Adv Ther
https://doi.org/10.1007/s12325-025-03138-2

ORIGINAL RESEARCH

A Randomised, Double-Blind Trial to Compare the Efficacy, Safety, and Immunogenicity of the Biosimilar Ustekinumab FYB202 with Reference Ustekinumab in Patients with Moderate-to-Severe Plaque Psoriasis

Kim Papp · Sigrid Balser · Katrin Nopora · Piotr Rewerski · Brigitte Freudensprung · Michael Trieb

Received: November 30, 2024 / Accepted: February 7, 2025

ABSTRACT

Introduction: Biosimilars allow more patients access to affordable treatment options and help reduce the financial burden on healthcare systems. This multicentre trial compared the efficacy, safety, and immunogenicity of the approved biosimilar ustekinumab FYB202 with reference ustekinumab.

Methods: Eligible patients were ≥ 18 years old with stable moderate-to-severe plaque psoriasis for ≥ 6 months and inadequate treatment response to or intolerance of ≥ 1 previous systemic treatment. Patients were randomised (1:1) to double-blind treatment with FYB202 or reference ustekinumab; patients in the reference group who achieved Psoriasis Area and Severity Index (PASI) 75 percent improvement at week 28 were re-randomised to FYB202 or reference product. The primary efficacy endpoint was percent improvement in PASI score from baseline to week 12. Therapeutic equivalence was demonstrated if, depending on the regulatory requirement with respect to the significance level, the two-sided 95% and 90% confidence intervals (CIs) were within the pre-defined equivalence intervals of ± 11% and ± 10%, respectively.

Results: A total of 392 patients were randomised to FYB202 ($n = 197$) or reference ustekinumab ($n = 195$). Baseline characteristics were well balanced between groups. Mean percent improvement in PASI score at week 12 was equivalent between FYB202 and reference ustekinumab with an estimated least-squares mean treatment difference of 3.27% and the two-sided 95% (− 0.90%, 7.44%) and 90% (− 0.22%, 6.77%) CIs fully contained within the pre-defined equivalence margins. Safety

Supplementary Information The online version contains supplementary material available at https://doi.org/10.1007/s12325-025-03138-2.

K. Papp
Alliance Clinical Trials and Probity Medical Research, Waterloo, ON, Canada

K. Papp
Division of Dermatology, Department of Medicine, University of Toronto, Toronto, ON, Canada

S. Balser (✉) · K. Nopora · B. Freudensprung · M. Trieb
Formycon AG, Fraunhoferstr. 15, 82152 Martinsried/Planegg, Germany
e-mail: sigrid.balser@formycon.com

P. Rewerski
Diamond Clinic, Krakow, Poland

Published online: 06 March 2025

and immunogenicity profiles were comparable between groups. Switching from reference product to FYB202 had no clinically relevant effect on efficacy, safety, or immunogenicity.
Conclusion: FYB202 demonstrated therapeutic equivalence to reference ustekinumab in patients with moderate-to-severe plaque psoriasis.
Trial Registration: NCT04595409; EudraCT 2019-004364-21.

Keywords: Biosimilar; Ustekinumab; Psoriasis; Randomised controlled trial; Therapeutic equivalence

Key Summary Points

Why carry out this study?

Biosimilars can increase the number of patients able to receive biologic therapies and may allow patients to be treated earlier in the disease course, thereby reducing the risk of comorbidities.

This multicentre trial in patients with moderate-to-severe plaque psoriasis was conducted to demonstrate equivalence in PASI response after 12 weeks of treatment between the biosimilar ustekinumab FYB202 and reference ustekinumab and to compare the efficacy, safety, and immunogenicity of the products over 52 weeks.

What was learned from the study?

FYB202 demonstrated therapeutic equivalence to reference ustekinumab in patients with moderate-to-severe plaque psoriasis, with comparable efficacy, safety, and immunogenicity.

Proof of therapeutic equivalence in this sensitive psoriasis population allows for extrapolation to other indications, with similar clinical performance of FYB202 and reference ustekinumab assumed across all approved indications.

INTRODUCTION

Biological therapies have improved the management of psoriasis and other inflammatory conditions, but their high cost can limit access. Biosimilars are less expensive, thereby giving an opportunity for more patients to receive treatment while at the same time reducing healthcare costs. Biosimilars of the tumour necrosis factor (TNF) inhibitors adalimumab, infliximab, and etanercept have been widely adopted over the past decade and have helped increase the number of patients benefitting from these treatments [1, 2]. Real-world studies have shown that TNF inhibitor biosimilars offer similar efficacy and safety as their reference product, both when given as a new treatment and when switching from the reference product [3–7].

Ustekinumab is an interleukin (IL)-12 and IL-23 antagonist approved for the treatment of moderate-to-severe plaque psoriasis, active psoriatic arthritis, and active inflammatory bowel disorders. Ustekinumab has been shown to be effective and well tolerated for the treatment of moderate-to-severe psoriasis [8–11], active psoriatic arthritis [12, 13], Crohn's disease [14, 15], and ulcerative colitis [16] in several clinical trials. Ustekinumab was also more effective than the TNF inhibitor etanercept in patients with moderate-to-severe plaque psoriasis [17].

Regulatory approval of biosimilars requires evidence that the molecule is similar to the reference product in terms of structure, function, pharmacokinetics, clinical efficacy, and safety. This multicentre, randomised trial compared the efficacy, safety, immunogenicity and pharmacokinetics of the biosimilar ustekinumab FYB202 with reference ustekinumab in patients with moderate-to-severe plaque psoriasis. The impact of switching from reference ustekinumab to FYB202 and the effect of longer-term treatment were also evaluated through a treatment switch at week 28 and an extended treatment period up to week 52.

METHODS

This was a randomised, double-blind, parallel-group, phase 3 study conducted between 23 September 2020 and 21 March 2022 at 27 sites in Estonia, Georgia, Poland, and Ukraine (NCT04595409; EudraCT 2019-004364-21). All patients provided written informed consent. The study was conducted in accordance with the Declaration of Helsinki, the US Investigational New Drug regulations (21 Code of Federal Regulations 312), and the International Council for Harmonisation Good Clinical Practice guidelines, and in compliance with all local or regional regulatory requirements. The study protocol was reviewed and approved by the independent ethics committee or institutional review board for each centre.

Participants

Eligible patients were ≥ 18 years old with body weight ≤ 100 kg at screening and baseline and stable moderate-to-severe plaque psoriasis for ≥ 6 months with a Psoriasis Area and Severity Index (PASI) score of ≥ 12, plaque psoriasis affecting ≥ 10% of body surface area, a Physician's Global Assessment (PGA) score of ≥ 3, and inadequate treatment response to or intolerance of ≥ 1 previous systemic treatment for psoriasis (including but not limited to ciclosporin, methotrexate, acitretin, fumaric acid esters, and psoralen with ultraviolet A light). Exclusion criteria included erythrodermic, pustular, guttate, and medication-induced psoriasis, any other skin disease or other systemic inflammatory autoimmune disorder that would interfere with evaluation of the effect of study intervention on psoriasis, concomitant psoriatic arthritis, any psoriasis treatment within 4 weeks prior to randomisation, and previous use of ≥ 2 biological treatments for psoriasis. Full eligibility criteria are listed in Supplementary Table S1.

