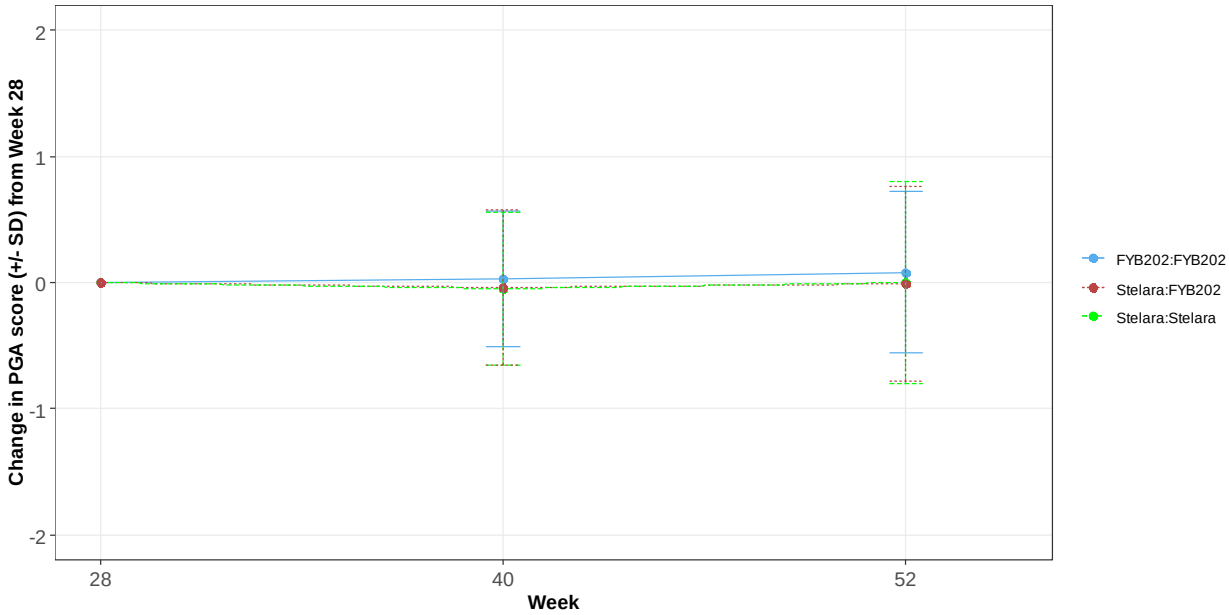
Figure 10 shows the change from baseline in PGA scores throughout at weeks 4, 12, 16, and 28. Figure 11 shows the change from week 28 to weeks 40 and 52 in PGA score after rerandomization from week 28. As seen in Figures 10 and 11, changes in PGA scores appear to be comparable trends in all groups. In Table 14, the MMRM analysis for the difference between treatment groups in PGA score change showed similar reductions from baseline to weeks 4, 12, 16, and 28.

Figure 10: Change from baseline in PGA score up to week 28 (FAS)



Source: Reviewer's analysis

Figure 11: Change from week 28 in PGA score up to week 52 (RRAS)



Source: Reviewer's analysis

Table 14: MMRM: Comparison of change from baseline in PGA score from baseline to weeks 4, 12, 16, and 28 (FAS)

