Received: 14 June 2024 | Accepted: 21 August 2024

DOI: 10.1002/ueg2.12682

REVIEW ARTICLE

UNITED EUROPEAN GASTROENTEROLOGY ueg journal WILEY

Unlocking hope: The future of ustekinumab biosimilars in Crohn's disease treatment

Ferdinando D'Amico[1] | Sarah Bencardino[1] | André Gonçalves[2] | Mariangela Allocca[1] | Federica Furfaro[1] | Alessandra Zilli[1] | Tommaso Lorenzo Parigi[1] | Gionata Fiorino[3] | Laurent Peyrin-Biroulet[4,5,6,7,8,9] | Silvio Danese[1]

[1]Gastroenterology and Endoscopy, IRCCS Ospedale San Raffaele, Vita-Salute San Raffaele University, Milan, Italy

[2]Department of Gastroenterology, Unidade de Saúde Local da Região de Leiria, Leiria, Portugal

[3]Gastroenterology and Digestive Endoscopy, San Camillo-Forlanini Hospital, Rome, Italy

[4]Department of Gastroenterology, Inserm NGERE U1256, University Hospital of Nancy, University of Lorraine, Vandoeuvre-lès-Nancy, France

[5]Department of Gastroenterology, Nancy University Hospital, Vandœuvre-lès-Nancy, France

[6]INFINY Institute, Nancy University Hospital, Vandœuvre-lès-Nancy, France

[7]FHU-CURE, Nancy University Hospital, Vandœuvre-lès-Nancy, France

[8]Groupe Hospitalier privé Ambroise paré - Hartmann, Paris IBD Center, Neuilly sur Seine, France

[9]Division of Gastroenterology and Hepatology, McGill University Health Centre, Montreal, Quebec, Canada

Correspondence
Silvio Danese, Gastroenterology and Endoscopy, IRCCS Ospedale San Raffaele, Vita-Salute San Raffaele University, Via Olgettina 60, Milan, Italy.
Email: sdanese@hotmail.com

Funding information
Alvotech; STADA

Abstract

Biologic therapies have revolutionized Crohn's disease (CD) management, but their high costs pose a significant barrier to access. Biosimilars can provide increased access to treatment because of significant cost-savings. Ustekinumab is a biological drug against interleukin 12–23 that is employed in treating moderate-to-severe CD. As the patent of the reference product (RP) is expiring, ustekinumab biosimilars have been developed and are currently becoming available for patients. Available data demonstrate that ustekinumab biosimilars exhibit comparable efficacy, pharmacokinetics, safety and immunogenicity as the RP. Ustekinumab biosimilars have been approved for CD based on extrapolation and there is no real-world data available yet for this indication. While biosimilars of ustekinumab promise cost savings in treating moderate-to-severe CD, it is not yet known whether their availability will change the treatment algorithm in CD. This review focuses on the available data on ustekinumab biosimilars, focusing on their pros and cons for their forthcoming role in treating moderate to severe CD.

Ferdinando D'Amico and Sarah Bencardino contributed equally to this paper.

KEYWORDS
ABP 654, AVT04, BFI-751, Crohn disease, CT-P43, IBD, inflammatory bowel diseases, originator, SB17, therapy

INTRODUCTION

Crohn's disease (CD) is a chronic inflammatory bowel disease (IBD) that can involve the entire gastrointestinal tract, extending from the mouth to the anus.[1] CD is a progressive disorder potentially leading to bowel damage defined as the occurrence of abscesses, fistulas, and strictures, affecting the patients' quality of life.[2] The implementation of biological drugs has undeniably revolutionized the care of these patients, leading to a substantial improvement in the disease's course.[2] The existing therapeutic options for handling moderate to severe CD encompass steroids, immunosuppressants (thiopurines and methotrexate) and biological therapy such as TNFα inhibitors (infliximab, adalimumab, and certolizumab), anti-integrins (vedolizumab and natalizumab), and anti-interleukin 12–23 agent ustekinumab.[3]