Procedures

Patients were randomised (1:1) to double-blind treatment with biosimilar ustekinumab (FYB202, Formycon AG, Martinsried/Planegg, Germany) or EU-approved reference ustekinumab (both 45 mg by subcutaneous injection at weeks 0, 4, and 16). Dosing throughout the study was based on baseline body weight, which was below 100 kg in all patients. Patients in the reference group who achieved PASI 75 at week 28 were re-randomised to receive FYB202 or reference ustekinumab at weeks 28 and 40, while responders in the FYB202 group continued the same treatment; FYB202 responders were included in the re-randomisation procedure to maintain blinding. Patients who did not achieve a PASI 75 response at week 28 were discontinued from study intervention but were followed until the end of the study at week 52 and underwent all study-related assessments. The study design is shown in Supplementary Fig. S1.

Patients were randomly assigned to treatment groups in accordance with the randomisation schedules generated using permuted block randomisation, stratified by prior inadequate response or intolerance to systemic biological treatment in the opinion of the investigator. Patients and investigators were blinded to the study intervention assignment; as a result of the differing appearances of the two trial treatments, injections were administered by an unblinded independent study intervention administrator at each site who was not involved in any study-related assessments.

Assessments and Endpoints

Efficacy assessments were PASI, PGA, Dermatology Life Quality Index (DLQI), and Itching Visual Analogue Scale (I-VAS). PASI and PGA were assessed at all visits (screening, baseline, and weeks 4, 12, 16, 28, 40, and 52); DLQI and I-VAS were assessed at all visits except screening. Body surface area affected by psoriasis was an inclusion criterion and was also assessed at all visits but was not an efficacy endpoint. Safety assessments included adverse events, serious adverse events, vital signs, body weight, ECG, and physical examination.

The incidence of antidrug antibodies (ADAs) was assessed using a highly sensitive and

drug-tolerant validated electrochemiluminescence immunoassay method (sensitivity of 4.0 ng/mL with a drug tolerance of 25 µg/mL at the low positive control level of 13.6 ng/mL). A competitive ligand-binding enzyme-linked immunosorbent assay was used to assess neutralising antibodies (NAbs) (sensitivity 458 ng/mL; drug tolerance 6 µg/mL at the low positive control level of 873 ng/mL).

Predose serum concentrations of FYB202 and reference ustekinumab were measured at baseline and at weeks 4, 12, 16, 28, 40, and 52. Serum concentrations were quantified using a validated enzyme-linked immunosorbent assay in a central clinical laboratory.

Statistical Analysis

The primary efficacy endpoint was percent improvement in PASI score from baseline to week 12. Percent improvement in PASI score was chosen as the primary endpoint as it is more sensitive than categorical endpoints such as PASI 75 and PASI 90 for the assessment of equivalence. A sample size of 392 patients was planned, with approximately 196 patients in each treatment group in order to reach 90% power, using the two one-sided test procedures for testing for equivalence, assuming no difference between both treatment groups and a common standard deviation of 30%.

A mixed model repeated measures (MMRM) was used for the analyses of the primary efficacy endpoint. The MMRM was adjusted for baseline PASI score, baseline body weight, time since onset of psoriasis, and prior inadequate response or intolerance to a systemic biological treatment as independent variables.

Two different analyses were planned in order to comply with the different regulatory requirements of the European Medicines Agency (EU-specific analysis) and the US Food and Drug Administration (US-specific analysis). The difference in least-square (LS) means (FYB202—reference ustekinumab) was estimated from the MMRM for the percent improvement in PASI score from baseline to week 12, with a two-sided 95% confidence interval (CI) for the EU-specific analysis and a two-sided 90% CI for the US-specific analysis. If the two-sided 95% CI was completely contained in the interval (– 11%; 11%), equivalence of FYB202 and reference ustekinumab could be concluded in terms of the EU-specific primary efficacy analysis. If the two-sided 90% CI was completely contained in the interval (– 10%; 10%), equivalence of FYB202 and reference ustekinumab could be concluded in terms of the US-specific primary efficacy analysis. A hierarchical testing procedure was followed for the EU- and US-specific analyses with equivalence using the US-specific analysis performed only if equivalence for the EU-specific analysis could be shown. Various supportive sensitivity analyses and supplemental estimands for the primary efficacy endpoint were pre-planned and are described in Supplementary Table S2. Subgroup analyses of the primary efficacy endpoint analysis based on sex, baseline body weight, duration of psoriasis, prior response to biological therapy, and baseline PASI were also pre-planned and performed if the subgroup size allowed the calculation of meaningful CIs. A post hoc subgroup analysis based on ADA status until week 28 was also performed.

Secondary efficacy endpoints were percent improvement in PASI score from baseline to weeks 4, 16, 28, 40, and 52; absolute PASI scores at baseline and weeks 4 and 12; the proportion of patients with PASI 75 and PASI 90 responses at weeks 4, 12, 16, 28, 40, and 52; changes in PASI 75 and PASI 90 response from week 28 through to week 52 in patients switching from reference ustekinumab to FYB202; and changes in PGA, DLQI total score and I-VAS at weeks 4, 12, 16, 28, 40, and 52.

Secondary immunogenicity endpoints were the number of patients with antibodies to ustekinumab at baseline and weeks 4, 12, 16, 28, 40, and 52 and change in the number of patients with antibodies to ustekinumab from week 28 through week 52 following the switch from reference ustekinumab to FYB202. Secondary pharmacokinetic endpoints were serum trough levels of ustekinumab (C_{trough}) at weeks 4, 12, 16, 28, 40, and 52 and change in ustekinumab C_{trough} from week 28 through week 52 in patients following the switch from reference ustekinumab to FYB202.

Secondary endpoints were also assessed using MMRM. The two-sided 95% CIs for the differences between the treatment groups were not compared to any pre-defined equivalence margin.

The full analysis and safety analysis sets included all patients randomised who received study treatment at least once; in the full analysis set, patients were analysed according to the study treatment to which randomised, whereas in the safety analysis set patients were analysed according to study treatment received at week 0 and/or 28. The re-randomised analysis set included all patients who were re-randomised and treated with study treatment at least once at or after week 28, with patients analysed according to the study treatment received. The periods from week 0 until re-randomisation at week 28 and from week 28 until end-of-study were analysed separately.