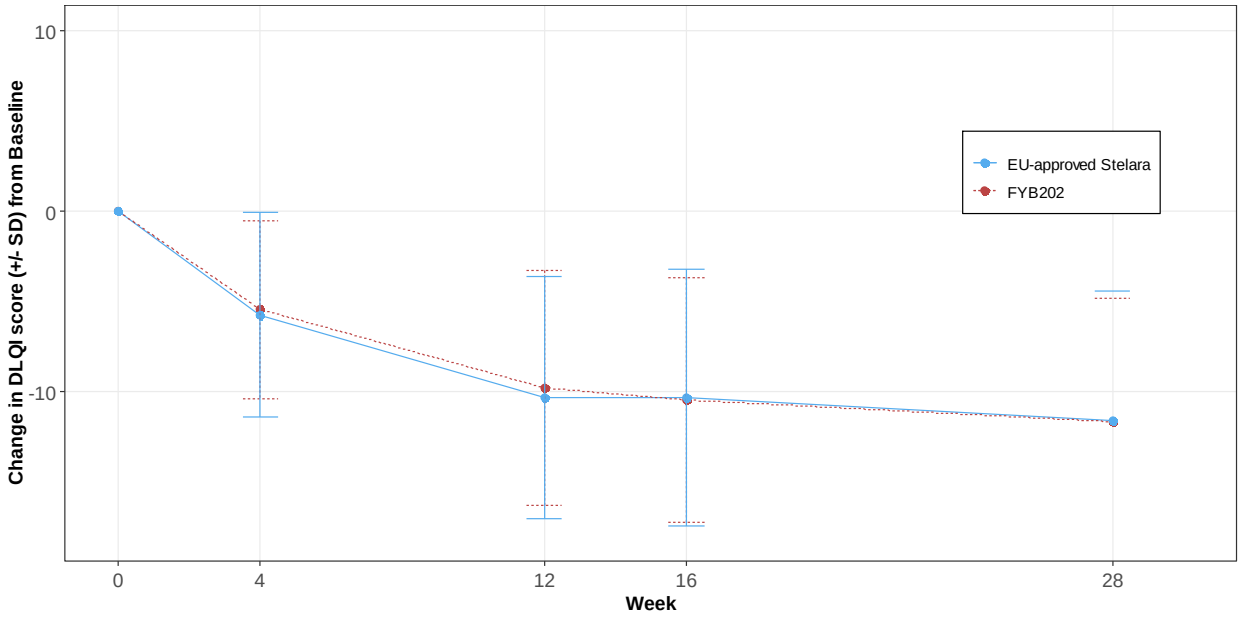
	LS Mean (SE)		Difference (FYB202 - Stelara)	
	FYB202	Stelara	Mean (SE)	95% CI
Week 4	-0.84 (0.117)	-0.76 (0.114)	-0.08 (0.071)	(-0.22, 0.06)
Week 12	-2.09 (0.125)	-1.99 (0.123)	-0.10 (0.094)	(-0.29, 0.08)
Week 16	-2.34 (0.123)	-2.13 (0.121)	-0.20 (0.090)	(-0.38, -0.03)
Week 28	-2.68 (0.119)	-2.53 (0.116)	-0.15 (0.076)	(-0.30, -0.00)

LS means calculation is based on the MMRM; Two-sided 95% confidence interval based on normal approximation.
Estimates are adjusted for baseline PASI score, baseline weight, time since onset of psoriasis and prior inadequate response or intolerance to a systemic biological treatment.
Source: Reviewer's analysis