Other recently approved treatment options for CD therapy include a selective interleukin 23 inhibitor (risankizumab)[4] and a small molecule drug that inhibits JAK1 (upadacitinib).[5] However, advanced therapies have also exerted a substantial economic influence on healthcare budgets, constituting the primary financial burden associated with IBD management.[6] The biologics price competition and innovation act of 2009 was established to encourage competition and control costs in medicine by establishing an expedited regulatory pathway for biological products highly similar to licensed biologics, commonly known as biosimilars.[7] With the expiration of patents for biological originators, numerous biosimilars are emerging.[8] Biosimilars have an amino acid chain identical to the reference biological and exhibit a closely related biochemical activity.[9] Nevertheless, owing to their intricate molecular structure, biologics and biosimilars may exhibit slight molecular variations due to changes in raw materials and manufacturing conditions. In accordance with regulatory requirements, robust evidence shows that biosimilars of TNFα inhibitors are clinically equivalent to the reference product (RP) with consistent data of efficacy and safety.[10] Ustekinumab (Stelara®) is a monoclonal antibody composed of fully human immunoglobulin, designed to inhibit the p40 subunit of both IL-12 and IL-23.[11] It received approval from the U.S. Food and Drug Administration (FDA)[12] and the European Medicines Agency (EMA) for treating moderate-to-severe CD in 2016.[13] It is administered intravenously during the induction phase and there is a subcutaneous administration during the maintenance phase.[3] Ustekinumab can be used both in patients naïve to biologics and in patients who have already failed biologics.[14] However, it is still reserved for later stages of CD therapy due to high cost issues (after failure of one or more TNFα inhibitor). The arrival of more affordable ustekinumab biosimilars could lead to a significant reduction in costs and facilitate the access to therapy, shifting its use to earlier phases of the treatment pathway. The aim of this review is to provide an overview of the available data on the efficacy and safety of ustekinumab and its biosimilars for treating moderate to severe CD, focusing on key challenges and opportunities with the arrival of biosimilars.

EFFICACY OF USTEKINUMAB (REFERENCE PRODUCT) IN CD

Data from randomized clinical trials

Several clinical trials have been conducted to support the efficacy and safety of ustekinumab in CD. In a phase 2a, placebo-controlled trial by Sandborn and colleagues, patients with CD were randomly assigned to receive either placebo, subcutaneous ustekinumab at a dose of 90 mg, or intravenous ustekinumab at a dose of 4.5 mg/kg.[15] Notably, a greater proportion of subjects in the intravenous group achieved clinical response and clinical remission at week 6 compared with those in the subcutaneous group (62.0% vs. 36.0% and 31.0% vs. 14.0%, respectively).[15]

In a phase 2b randomized and placebo-controlled study, the efficacy and safety of ustekinumab were assessed in patients with CD. During the induction phase of the study, 526 patients were randomly assigned to receive one of three different doses of intravenous ustekinumab (1, 3, or 6 mg per kilogram of body weight) or placebo.[16] Subsequently, responders from the induction phase were randomly assigned to receive either ustekinumab subcutaneously at a dose of 90 mg or placebo at weeks 8 and 16 for the maintenance study. The percentage of patients achieving the primary endpoint of clinical response (defined as a ≥100-point decrease from baseline in the Crohn's Disease Activity Index [CDAI] score) at week 6 was significantly higher in those treated with intravenous ustekinumab at a dose of 6 mg/kg compared to the placebo group (39.7% vs. 23.5%, $p = 0.005$). No significant disparity was observed with lower concentrations of ustekinumab. Likewise, a higher proportion of patients achieved clinical response at week 22 with ustekinumab treatment compared to placebo (69.4% vs. 42.5%, $p < 0.001$).[16]

Ustekinumab demonstrated efficacy in treating moderate-to-severe CD in two phase 3, randomized, placebo-controlled induction trials (UNITI-1 and UNITI-2) and one phase 3, randomized, placebo-controlled maintenance trial (IM-UNITI).[17] UNITI-1 comprised patients previously treated unsuccessfully with TNFα inhibitors, whereas UNITI-2 recruited biologic-naive patients or those not definitively categorized as primary or secondary non-responders to anti-TNFα. Patients who completed the induction studies were enrolled in the maintenance trial. In UNITI-1 and UNITI-2, patients were randomized in a 1:1:1 ratio to receive a