RESULTS

A total of 507 patients were screened, of whom 392 were randomised to FYB202 ($n = 197$) or reference ustekinumab ($n = 195$); 387 patients completed the study to week 28. Twelve patients were not re-randomised; nine patients were non-responders (FYB202, $n = 4$; reference ustekinumab, $n = 5$) and a further three patients in the reference ustekinumab group were not re-randomised because of adverse events leading to study discontinuation ($n = 2$) or non-attendance at the week 28 visit ($n = 1$). In the FYB202 group, 189 patients continued treatment to week 52 and 186 in the reference group were re-randomised (FYB202, $n = 89$; reference ustekinumab, $n = 97$). Following re-randomisation, the study was completed to week 52 by 372 patients: 187 patients who remained on FYB202, 97 patients who remained on reference ustekinumab, and 88 patients who switched from reference ustekinumab to FYB202. Patient disposition is shown in Fig. 1.

Baseline demographics and clinical characteristics were well balanced between treatment groups; overall, 40% of patients were female, mean age was 42 years, mean BMI was 27 kg/m^2, and mean PASI score was 24.4 (Table 1). Median time since onset of psoriasis was 14.1 years (range 1.1–51.1) and 76 (19.4%) patients reported prior systemic biological treatment for psoriasis, with only seven (9.2%) of these reporting an inadequate response or intolerance. Patients with concomitant psoriatic arthritis at screening or baseline were excluded.

Efficacy

For the primary endpoint, the estimated mean percent improvement in PASI score from baseline to week 12 was 79.5% (95% CI 74.6%, 84.4%) in patients treated with FYB202 and 76.2% (95% CI 71.5%, 81.0%) in patients treated with reference ustekinumab (Fig. 2). The estimated least-squares mean treatment difference was 3.27%, and the two-sided 95% CI (−0.90%, 7.44%) was fully contained within the pre-defined (−11%; 11%) equivalence margins, and the 90% CI (−0.22%, 6.77%) fully contained within the pre-defined (−10%; 10%) equivalence margins, confirming therapeutic equivalence between FYB202 and reference ustekinumab for the EU and US analyses, respectively.

All sensitivity and supplemental analyses for the primary endpoint supported the primary analysis, with similar treatment differences for the percent improvement in PASI score between FYB202 and reference ustekinumab and the 95% CI and 90% CI fully contained within the respective equivalence margins (Supplementary Table S3). Subgroup analyses based on sex, baseline body weight, duration of psoriasis, prior response to biologic, baseline PASI and ADA status until week 28 also supported the primary analysis (Supplementary Fig. S2).

All secondary efficacy endpoints were also similar between treatment groups. Percentages of patients reaching PASI 75 and PASI 90 at week 28 were similar, with PASI 75 achieved by 97.9% and 96.4% and PASI 90 achieved by 81.7% and 78.2% in the FYB202 and reference ustekinumab groups, respectively

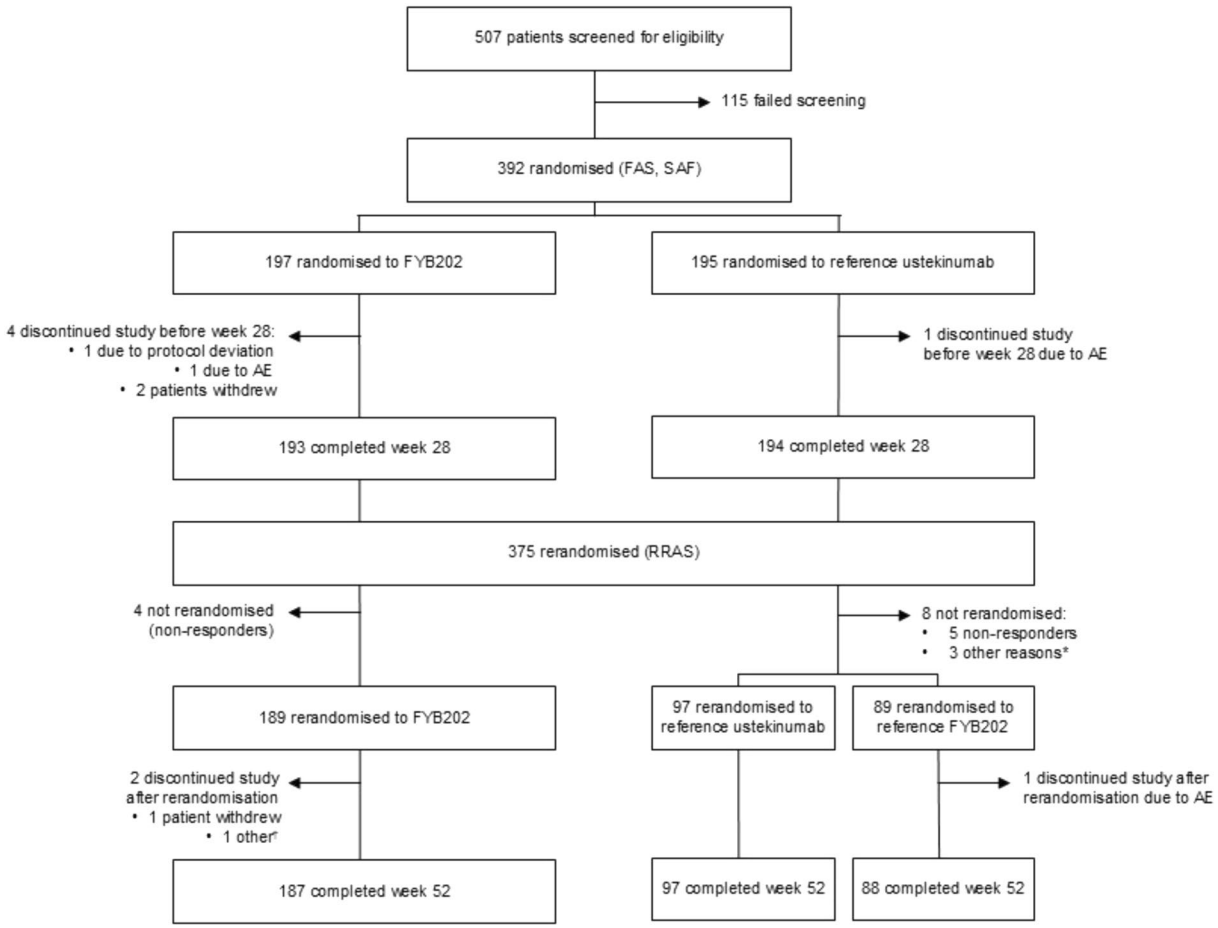

Fig. 1 Study disposition. *Other reasons were AE ($n=2$) or unable to attend week 52 visit ($n=1$). †Patient was unable to attend week 52 visit within time limit set by sponsor. *AE* adverse event, *FAS* full analysis set, *RRAS* re-randomised set, *SAF* safety analysis set

(Fig. 3). Improvements in PGA, I-VAS, and health-related quality-of-life as measured by DLQI were also similar between groups. Other secondary efficacy endpoints are summarised in Table 2 and Supplementary Fig. S3. Absolute decrease in percentage body surface area affected by psoriasis was similar at all time points in both groups (Supplementary Fig. S4).