Improvement of DLQI total score from baseline at weeks 4, 12, 16, 28, 40, and 52

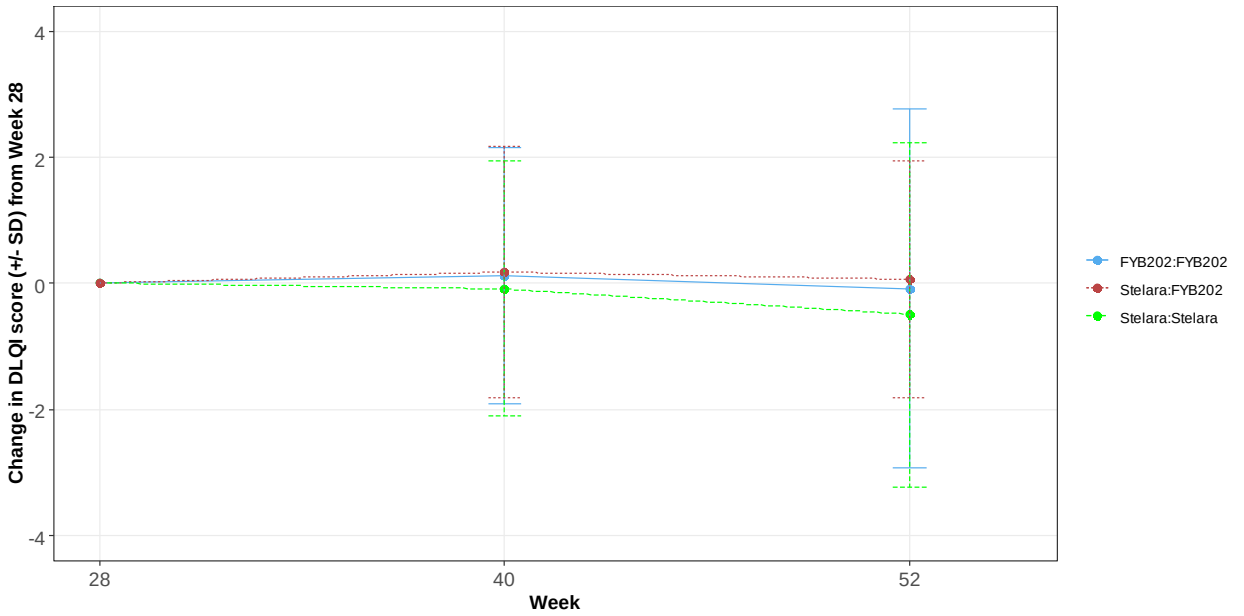
Figure 12 shows the change from baseline in DLQI scores throughout at weeks 4, 12, 16, and 28. Figure 13 shows the change from week 28 to weeks 40 and 52 in DLQI score after rerandomization from week 28. As seen in Figures 12 and 13, changes in DLQI scores appear to be comparable trends in all groups. In Table 15, the MMRM analysis for the difference between treatment groups in DLQI score change showed similar reductions from baseline to weeks 4, 12, 16, and 28.

Figure 12: Change from baseline in DLQI score up to week 28 (FAS)



Source: Reviewer's analysis

Figure 13: Change from week 28 in DLQI score up to week 52 (RRAS)



Source: Reviewer's analysis

Figure 14: Comparison of change from baseline in DLQI score from baseline to weeks 4, 12, 16, and 28 (FAS)

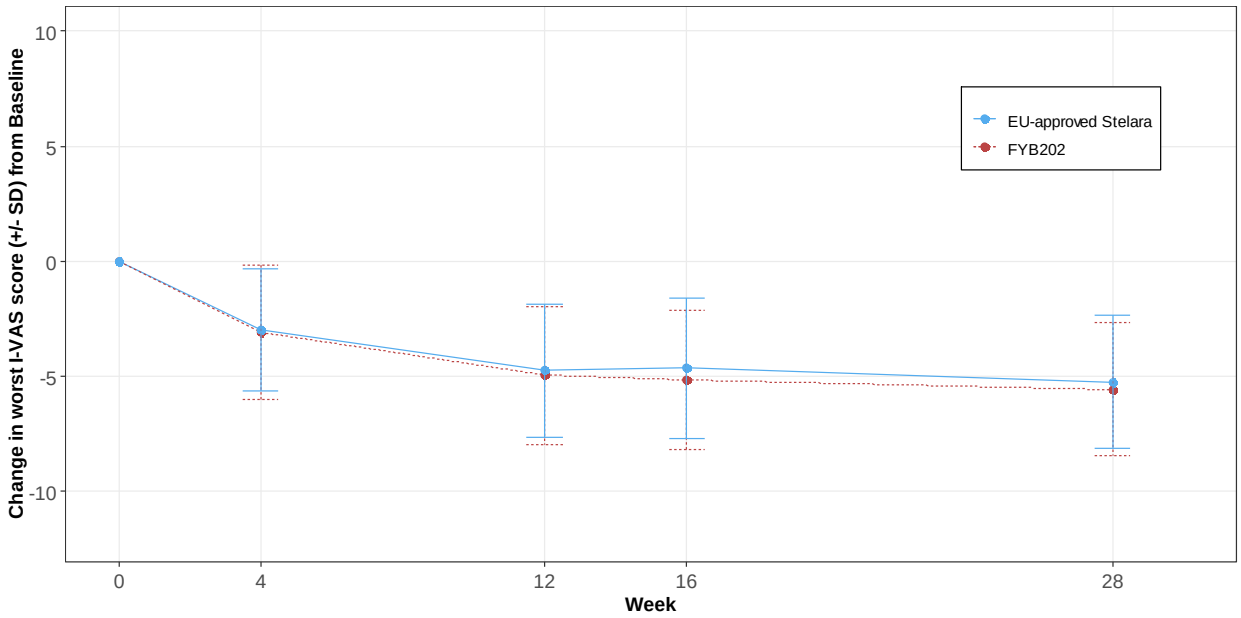
	LS Mean (SE)		Difference (FYB202 - Stelara)	
	FYB202	Stelara	Mean (SE)	95% CI
Week 4	-5.77 (0.700)	-5.73 (0.686)	-0.05 (0.484)	(-1.00, 0.91)
Week 12	-10.12 (0.681)	-10.20 (0.667)	0.07 (0.428)	(-0.77, 0.92)
Week 16	-10.75 (0.684)	-10.36 (0.669)	-0.39 (0.437)	(-1.24, 0.47)
Week 28	-11.93 (0.670)	-11.53 (0.655)	-0.40 (0.390)	(-1.16, 0.37)