single intravenous infusion of either 130 mg of ustekinumab, a weight-range-based dose of 6 mg/kg of body weight ustekinumab, or placebo. Responders to ustekinumab induction at week 8 were re-randomized in the maintenance trial to receive 90 mg of subcutaneous ustekinumab every 8 or 12 weeks or placebo. All patients fulfilling the criteria for loss of response in the maintenance trial underwent dose adjustment. The primary endpoint of both induction trials was clinical response at week 6, defined as a CDAI score <150 or a decrease of at least 100 points from baseline. Clinical remission at week 44 (CDAI score <150) was the primary endpoint in the maintenance trial. A significantly greater proportion of patients treated with intravenous ustekinumab at either 130 mg or 6 mg/kg achieved the primary endpoint in the induction studies compared to the placebo arm (34.3% and 33.7% vs. 21.5% in UNITI-1, $p = 0.002$ and $p = 0.003$, respectively; 51.7% and 55.5% vs. 28.7% in UNITI-2, $p < 0.001$ for both comparisons). Patients who received intravenous ustekinumab at a dose of 6 mg/kg exhibited numerically higher rates of clinical response and clinical remission, along with higher serum drug concentrations (6.4 μg per milliliter vs. 2.1 μg per milliliter in UNITI-1 and 6.3 μg per milliliter vs. 2.0 μg per milliliter in UNITI-2) compared to those treated with intravenous ustekinumab at a dose of 130 mg at the end of the induction phase, thereby supporting the use of this dosage regimen. Similarly, in the maintenance trial, a significantly higher proportion of patients achieved clinical remission with 90 mg subcutaneous ustekinumab administered every 8 or 12 weeks compared with placebo (53.1% and 48.8% vs. 35.9%, $p = 0.005$ and $p = 0.04$, respectively). Notably, mean levels of C-reactive protein and fecal calprotectin either remained stable or decreased from baseline in a greater proportion of patients treated with ustekinumab than those receiving placebo. These clinical and biochemical improvements were evident as early as the third week of ustekinumab initiation.[17]

Recently, the 5-year efficacy data of ustekinumab in CD were reported from the IM-UNITI long-term extension (LTE) trial.[18] All patients who completed the maintenance study were eligible for the LTE phase, with those receiving placebo discontinued and no dose adjustments allowed. Of the 237 patients entering the LTE study, approximately half (124/237; 52.3%) completed the 5-year follow-up. At week 252, clinical remission rates were 28.7% for patients treated with ustekinumab every 12 weeks and 34.4% for those treated every 8 weeks.

Additionally, the 48-week results of the STARDUST trial, a phase 3b randomized trial, have been released.[19] This trial compared the efficacy of ustekinumab in patients with CD who have failed conventional therapy or one biological therapy, or both stratified according to different management strategies (standard care vs. treatment target). The primary endpoint of endoscopic improvement at week 48 (≥50% reduction in Simple Endoscopic Score-CD [SES-CD] vs. baseline) was achieved in a similar proportion of patients in both the treatment target group and the control arm (38% vs. 30%, $p > 0.05$). Likewise, rates of corticosteroid-free clinical remission did not differ between the study groups (56.4% and 63.3%, $p > 0.05$).

Data from real-life studies

To date, SUSTAIN stands out as the largest study, involving 463 patients, assessing ustekinumab's effectiveness in real-world scenarios among CD patients.[20] At week 16, a substantial percentage of participants achieved clinical remission and clinical response (56.0% and 70.0%, respectively) with over 80.0% probability of continuing the drug after a year of therapy. Another noteworthy investigation is the Initiative on Crohn and Colitis (ICC) Registry, a Dutch prospective registry tracking IBD patients initiating new treatments.[21] This registry followed 252 CD patients receiving ustekinumab for 2 years, revealing that approximately a third (34.0%) attained clinical remission without steroid usage after this period, while one-fifth (21.5%) achieved biochemical remission by week 104. Long-term real-world efficacy findings of ustekinumab in CD were also documented in the Spanish ENEIDA registry, encompassing over 400 CD patients treated with ustekinumab.[22] After 1 year, nearly two-thirds of patients with clinical disease activity at baseline (Harvey-Bradshaw Index [HBI] >4) attained clinical remission (190 out of 295, 64%), with approximately half showing normalization of fecal calprotectin levels by week 52 (54.0%).