Switching from reference ustekinumab to FYB202 had no impact on therapeutic efficacy. A total of 85 (97.7%) patients in the switch group maintained their PASI 75 response at week 52. There were also no differences between the groups that maintained their initial treatment for the entire 52 weeks, with a PASI 75 response maintained at week 52 by 173 (96.2%) patients in the FYB202 group and 87 (94.6%) patients in the reference ustekinumab group. A similar pattern was seen with other efficacy assessments.

Safety

Both treatments were well tolerated and the safety profiles were comparable between groups, with 39.6% of patients in the FYB202 group and 41.0% in the reference group reporting at least one adverse event during the first 28 weeks. The most frequently reported adverse events before re-randomisation were injection site pain, which was reported in 11.2% of patients in the FYB202

Table 1 Baseline demographics and clinical characteristics

	FYB202 (*n* = 197)	Reference ustekinumab (*n* = 195)
Female, *n* (%)	80 (40.6%)	78 (40.0%)
Age (years), mean ± SD[a]	41.3 ± 12.9	42.1 ± 13.2
Race: white	197 (100%)	195 (100%)
Body weight (kg), mean ± SD[a]	79.8 (13.9)	82.6 ± 13.3
Body mass index (kg/m^2), mean ± SD[a]	26.6 ± 4.2	27.4 ± 4.4
Concurrent illnesses[b]		
Obesity	12 (6.1%)	15 (7.7%)
Hypertension	28 (14.2%)	30 (15.4%)
Duration of psoriasis (years), mean ± SD, median (range)	16.5 ± 10.9, 15.1 (1.1–47.1)	15.9 ± 10.1, 13.1 (1.3–51.1)
Previous psoriasis therapies, *n* (%)[c]		
Corticosteroids, plain	129 (65.5%)	137 (70.3%)
Corticosteroids, other combinations	72 (36.5%)	67 (34.4%)
Topical anti-psoriasis drugs	78 (39.6%)	82 (42.1%)
Systemic anti-psoriasis drugs	53 (26.9%)	35 (17.9%)
Immunosuppressants	145 (74.1%)	141 (72.3%)
Previous biologic therapy for psoriasis, *n* (%)	40 (20.3%)	36 (18.5%)
Number of previous biologic therapies		
1	36 (18.3%)	31 (15.9%)
2	4 (2.0%)	5 (2.6%)
Inadequate response or intolerance	2 (5.0%)	5 (13.9%)
PASI, mean ± SD, median (range)	24.1 ± 8.5, 21.6 (12.3–52.8)	24.8 ± 10.0, 21.8 (12.0–63.3)
BSA affected (%), mean ± SD, median (range)	29.4 ± 16.0, 24 (10–77)	30.4 ± 17.3, 25 (11–92)
PGA, *n* (%)		
3 (moderate)	133 (67.5%)	139 (71.3%)
4 (severe)	64 (32.5%)	56 (28.7%)
Worst I-VAS, mean ± SD	6.3 ± 2.5	6.2 ± 2.6
Average I-VAS, mean ± SD	4.7 ± 2.4	4.6 ± 2.6
DLQI, mean ± SD	13.1 ± 6.4	13.6 ± 6.5

BSA body surface area, *DLQI* Dermatology Life Quality Index, *I-VAS* Itching Visual Analogue Scale, *PASI* Psoriasis Area and Severity Index, *PGA* Physician's Global Assessment, *SD* standard deviation

[a]At screening

[b]Up to and including week 28 (in ≥ 5% in either group)