LS means calculation is based on the MMRM; Two-sided 95% confidence interval based on normal approximation.
Estimates are adjusted for baseline PASI score, baseline weight, time since onset of psoriasis and prior inadequate response or intolerance to a systemic biological treatment.
Source: Reviewer's analysis

I-VAS at baseline and at weeks 4, 12, 16, 28, 40, and 52

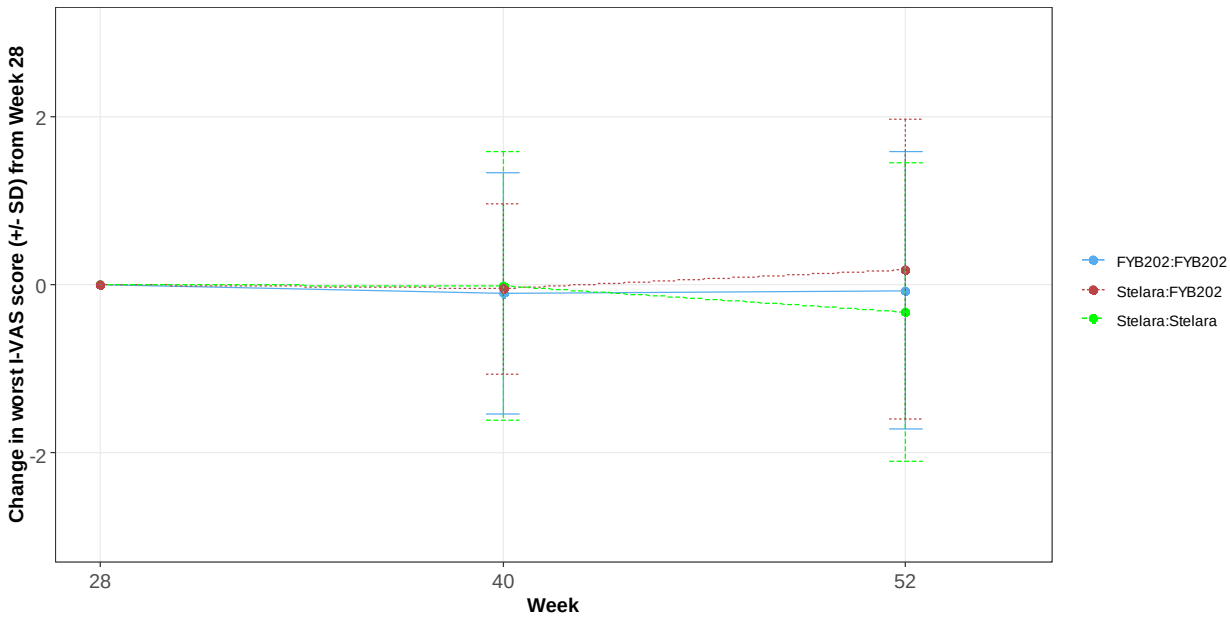
The analysis of the I-VAS is carried out separately for the average itch experience and the worst itch experience (Worst I-VAS: Figures 15 and 16, and Table 15; Average I-VAS: Figures 17 and 17, and Table 16). It appears that both worst and average I-VAS improvements were similar and substantial for both FYB202 and EU-approved Stelara.