SAFETY OF USTEKINUMAB (REFERENCE PRODUCT) IN CD

Data from randomized clinical trials

The safety profile is one of the main strengths of ustekinumab. In UNITI-1, the incidence of AEs was consistent across the ustekinumab 130 mg, ustekinumab 6 mg/kg, and placebo groups (64.6%, 65.9%, and 64.9%, respectively).[17] Likewise, there was no significant difference in the occurrence of serious AEs (4.9%, 7.2%, and 6.1%, respectively). In UNITI-2, patients treated with ustekinumab at the same doses exhibited similar rates of AEs compared to those in the placebo group (50.0%, 55.6%, and 54.3%, respectively) as well as serious AEs (4.7%, 2.9%, and 5.8%, respectively). At the end of the maintenance study, the occurrence of AEs and serious AEs was comparable among patients receiving ustekinumab every 8 weeks, ustekinumab every 12 weeks, or placebo (81.7%, 80.3%, and 83.5% for AEs, and 9.9%, 12.1%, and 15.0% for serious AEs, respectively).[17] The most common AEs reported were arthralgia (at maximum of 16.7% with ustekinumab 90 mg every 12 weeks), headache (at maximum of 12.2% with ustekinumab 90 mg every 8 weeks), nasopharyngitis (at maximum of 12.9% with ustekinumab 90 mg every 12 weeks), and exacerbations of CD (at maximum of 14.3% with placebo during IM-UNITI). Notably, in the IM-UNITI LTE trial, the incidence of safety events per 100 patient-years did not differ significantly between the placebo and combined ustekinumab groups for AEs (440.3 vs. 327.6), serious AEs (19.3 vs. 17.5), infections (99.8 vs. 93.8), and serious infections (3.9 vs. 3.4).[18] Regarding malignancies, the incidence per 100 patient-years was 1.70 in the placebo group and 1.06 in the combined ustekinumab group, with a total of

10 malignancies (excluding non-melanoma skin cancer) during the study period.[18]

Data from real-life studies

Safety data from real-life studies are consistent with those from the clinical trials. In the ICC registry, a total of 81 possibly and 18 probably related AEs were observed during the study period.[21] The most frequent AEs included headache, skin reactions, and musculoskeletal complaints. Severe infections were reported in 13 patients (with 53.8% concurrently treated with an immunosuppressant), and malignancies were diagnosed in three cases (with two patients concurrently treated with a thiopurine). Additionally, one unrelated death was recorded. In the ENEIDA registry, AEs were observed in only a small percentage of patients (14.7%) and primarily consisted of bacterial infections (34.0%).[22]

DOSE ADJUSTMENT AND RE-INDUCTION

Several studies have been conducted in off-label areas to raise the bar for ustekinumab treatment. A retrospective observational multicenter study by GETECCU explored the effectiveness of re-induction with intravenous ustekinumab in 53 patients who initially responded well to ustekinumab but later experienced loss of response (HBI $\geq$5).[23] Surprisingly, about 43.4% of subjects achieved clinical remission (HBI $\leq$4) at week 16 post re-induction, with no observed infusion reactions or additional adverse events (AEs). Fumery et al. investigated the efficacy of a modified ustekinumab treatment regimen, administered every 4 weeks instead of every 8 weeks, in patients who had lost response to the latter.[24] Within 2 months, approximately 61.0% achieved clinical response, and 31.0% achieved clinical remission. After an average follow-up of 8 months, the majority (61.0%) remained on ustekinumab, and nearly half (49.0%) were in steroid-free clinical remission.

OVERVIEW ON BIOSIMILARS OF USTEKINUMAB

The RP of ustekinumab was approved by the FDA on 25 September 2009[12] and by the European Medicines Agency EMA on 16 January 2009.[13]

FDA approved ABP 654 (Wezlana®), the first ustekinumab biosimilar in November 2023.[25] Like its RP, ustekinumab-auub has received approval for adult patients experiencing moderate to severe plaque psoriasis, who may require phototherapy or systemic therapy along with active psoriatic arthritis, moderately to severely active CD, and moderately to severely active UC. In pediatric populations, the drug is utilized for subjects with moderate to severe plaque psoriasis who are candidates for phototherapy or systemic therapy as well as those with active psoriatic arthritis.[26] In Europe, AVT04 (Uzpruvo®) is the first biosimilar of ustekinumab approved by EMA on January 2024 and by FDA in April 2024 for moderate to severe plaque psoriasis, active psoriatic arthritis in adults and moderately to severely active CD in adults.[27,28]

Some of the additional ustekinumab biosimilars beyond ABP 654 and AVT04 approved or in development are presented in Table 1.