[c]Anatomical Therapeutic Chemical classification, WHO-DD Version March 2021

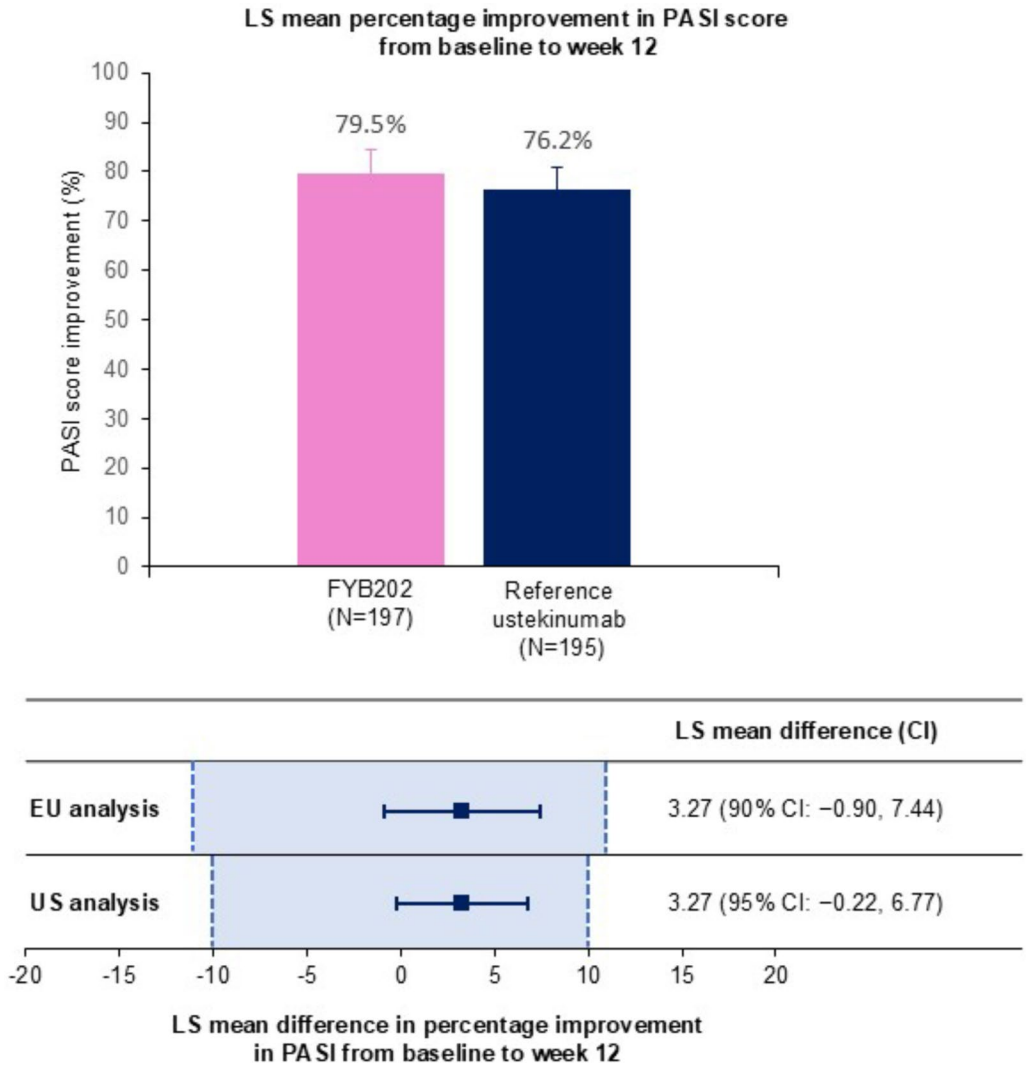

Fig. 2 Primary efficacy endpoint: Mean percentage improvement in PASI score (full analysis set). PASI score was analysed using an MMRM that adjusted for baseline PASI score, baseline weight, time since onset of psoriasis, and prior inadequate response or intolerance to a systemic biological treatment as independent variables. For the calculation of LS means based on the MMRM, patients with missing assessments at all post-baseline visits until week 28 were not considered. For the EU analysis, FYB202 and reference ustekinumab were considered equivalent if the CI for difference in LS means was completely contained in the interval [− 11%, 11%]. For the US analysis, FYB202 and reference ustekinumab were considered equivalent if the CI for difference in LS means was completely contained in the interval [− 10%, 10%]. *CI* confidence interval, *LS* least squares, *MMRM* mixed model repeated measures, *PASI* Psoriasis Area and Severity Index

group and 7.7% in the reference ustekinumab group, nasopharyngitis (FYB202, 4.6%; reference ustekinumab, 2.6%), and COVID-19 (FYB202, 3.6%; reference ustekinumab, 2.6%). All injection site pain events were mild in severity and, overall, most adverse events were of mild or moderate severity with a similar pattern in both treatment groups (Table 3).

Four serious adverse events were reported in three (1.5%) patients treated with FYB202 (one patient with COVID-19 pneumonia and pulmonary embolism, one with COVID-19,

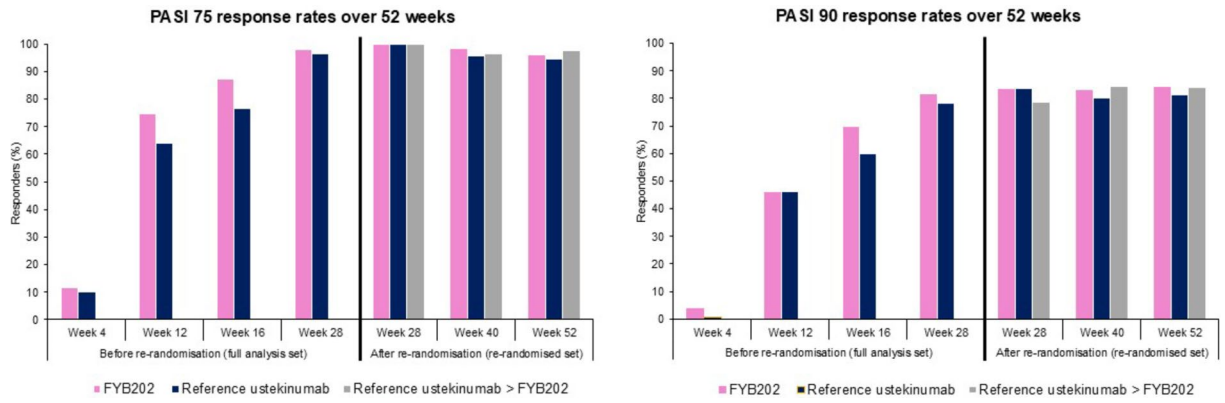

Fig. 3 Proportions of patients with PASI 75 and PASI 90 responses over 52 weeks. *PASI* Psoriasis Area and Severity Index

Table 2 Other secondary efficacy endpoints

	FYB202 ($n = 197$)	Reference ustekinumab ($n = 195$)	FYB202—reference ustekinumab	
	LS mean ± SE change from baseline		LS mean ± SE treatment difference	95% CI
Change in percent PASI				
At week 4	39.6 ± 2.64	37.3 ± 2.60	2.33 ± 2.47	(− 2.54, 7.20)
At week 16	85.7 ± 2.35	82.2 ± 2.31	3.50 ± 1.81	(− 0.06, 7.05)
At week 28	91.5 ± 2.12	90.1 ± 2.07	1.40 ± 1.09	(− 0.74, 3.54)
Change in PGA				
At week 12	− 2.09 ± 0.12	1.99 ± 0.12	− 0.10 ± 0.09	(− 0.29, 0.08)
At week 28	− 2.68 ± 0.12	− 2.53 ± 0.12	− 0.15 ± 0.08	(− 0.30, − 0.00)
Change in worst I-VAS				
At week 12	− 5.05 ± 0.33	− 4.94 ± 0.32	− 0.11 ± 0.22	(− 0.55, 0.32)
At week 28	− 5.61 ± 0.32	− 5.44 ± 0.31	− 0.17 ± 0.19	(− 0.54, 0.19)
Change in average I-VAS				
At week 12	− 3.80 ± 0.24	− 3.75 ± 0.24	− 0.05 ± 0.16	(− 0.37, 0.28)
At week 28	− 4.22 ± 0.23	− 4.08 ± 0.23	− 0.14 ± 0.13	(− 0.40, 0.12)
Change in DLQI				
At week 12	− 10.1 ± 0.68	− 10.2 ± 0.67	0.07 ± 0.43	(− 0.77, 0.92)
At week 28	− 11.9 ± 0.67	− 11.5 ± 0.66	− 0.40 ± 0.39	(− 1.16, 0.37)

CI confidence interval, *DLQI* Dermatology Life Quality Index, *I-VAS* Itching Visual Analogue Scale, *PASI* Psoriasis Area and Severity Index, *PGA* Physician's Global Assessment, *SE* standard error