Figure 15: Change from baseline in worst I-VAS score up to week 28 (FAS)



Source: Reviewer's analysis

Figure 16: Change from week 28 in worst I-VAS score up to week 52 (RRAS)



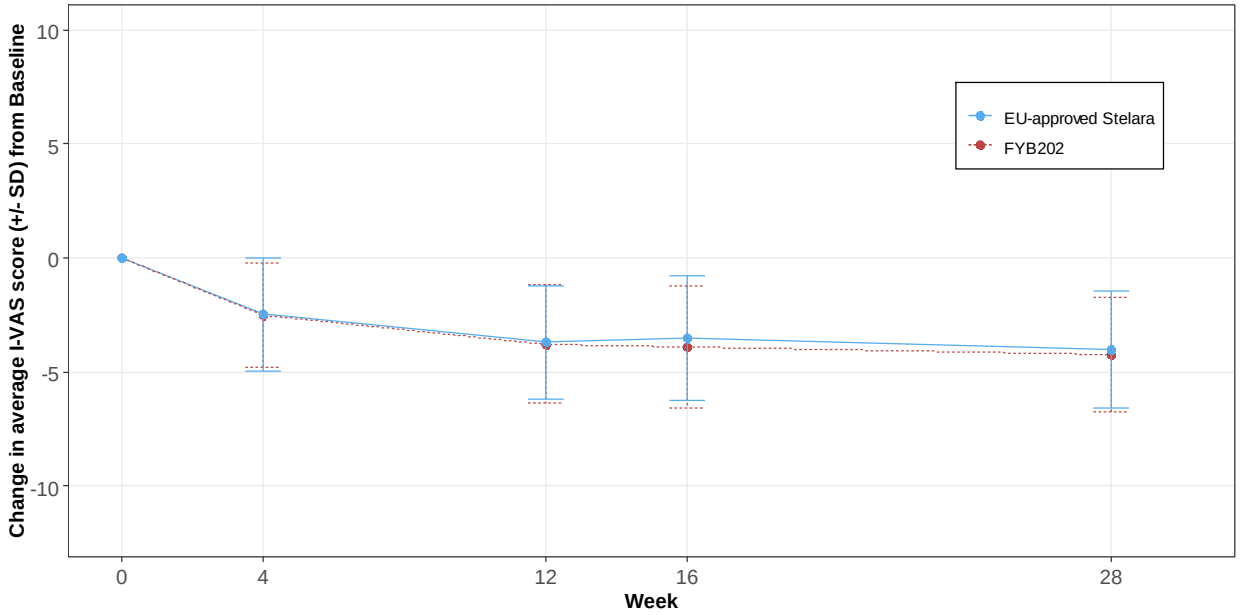
Source: Reviewer's analysis

Table 15: Comparison of change from baseline in worst I-VAS score from baseline to weeks 4, 12, 16, and 28 (VAS)

	LS Mean (SE)		Difference (FYB202 - Stelara)	
	FYB202	Stelara	Mean (SE)	95% CI
Week 4	-3.14 (0.339)	-3.18 (0.332)	0.04 (0.245)	(-0.44, 0.52)
Week 12	-5.05 (0.331)	-4.94 (0.324)	-0.11 (0.221)	(-0.55, 0.32)
Week 16	-5.21 (0.333)	-4.88 (0.326)	-0.33 (0.227)	(-0.78, 0.12)
Week 28	-5.61 (0.320)	-5.44 (0.312)	-0.17 (0.185)	(-0.54, 0.19)