TABLE 1 Summary of biosimilars of ustekinumab approved or in development.

Product name	Stage of development	Phase I	Phase III
ABP654 (Ustekinumab-auub, Wezlana®)	Approved by FDA (November 2023) Similarity in efficacy safety, tolerability, immunogenicity and pharmacokinetic features with reference product[29,30,31]	✓	✓
AVT04 (Uzpruvo®)	Approved by EMA (January 2024) and FDA (April 2024) Similarity in efficacy, safety, tolerability, immunogenicity, and pharmacokinetic features with reference product[32,33]	✓	✓
BAT2206	Similarity in pharmacokinetic, safety and immunogenicity characteristics with reference product[29]	✓	
CT-P43	Equivalent efficacy, comparable pharmacokinetic, safety and immunogenicity profiles with reference product[34]	✓	✓
DMB-3115	Therapeutic equivalence with reference product and showed no statistically significant difference in safety[35]		✓
FYB202	Comparable efficacy with the reference product[36]		✓
SB-17 (Pyzchiva®)	Approved by EMA (April 2024) Phase I and Phase III demonstrated similarity in efficacy safety, tolerability, immunogenicity and pharmacokinetic features with reference product[37,38]	✓	✓

Pharmacokinetic features of ustekinumab biosimilars (in healthy subjects)

Ustekinumab biosimilars have the same pharmacokinetic (PK) features as their RPs.[29,37,39,32] On the clinical level, this has been demonstrated in a randomized double-blinded single-dose, 3-arm, parallel-group in which 238 healthy subjects were randomized 1:1:1 and stratified by gender and ethnicity (Japanese vs. non-Japanese) to receive a single 90 mg subcutaneous injection of ABP 654 or ustekinumab sourced from the United States (US) or ustekinumab sourced from the European Union (EU).[39] When comparing ABP 654 to ustekinumab US, ABP 654 to ustekinumab EU, and ustekinumab US to ustekinumab EU, the point estimates and 90% confidence intervals (CIs) of the geometric mean ratios were completely within the specified margin of 0.8–1.25 for both primary pharmacokinetic (PK) endpoints (AUC_{0-inf} and C_{max}) and the secondary PK endpoint of area under the curve from time zero to last sampling time.[39] Regarding AVT04, data show PK similarity to ustekinumab RP.[32] PK was evaluated in a randomized, double-blind, 3-arm, parallel study involving 298 healthy subjects. They were randomly assigned in a 1:1:1 ratio to receive a single 45 mg dose of AVT04, EU-UST, or US-UST. The protein content of EU-UST was observed to deviate from the expected nominal value of 90 mg/ml. Following protein content normalization, a statistical analysis was conducted to assess PK similarity. The 90% CIs of the geometric mean ratios for both primary parameters, C_{max} and AUC_{0-inf}, were completely within the determined margins of 80% and 125% for each of the three comparisons.[32] This supports the demonstration of PK similarity between AVT04 and both EU-UST and US-UST.[32] Also, BAT2206, an ustekinumab biosimilar developed by another company, has similar PK features to reference molecule as demonstrated in a double-blinded, randomized, single-dose, parallel-group phase I clinical trial.[29] In this study, a total of 270 male individuals in good health were recruited and randomly assigned to receive a single subcutaneous injection of either BAT2206 or ustekinumab (licensed from US or Europe) at a ratio of 1:1:1. The average serum concentration-time profiles for both the BAT2206 and ustekinumab groups (Europe/US) displayed a similar pattern.[29] Pharmacokinetic parameters such as C_{max}, AUC_{0-t} (area under the plasma concentration–time curve over the dosing interval), and AUC_{0-inf} (AUC from time zero to infinity) were comparable across all three treatment groups, with a median time to C_{max} observed at 6–7 days post-dosing. Similar values were also observed for apparent clearance and the apparent volume of distribution. No significant differences were observed in other PK parameters, including AUC_{0-672h}, elimination half-life, the first-order rate constant associated with the terminal portion of the curve, and apparent clearance, between the two drugs ($p > 0.05$). Regarding the primary PK parameters, C_{max} and AUC_{0-inf}, following a single subcutaneous injection of either BAT2206 or Ustekinumab RP (sourced from EU or USA, respectively), the 90% confidence intervals (CIs) for the ratios of geometric means were confined within the range of 0.80–1.25, indicating the bioequivalence between the two drugs.[29] Similar results were obtained in a randomized double-blind single-dose phase I study in which SB17, another ustekinumab biosimilar, was compared with its RP.[37] In this study, 201 healthy adult subjects were randomized to receive 45 mg via subcutaneous injection of SB17, European Union-sourced (EU-UST), or US-sourced UST (US-UST). All 90% CIs for the AUC_{inf} and C_{max} ratios between groups fell within the predefined bioequivalence margin of 0.8–1.25. The least square geometric means ratios of AUC_{inf} and C_{max} were 0.99 and 0.90 for SB17/EU-UST, 1.01 and 0.94 for SB17/US-UST, and 1.02 and 1.05 for EU-UST/US-UST, respectively.[37] Table 2 summarizes the pharmacokinetic characteristics of the ustekinumab biosimilars compared with RP.