Table 3 Adverse events

	Before re-randomisation, weeks 0–28 (safety analysis set)		After re-randomisation, weeks 28–52 (re-randomised set)		
	FYB202 ($n = 197$)	Reference ustekinumab ($n = 195$)	FYB202 ($n = 189$)	Reference ustekinumab ($n = 97$)	FYB202 after switch from reference ustekinumab ($n = 89$)
	n (%), *E*	*n* (%), *E*	*n* (%), *E*	*n* (%), *E*	*n* (%), *E*
Any AE	78 (39.6%), 133	80 (41.0%), 141	33 (17.5%), 44	16 (16.5%), 33	18 (20.2%), 32
Treatment-related AE	32 (16.2%), 48	26 (13.3%), 32	2 (1.1%), 2	0	2 (2.2%), 3
Serious AE	3 (1.5%), 4	3 (1.5%), 6	3 (1.6%), 3	1 (1.0%), 1	1 (1.1%), 1
Serious treatment-related AE	0	0	0	0	0
AE leading to treatment discontinuation	2 (1.0%), 4	3 (1.5%), 6	0	0	1 (1.1%), 1
Deaths	0	0	0	0	0
Most frequent AEs[a]					
Injection site pain	22 (11.2%), 32	15 (7.7%), 18	1 (0.5%), 1	0	1 (1.1%), 1
Nasopharyngitis	9 (4.6%), 9	5 (2.6%), 6	6 (3.2%), 8	2 (2.1%), 3	3 (3.4%), 3
COVID-19	7 (3.6%), 7	5 (2.6%), 5	13 (6.9%), 13	6 (6.2%), 6	5 (5.6%), 5
Upper respiratory tract infection	2 (1.0%), 2	2 (1.0%), 3	3 (1.6%), 3	4 (4.1%), 4	2 (2.2%), 2

AE adverse event, *COVID* corona virus disease, *E* event, *n* number of patients

[a] ≥ 3 patients in any group either before or after randomisation

and one with a spontaneous pneumothorax) and six were reported in three (1.5%) patients treated with reference ustekinumab (one patient with acute pancreatitis, bile duct stone, and cholelithiasis, one in a road traffic accident with multiple injuries, and one with metastatic renal cancer). None of these were considered by the investigator to be related to study treatment. No deaths occurred during the study. Adverse events leading to study withdrawal occurred in two (1.0%) patients treated with FYB202 and three (1.5%) patients treated with reference ustekinumab.

After re-randomisation, the proportions of patients reporting adverse events were similar in the three treatment groups. Three (1.6%) patients in the FYB202 group, one (1.0%) patient in the reference ustekinumab group, and one (1.1%) patient in the reference ustekinumab to FYB202 switch group reported serious adverse events. One (1.1%) patient in the reference ustekinumab to FYB202 switch group discontinued because of an adverse event (congenital anomaly).

Vital signs, body weight, ECG, and physical examination were similar in both treatment groups.

Immunogenicity

At baseline, there were 10 (5.1%) patients in the FYB202 group and none in the reference ustekinumab group with confirmed positive ADA tests; the geometric mean (CV) titer was 108.8 (69.5) in the positive samples. In seven (3.6%) patients, ADAs were NAbs.

ADA prevalence from week 4 to week 52 was lower for FYB202 compared with reference ustekinumab with the maximum proportion of patients with ADAs observed at week 28 in both groups (Supplementary Fig. S5). Geometric mean ADA titers were low (< 300) and comparable for FYB202 and reference ustekinumab. The proportions of patients with NAbs were similar in both treatment groups, with the maximum proportion observed at week 28 for both treatments (FYB202, 7.3%; reference ustekinumab, 9.4%).

After re-randomisation, ADA and NAb positivity declined in all three groups, with similar proportions of patients with ADAs, similar geometric mean (CV) titers and proportions of patients with reactive NAbs were observed in all three groups. No patients who were ADA-negative at week 28 became ADA-positive following the switch from reference ustekinumab to FYB202, indicating that switching from reference ustekinumab to FYB202 had no impact on immunogenicity.

Mean percent improvement in PASI score from baseline to week 12 was slightly lower in ADA-positive patients compared with ADA-negative patients with a similar reduction in both treatment groups (Supplementary Fig. S6). The two-sided CIs for the MMRM least-squares estimation did not indicate any statistically significant differences between FYB202 and reference ustekinumab for either the ADA-negative (3.2, 95% CI − 1.1, 7.6) or ADA-positive (− 4.7; 95% CI − 17.4, 8.0) subgroups, supporting that the lower ADA prevalence seen at week 12 for FYB202 compared to reference ustekinumab had no impact on the overall equivalence in the primary efficacy endpoint.

Pharmacokinetics

Higher geometric mean C_{trough} levels for patients treated with FYB202 compared to patients treated with reference ustekinumab were observed, especially at early timepoints (weeks 4 and 12), which may be due to the differences in ADA incidences at the early timepoints as well some differences in the protein content. C_{trough} levels were low and comparable at steady state from week 16 onwards (Supplementary Fig. S6). The serum C_{trough} levels of ustekinumab showed a high interpatient variability particularly at weeks 4 and 12. Smaller interpatient variability was observed during steady state at weeks 16, 28, 40, and 52. Similar and stable C_{trough} levels from week 16 to week 52 were observed in all three re-randomised groups from week 28 to week 52.

DISCUSSION

FYB202 was shown to be equivalent to reference ustekinumab with the mean percent improvement in PASI score from baseline to week 12 within the predefined equivalence intervals for both the EU- and US-specific analyses. Extensive sensitivity, supplemental, and subgroup analyses supported the primary analysis. Similarity between FYB202 and reference ustekinumab was also shown for percent improvement in PASI score from baseline up to week 52. All other secondary efficacy endpoints also supported the equivalence of treatments.

Mean percent improvement from baseline in PASI score at week 12 (79.5% with FYB202 and 76.2% with reference ustekinumab) was similar to that observed with reference ustekinumab in the pivotal phase 3 trials (76–77% with 45 mg dose) [8, 9], as well as in studies of other ustekinumab biosimilars (76–87%) [18, 19]. Similarly, the proportions of patients achieving PASI 75 and PASI 90 were broadly comparable with previous studies. However, consistent with other studies of biosimilars in psoriasis [18, 19], PASI response rates in this study (PASI 75 and PASI 90 at week 28 were 98% and 82% with FYB202, 96% and 78% with reference ustekinumab, respectively) were higher

than those observed in the original trials of the reference product (PASI 75, 70–71% and PASI 90, 49–54% with 45 mg dose at week 28) [8, 9]. This may reflect improved overall management of psoriasis over the past 10–15 years. In addition, unlike the studies of reference ustekinumab, this trial limited the population to patients with a body weight ≤ 100 kg to increase the sensitivity to detect a treatment difference if any exists. As such, the mean body weight of patients was lower in this trial than in the reference ustekinumab studies (81.2 kg vs. 90–94 kg) which may have contributed to the higher response rates for the 45 mg dosing regimen in this study.

Both treatments were well tolerated with no new safety signals. Safety findings were consistent with the reported safety profile of reference ustekinumab [20]. Injection site pain was the most frequently reported adverse event in both groups (11.2% with FYB202 versus 7.7% with reference ustekinumab). These events mainly occurred after the first injection and all were mild in intensity. The injection site reaction profile with ustekinumab was comparable with the known profile for reference ustekinumab and other biological treatments for psoriasis.