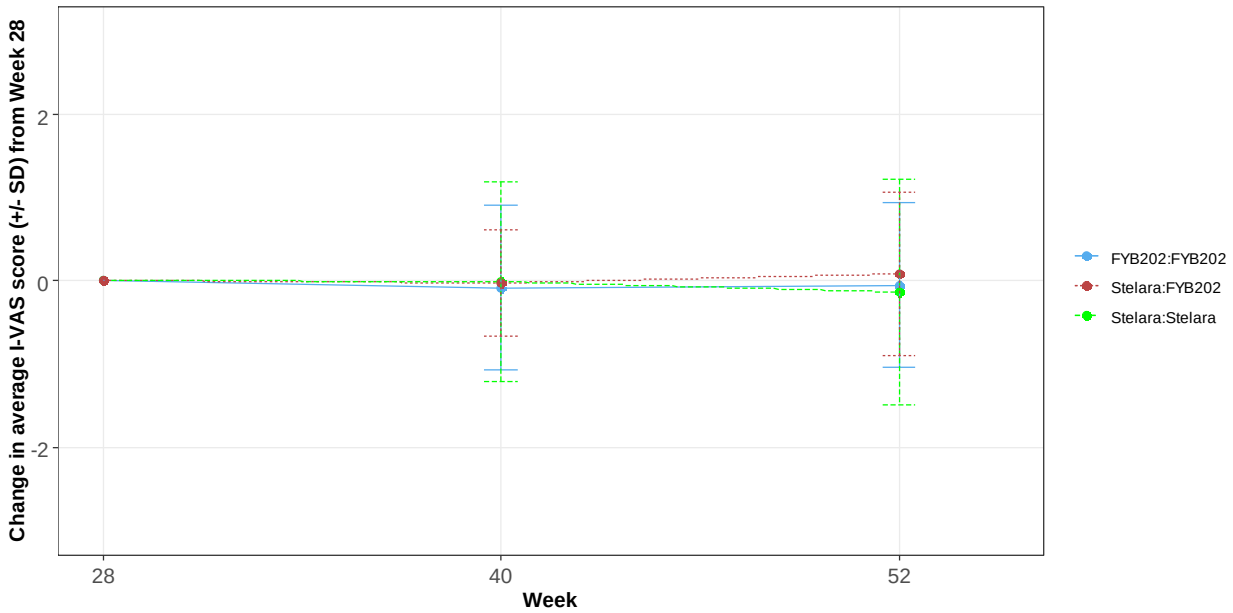
LS means calculation is based on the MMRM; Two-sided 95% confidence interval based on normal approximation.
Estimates are adjusted for baseline PASI score, baseline weight, time since onset of psoriasis and prior inadequate response or intolerance to a systemic biological treatment.
Source: Reviewer's analysis

Figure 17: Change from baseline in average I-VAS score up to week 28 (FAS)



Source: Reviewer's analysis

Figure 18: Change from week 28 in average I-VAS score up to week 52 (RRAS)



Source: Reviewer's analysis

Table 16: Comparison of change from baseline in average I-VAS score from baseline to weeks 4, 12, 16, and 28 (VAS)

	LS Mean (SE)		Difference (FYB202 - Stelara)	
	FYB202	Stelara	Mean (SE)	95% CI
Week 4	-2.50 (0.253)	-2.54 (0.248)	0.04 (0.197)	(-0.35, 0.43)
Week 12	-3.80 (0.241)	-3.75 (0.236)	-0.05 (0.165)	(-0.37, 0.28)
Week 16	-3.88 (0.248)	-3.62 (0.243)	-0.26 (0.184)	(-0.62, 0.10)
Week 28	-4.22 (0.232)	-4.08 (0.226)	-0.14 (0.134)	(-0.40, 0.13)

LS means calculation is based on the MMRM; Two-sided 95% confidence interval based on normal approximation.
Estimates are adjusted for baseline PASI score, baseline weight, time since onset of psoriasis and prior inadequate response or intolerance to a systemic biological treatment.
Source: Reviewer's analysis

3.2.4.3 Efficacy Conclusion

Study 0301 provides adequate statistical evidence to support that there is no clinically meaningful difference between FYB202 and EU-approved Stelara with respect to the percent improvement in PASI score from baseline to week 12 according to the prespecified similarity margin, [-10%, 10%]. Sensitivity and supplementary analyses also confirm the robustness of the primary analysis and support the similarity of FYB202 and EU-approved Stelara.