Safety profile of ustekinumab biosimilars (in healthy subjects)

Ustekinumab biosimilars have a safety profile comparable to their RP.[29,37,39,32] In the previous cited study on BAT2206, the number of treatment emergent adverse events (TEAEs) was comparable across all three treatment groups (425 clinical TEAEs in 186 subjects: 70.0% in the BAT2206 group, 70.8% in the ustekinumab RP EU group, and 66.7% in the ustekinumab RP US group).[29] Regarding SB-17, the percentage of individuals experiencing TEAEs was similar across SB17, EU-UST RP, and US-UST RP groups (68.7%, 58.2%, and 65.7% respectively).[37] Safety data were consistent for ABP-654, considering that adverse events were documented in 22 (28.2%) participants in the ABP 654 group, 18 (22.8%) participants in the ustekinumab US RP group, and 29 (36.3%) participants in the ustekinumab RP EU group.[39] In addition, there were no differences in safety between AVT04 and ustekinumab RP.[32] Out of the 294 individuals treated with ustekinumab, 203 (69.0%) reported at least one TEAE. The incidence of participants encountering TEAEs was similar across all treatment groups, with rates of 68.4% in the AVT04 group, 67.7% in the EU-UST RP group, and 71.1% in the US-UST RP group.[32] However, the US-UST RP group had a higher number of events (190 events) compared to the AVT04 (151 events) and EU-UST RP (155 events) groups.[32]

Immunogenicity of ustekinumab biosimilars (in healthy subjects)

Beyond efficacy and safety, the assessment of immunogenicity is very important in biosimilar trials to assure there is no clinical difference compared to the RP. Results for immunogenic features were consistent for APB-654.[39] In this study, blood samples for anti-drug antibodies (ADAs) assessments were collected at pre-dose and on days 11, 35, and 112. Particularly, 12 (15.4%), 30 (38.0%), and 29 (36.3%) participants tested positive for ADAs in the ABP-654, in the ustekinumab US and in the ustekinumab EU treatment groups, respectively.[39] Two (2.6%), 10 (12.7%), and 6 (7.5%) participants tested positive for neutralizing antibodies (NAbs) in the ustekinumab US and in the ustekinumab EU treatment groups, respectively.[39] The

TABLE 2 Pharmacokinetic characteristics of ustekinumab biosimilars compared with reference products.