ADA prevalence was generally lower for FYB202 with the highest incidence rates for both treatments observed at week 28. The corresponding ADA titers were low and comparable between both groups at all timepoints. Incidences for NAbs were also similar between both groups. PASI response was lower in ADA-positive patients, and the magnitude of the reduction was comparable for both treatments and the time-course of percent improvement in PASI score during the complete 52-week treatment period was similar for the two treatment groups independent of ADA status. Overall, the difference in ADA incidence did not translate into any clinically meaningful differences in terms of efficacy or safety. The higher incidence of ADAs in the reference ustekinumab group may explain the higher geometric mean ustekinumab C_{trough} levels for patients treated with FYB202 compared to patients treated with reference ustekinumab, especially at early timepoints (weeks 4 and 12). These data are not indicative of a generally higher exposure with FYB202 and C_{trough} levels were low and comparable at steady state from week 16 onwards.

Switching from reference product to FYB202 had no clinically relevant effect on efficacy, safety, or immunogenicity. In particular, the switch did not induce any new ADA formation, with proportions of patients with ADAs and NAbs similar in the group who switched from reference ustekinumab to FYB202 and the groups who remained on FYB202 or on reference ustekinumab. This is consistent with previous trials that have indicated that switching between biosimilar and reference products, including on multiple occasions, has no impact on efficacy, safety, or immunogenicity [21–24].

Limitations include that the study was not powered for statistical comparisons of equivalence after switching from reference ustekinumab to FYB202. However, the study design is consistent with the majority of biosimilar equivalence studies that incorporate switching [18, 19, 23, 25]. The study also only included a single switch, whereas multiple switches between treatments may occur in clinical practice. In addition, as required by regulatory authorities for biosimilar approval, the trial was designed to detect differences between treatments rather than to prove efficacy de novo. Therefore, a narrower patient population than might be expected in clinical practice was selected to ensure sensitivity of the comparison. Finally, in common with most trials in this indication, the lack of racial diversity may also be a limitation given all patients were white, although the concept of extrapolation allows similarity of the treatment effect to be inferred for other populations.

CONCLUSION

Biosimilars can increase the number of patients able to receive biologic therapies, and also may allow patients to be treated earlier in the disease course, thereby reducing the risk of comorbidities [1]. In this study, the biosimilar ustekinumab FYB202 demonstrated equivalence to reference ustekinumab in patients

with moderate-to-severe plaque psoriasis, with comparable efficacy, safety, and immunogenicity. FYB202 was approved in both Europe [26] and the USA [27] in September 2024 as a biosimilar to reference ustekinumab based on extensive comparative analytical characterization data and proof of equivalence in clinical performance. Using a totality of evidence approach, proof of therapeutic equivalence in this sensitive psoriasis population allows for extrapolation to other indications, with similar clinical performance of FYB202 and reference ustekinumab assumed across all approved indications.

ACKNOWLEDGEMENTS

The authors would like to thank the patients and study personnel involved in this study.

Medical Writing/Editorial Assistance. Medical writing and editorial support were provided by Andy Bond of Felt Medical Communications Ltd, funded by Formycon AG.

Author Contributions. Kim Papp, Sigrid Balser, Katrin Nopora, Brigitte Freudensprung, and Michael Trieb contributed to the study design. Piotr Rewerski collected study data. All authors contributed to data analysis or interpretation, reviewed and critically revised the manuscript, provided final approval of the version to be published, and agree to be accountable for accuracy and integrity.

Funding. This trial was originally funded by bioeq GmbH, which has since been acquired by Formycon AG. Formycon AG funded medical writing and editorial support for the preparation of this manuscript, and the journal's Rapid Service and Open Access Fees.

Data Availability. All data supporting the findings of this study are available within the paper and its Supplementary Information.

Declarations

Conflict of Interest. Kim Papp has received honoraria and/or grants from AbbVie, Acelyrin, Akros, Alumis, Amgen, Arcutis, Bausch Health/Valeant, Boehringer Ingelheim, Bristol Myers Squibb, Can-Fite Biopharma, Celltrion, Concert Pharmaceuticals, Dermavant, Dermira, DiCE Pharmaceuticals, DiCE Therapeutics, Evelo Biosciences, Forbion, Galderma, Horizon Therapeutics, Incyte, Janssen, Kymab, Kyowa Hakko Kirin, LEO, Lilly, Meiji Seika Pharma, Mitsubishi Pharma, Nimbus Therapeutics, Novartis, Pfizer, Reistone, Sanofi-Aventis/Genzyme, Sandoz, Sun Pharma, Takeda, Tarsus Pharmaceuticals, UCB, and Zai Lab. Piotr Rewerski has received honoraria as a consultant for Eli Lilly and Bayer AG. Sigrid Balser, Katrin Nopora, Brigitte Freudensprung, and Michael Trieb are employees of Formycon AG.

Ethical Approval. The study protocol was reviewed and approved by the independent ethics committee or institutional review board for each centre.

REFERENCES

1. Girolomoni G, Savage L, Gisondi P, et al. Increasing access to effective systemic treatments in patients with moderate-to-severe psoriasis: narrative review. Dermatol Ther (Heidelb). 2023;13(10):2171–85. https://doi.org/10.1007/s13555-023-01014-x.

2. Vázquez-Sánchez R, Navarro-Dávila M, Herráiz ER, et al. Biosimilars and access to biologic therapy in immune-mediated diseases. Expert Opin Biol Ther. 2024. https://doi.org/10.1080/14712598.2024.2350440.

3. Loft N, Egeberg A, Rasmussen MK, et al. Outcomes following a mandatory nonmedical switch from adalimumab originator to adalimumab biosimilars in patients with psoriasis. JAMA Dermatol. 2021;157(6):676–83. https://doi.org/10.1001/jamadermatol.2021.0221.

4. Giordano D, Capalbo A, Gagliostro N, et al. Biosimilar versus originator etanercept: a real-life clinical study. Ital J Dermatol Venerol. 2022;157(4):318–24. https://doi.org/10.23736/S2784-8671.22.07224-3.

5. Bellinato F, Gisondi P, Mason E, Ricci P, Maurelli M, Girolomoni G. Real-life effectiveness of adalimumab biosimilars in patients with chronic plaque psoriasis. Dermatol Ther (Heidelb). 2022;12(6):1303–11. https://doi.org/10.1007/s13555-022-00732-y.

6. Owczarek W, Walecka I, Nowakowska A, et al. Effectiveness of infliximab biosimilars in the treatment of moderate to severe chronic plaque psoriasis: experience of real-world data from the register of the program "Treatment of moderate and severe forms of plaque psoriasis (B.47)" of the National Health Fund in Poland. Postepy Dermatol Alergol. 2022;39(4):723–8. https://doi.org/10.5114/ada.2021.108442.