4 FINDINGS IN SPECIAL/SUBGROUP POPULATIONS

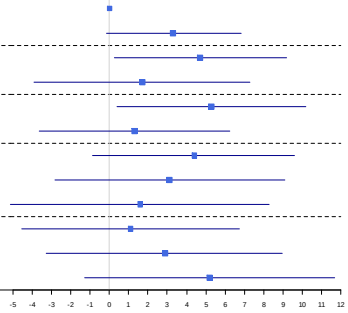
In this section, the primary efficacy endpoint is analyzed across the subgroups defined by the following factors:

- Prior inadequate response or intolerance to a systemic biological treatment (yes/no)
- Sex (male or female)
- Baseline PASI score (moderate or severe)
- Time since onset of psoriasis (≤ 10 years, > 10 years and ≤ 20 years, and ≥ 20 years)
- Baseline body weight (≤ 75 kg, > 75 kg and < 90 kg, and ≥ 90 kg).

Figure 19 shows the summary of the adjusted mean changes in the percent improvement in PASI score from baseline to week 12 by the subgroup variables. While some numerical variances noted among the subgroups, these variances were derived from relatively small number of the patients and the results did not indicate any clinically significant trend.

Figure 19: The percent improvement in PASI score from baseline to week 12 by subgroups (FAS)

Subgroup	Category	FYB202 (n, LS Mean)	EU Stelara (n, LS Mean)	LS mean diff (90% CI)
Prior inadequate response	Yes			
	No	192, 83.0	186, 79.6	3.3 (-0.15, 6.83)
Gender	Male	116, 76.6	115, 71.9	4.7 (0.27, 9.20)
	Female	78, 86.2	76, 84.5	1.7 (-3.91, 7.29)
Base PASI	Moderate	76, 83.3	76, 78.3	5.3 (0.37, 10.20)
	Severe	118, 77.3	115, 75.8	1.3 (-3.63, 6.23)
Time since psoriasis	<=10yrs	64, 87.0	57, 82.6	4.4 (-0.87, 9.61)
	>10yrs and <=20yrs	68, 79.2	79, 76.0	3.1 (-2.85, 9.12)
	>=20yrs	62, 79.3	55, 77.7	1.6 (-5.16, 8.27)
Base body weight	<=75kg	71, 87.7	56, 86.7	1.1 (-4.57, 6.74)
	>75kg and <90kg	65, 84.1	58, 81.2	2.9 (-3.27, 8.98)
	>=90kg	58, 73.6	77, 68.4	5.2 (-1.30, 11.70)



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.
Source: Reviewer's analysis

5 SUMMARY AND CONCLUSIONS

5.1 Statistical Issues

The reviewer did not identify any major statistical issues that can impact the overall conclusions.

5.2 Collective Evidence

The Applicant is seeking approval for FYB202 as a proposed biosimilar to US-licensed Stelara (Ustekinumab). Clinical similarity of FYB202 and EU-approved Stelara was evaluated in Study 0301.

The primary efficacy endpoint was the percent improvement in PASI score from baseline to week 12. The FAS was used as the primary efficacy analysis set. The adjusted mean change from baseline to week 12 was comparable between the two groups (79.51% for FYB202 and 76.24% for EU-approved Stelara). The 90% confidence interval for the mean treatment difference (FYB202 – EU-approved Stelara) was (-0.225%, 6.770%), which was contained within the pre-specified similarity margin [-10%, 10%]. Thus, the Study 0301 demonstrated the similarity of FYB202 and EU-approved Stelara for the primary efficacy endpoint.

5.3 Conclusions and Recommendations

Based on the totality of statistical evidence from the Study 0301, the reviewer concludes that the application has provided adequate statistical evidence to support the similarity of the proposed biosimilar product FYB202 and US-licensed Stelara in the primary efficacy endpoint, which is the percent improvement in PASI score from baseline to week 12.

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/s/

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05/07/2024 12:43:22 PM

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