	BAT2206			SB17			ABP 654			AVT04		
	BAT2206	EU- UST RP	US-UST RP	SB17	EU- UST RP	US-UST RP	ABP 654	EU- UST RP	US-UST RP	AVT04	EU- UST RP	US-UST RP
C_{max}	5.6 ± 1.7 µg/mL (30.5)	5.7 ± 1.6 µg/mL (27.6)	5.8 ± 1.5 µg/mL (26.6)	5,095 ng/mL (1,498)	5,689 ng/mL (1,877)	5,420 ng/mL (1,659)	12.2 µg/mL (3.7)	12.7 µg/mL (3.8)	11.8 µg/mL (3.7)	4019.2 ng/mL (33%)	3681.7 ng/mL (38%	4046.4 ng/mL (31%)
$AUC_{0\text{-}inf}$	4629 ± 1255 h* µg/mL (27.1)	4716 ± 1344 h* µg/mL (28.5)	4571 ± 1156 h* µg/mL (25.3)	5,143,600 h* ng/mL (1,401,400)	5,273,000 h* ng/mL (1,649,100)	5,116,600 h* ng/mL (1,526,800)	483 d * µg/mL (159)	508 d * µg/mL (165)	467 d * µg/mL (163)	3511612 h* ng/mL (33%)	3014505 h* ng/mL (39%)	3344427 h* ng/mL (36%
$AUC_{0\text{-}t}$ (h* µg/mL)	4500 ± 1195 (26.6)	4578 ± 1207 (26.4)	4403 ± 1168 (26.5)	NA	NA	NA	NA	NA	NA	3286173(32%)	287257(38%)	3171230(34%)
T_{max}	147 h (48 - 337)	144 h (96 - 337)	168 h (12.0 - 336)	168.000 h (48.00 – 672.00)	168.000 h (12.00 – 504.00)	168.000 h (48.00 – 1,008.00)	6.1 days (1.0 - 13.1)	7.9 days (2.0 - 27.0)	7.9 days (2.0 - 27.0)	168.0 h (46.4– 504.0)	167.7 h (47.8– 503.6)	168.1 h (48.0- 339.5)
$t_{1/2}$	459 ± 94 h (20.5)	470 ± 104 h (22.1)	444 ± 98.4 h (22.2)	582.70 h (171.00)	563.80 h (161.55)	541.07 h (134.93)	1.0 days (0.3)	1.0 days (0.3)	1.0 days (0.3)	477.9 h (24.9%)	431.94 h (27.8%)	438.17 h (39.9%)
λ_z (1/h)	0.0016 ± 0.0003 (20.7)	0.0016 ± 0.0004 (23.5)	0.0017 ± 0.0005 (30.5)	0.0013891 (0.00084317)	0.0014051 (0.00083473)	0.0013624 (0.00035215)	NA	NA	NA	NA	NA	NA
CL/F (mL/h)	10.5 ± 3.1 (29.5)	10.2 ± 2.6 (25.8)	10.5 ± 2.8 (26.8)	9.4308 (2.7416)	9.4592 (3.3800)	9.6075 (3.0698)	NA	NA	NA	0.01(33.1%)	0.02(39.2%)	0.01(36.3%)
V_z/F	6755 ± 1780 mL (26.3)	6684 ± 1407 mL (21.1)	6566 ± 1659 mL (25.3)	NA	NA	NA	NA	NA	NA	8.76 L (31.6%)	9.30 L (36.6%)	8.46 L (33.9%)

Note: For BATT2206 data are shown as mean ± standard deviation (% coefficient of variation), except T_{max} which is median (minimum–maximum). For SB17 and ABP654 data are shown as mean (Standard deviation), except T_{max} which is median (minimum–maximum). For AVT04 data are shown as geometric mean (geometric mean coefficient of variation as a percent) except T_{max} which is median (minimum–maximum).

Abbreviations: $AUC_{0\text{-}inf}$, area under the plasma concentration–time curve from time zero to infinity; $AUC_{0\text{-}t}$, area under the plasma concentration–time curve over the dosing interval; CL/F, apparent clearance; C_{max}, maximum plasma concentration; EU, European Union; h, hours; RP, reference product; $t_{1/2}$, elimination half-life; T_{max}, time to maximum plasma concentration; US, United States; V_z/F, apparent volume of distribution a Cmax; λ_z, apparent terminal elimination rate constant.