7. Phan DB, Elyoussfi S, Stevenson M, Lunt M, Warren RB, Yiu ZZN. Biosimilars for the treatment of psoriasis: a systematic review of clinical trials and observational studies. JAMA Dermatol. 2023;159(7):763–71. https://doi.org/10.1001/jamadermatol.2023.1338.

8. Leonardi CL, Kimball AB, Papp KA, et al. Efficacy and safety of ustekinumab, a human interleukin-12/23 monoclonal antibody, in patients with psoriasis: 76-week results from a randomised, double-blind, placebo-controlled trial (PHOENIX 1). Lancet. 2008;371(9625):1665–74. https://doi.org/10.1016/S0140-6736(08)60725-4.

9. Papp KA, Langley RG, Lebwohl M, et al. Efficacy and safety of ustekinumab, a human interleukin-12/23 monoclonal antibody, in patients with psoriasis: 52-week results from a randomised, double-blind, placebo-controlled trial (PHOENIX 2). Lancet. 2008;371(9625):1675–84. https://doi.org/10.1016/S0140-6736(08)60726-6.

10. Tsai TF, Ho JC, Song M, et al. Efficacy and safety of ustekinumab for the treatment of moderate-to-severe psoriasis: a phase III, randomized, placebo-controlled trial in Taiwanese and Korean patients (PEARL). J Dermatol Sci. 2011;63(3):154–63. https://doi.org/10.1016/j.jdermsci.2011.05.005.

11. Igarashi A, Kato T, Kato M, Song M, Nakagawa H, Japanese Ustekinumab Study Group. Efficacy and safety of ustekinumab in Japanese patients with moderate-to-severe plaque-type psoriasis: long-term results from a phase 2/3 clinical trial. J Dermatol. 2012;39(3):242–52. https://doi.org/10.1111/j.1346-8138.2011.01347.x.

12. McInnes IB, Kavanaugh A, Gottlieb AB, et al. Efficacy and safety of ustekinumab in patients with active psoriatic arthritis: 1 year results of the phase 3, multicentre, double-blind, placebo-controlled PSUMMIT 1 trial. Lancet. 2013;382(9894):780–9. https://doi.org/10.1016/S0140-6736(13)60594-2.

13. Ritchlin C, Rahman P, Kavanaugh A, et al. Efficacy and safety of the anti-IL-12/23 p40 monoclonal antibody, ustekinumab, in patients with active psoriatic arthritis despite conventional non-biological and biological anti-tumour necrosis factor therapy: 6-month and 1-year results of the phase 3, multicentre, double-blind, placebo-controlled, randomised PSUMMIT 2 trial. Ann Rheum Dis. 2014;73(6):990–9. https://doi.org/10.1136/annrheumdis-2013-204655.

14. Sandborn WJ, Gasink C, Gao LL, et al. Ustekinumab induction and maintenance therapy in refractory Crohn's disease. N Engl J Med. 2012;367(16):1519–28. https://doi.org/10.1056/NEJMoa1203572.

15. Feagan BG, Sandborn WJ, Gasink C, et al. Ustekinumab as induction and maintenance therapy for Crohn's disease. N Engl J Med. 2016;375(20):1946–60. https://doi.org/10.1056/NEJMoa1602773.

16. Sands BE, Sandborn WJ, Panaccione R, et al. Ustekinumab as induction and maintenance therapy for ulcerative colitis. N Engl J Med. 2019;381(13):1201–14. https://doi.org/10.1056/NEJMoa1900750.

17. Griffiths CE, Strober BE, van de Kerkhof P, et al. Comparison of ustekinumab and etanercept for moderate-to-severe psoriasis. N Engl J Med.

2010;362(2):118–28. https://doi.org/10.1056/NEJMoa0810652.

18. Feldman SR, Reznichenko N, Berti F, et al. Randomized, double-blind, multicenter study to evaluate efficacy, safety, tolerability, and immunogenicity between AVT04 and the reference product ustekinumab in patients with moderate-to-severe chronic plaque psoriasis. Expert Opin Biol Ther. 2023;23(8):759–71. https://doi.org/10.1080/14712598.2023.2235263.

19. Papp KA, Lebwohl MG, Thaçi D, et al. Efficacy and safety of candidate biosimilar CT-P43 versus originator ustekinumab in moderate to severe plaque psoriasis: 28-week results of a randomised, active-controlled, double-blind, phase III study. BioDrugs. 2024;38(1):121–31. https://doi.org/10.1007/s40259-023-00630-5.

20. European Medicines Agency. Stelara: summary of product characteristics. 2022. https://www.ema.europa.eu/en/documents/product-information/stelara-epar-product-information_en.pdf. Accessed July 11, 2024.

21. Griffiths CEM, Thaçi D, Gerdes S, et al. The EGALITY study: a confirmatory, randomized, double-blind study comparing the efficacy, safety and immunogenicity of GP2015, a proposed etanercept biosimilar, vs. the originator product in patients with moderate-to-severe chronic plaque-type psoriasis. Br J Dermatol. 2017;176(4):928–38. https://doi.org/10.1111/bjd.15152.

22. Blauvelt A, Lacour JP, Fowler JF Jr, et al. Phase III randomized study of the proposed adalimumab biosimilar GP2017 in psoriasis: impact of multiple switches. Br J Dermatol. 2018;179(3):623–31. https://doi.org/10.1111/bjd.16890.

23. Hercogová J, Papp KA, Chyrok V, Ullmann M, Vlachos P, Edwards CJ. AURIEL-PsO: a randomized, double-blind phase III equivalence trial to demonstrate the clinical similarity of the proposed biosimilar MSB11022 to reference adalimumab in patients with moderate-to-severe chronic plaque-type psoriasis. Br J Dermatol. 2020;182(2):316–26. https://doi.org/10.1111/bjd.18220.

24. Menter A, Cohen S, Kay J, et al. Switching between adalimumab reference product and BI 695501 in patients with chronic plaque psoriasis (VOLTAIRE-X): a randomized controlled trial. Am J Clin Dermatol. 2022;23(5):719–28. https://doi.org/10.1007/s40257-022-00708-w.

25. Feldman SR, Reznichenko N, Pulka G, et al. Efficacy, safety and immunogenicity of AVT02 versus originator adalimumab in subjects with moderate to severe chronic plaque psoriasis: a multicentre, double-blind, randomised, parallel group, active control, phase III study. BioDrugs. 2021;35(6):735–48. https://doi.org/10.1007/s40259-021-00502-w.

26. Otulfi. Summary of product characteristics. European Medicines Agency, Amsterdam, the Netherlands. https://www.ema.europa.eu/en/medicines/human/EPAR/otulfi. Accessed Jan 31, 2025.

27. OTULFI (ustekinumab-aauz). Prescribing information. Food and Drug Administration, Silver Spring, MD, USA. https://www.accessdata.fda.gov/drugsatfda_docs/label/2024/761379s001lbl.pdf. Accessed Jan 31, 2025.