immunogenicity characteristics of AVT04 were generally in line with ustekinumab RP.[32] Of note, in the AVT04 groups, there were numerically lower frequencies of ADAs and NAbs compared to the EU-UST and US-UST treatment groups (ADAs at the end of the study visit [at week 13]: 27.6% in AVT04 group, 48.5% in the EU-UST group, 45.4% in the US-UST group; NAbs at the end of the study visit: 30.6% in AVT04 group, 33.9% in the EU-UST group, 42.3% in US-UST group).[32] In a phase I study on BAT2206 in 54 healthy subjects (20.1%), ADAs were detected (26.7% in BAT2206, 14.8% reference ustekinumab [EU] and 18.9% in reference ustekinumab [USA] groups).[29] ADA tests were performed before drug administration and on days 10, 15, 29, 57, 85, and 113. Conversely, similar rates of positive NAbs were observed among all three groups (8.9% in BAT2206, 5.7% in ustekinumab [EU], and 6.7% in ustekinumab [USA]).[29] Considering SB-17, the prevalence of individuals testing positive for post-dose ADAs was similar (26.9% for SB17, 34.3% for EU-UST, and 34.3% for USA-UST).[37] Among those subjects with a positive ADA result at day 99/end of the study, 53.8% (5 from SB17, 12 from EU-UST, and 11 from US-UST) were found to be positive for NAbs.[37] Blood samples for immunogenicity analysis were collected at pre-dose and on day 29, 71, and 99.

EFFICACY AND SAFETY OF USTEKINUMAB BIOSIMILARS IN OTHER IMMUNE-MEDIATED INFLAMMATORY DISEASES

In November 2023, FDA approved the first ustekinumab biosimilar, Wezlana® (ustekinumab-auub),[25] for adults and children with severe plaque psoriasis or active psoriatic arthritis, as well as for adults with moderately to severely CD and UC. The indication for treating IBD was approved through extrapolation based on the results of a phase 3 multicenter, double-blind, randomized study.[30] Particularly, according to the FDA and EMA position, when the drug's mechanism of action is well understood and consistent across various indications, clinical data from equivalence studies in a primary reference indication can be used to extrapolate efficacy and safety data to other approved indications. This allows for the extension of the drug's use without necessitating specific clinical trials for each indication.[40] Later, in January 2024, EMA granted marketing authorization to Uzpruvo® as the first biosimilar to RP in Europe. This decision was based on the totality of evidence (analytical, non-clinical and clinical studies), including the phase III AVT04-GL-301 study, showcasing the same efficacy, safety, tolerability, PK and immunogenicity of AVT04 and the RP in participants with moderate-to-severe chronic psoriasis.[33] This study was conducted in two phases: an initial assessment of efficacy spanning from week 1 to week 15 followed by a long-term evaluation of safety and efficacy from week 16 to week 52. Patients received treatments at weeks 1, 4, 16, 28, and 40. A total of 581 patients were enrolled, with 544 completing the study. The patients were randomized at a 1:2 ratio to receive AVT04 (n = 194) or RP (n = 387), 45 mg (≤100 kg) or 90 mg (>100 kg) subcutaneously. The primary endpoint focused on analyzing the percentage improvement

in Psoriasis Area and Severity Index (PASI) from baseline to week 12. By week 16, patients in the biosimilar group showing at least a 50% improvement in the PASI remained on AVT04 treatment, while those in the RP group were re-randomized 1:1 to either continue receiving the RP or switch to AVT04. Patients who were nonresponsive (<50% improvement in PASI) at week 28 were not administered further study treatment but were encouraged to complete the end of study (EoS) assessments at week 52. In terms of results, both AVT04 and the RP demonstrated significant improvement in the primary endpoint of percent PASI score from baseline to week 12 (87.3% vs. 86.8%; CI: −2.14%, 3.01%), complying with the pre-defined equivalence margin of ±10% set by the FDA criteria.[33] Secondary endpoints, including achieving clear or almost clear in Physician's Global Assessment responses, improvements in Dermatology Life Quality Index and reduction in affected Body Surface Area, further reinforced the clinical similarity between the two products (78.4% vs. 80.5%; 12.5 vs. 11.4-point improvement; 26.02%–6.75% vs. 26.41%–6.35%; in the AVT04 vs. the RP).[33] Moreover, the long-term efficacy analysis until the end of study (week 52) demonstrated sustained improvement in both primary and secondary endpoints, indicating persistence of efficacy despite treatment switching of RP to AVT04. Notably, no patients discontinued treatment at week 28 due to nonresponse. Up to week 16, a total of 10 patients (5.2%) reported 13 treatment-related TEAEs in the AVT04 group and 37 patients (9.6%) reported 39 treatment-related TEAEs in the RP group.[33] Most TEAEs were mild and no serious TEAEs were reported in the AVT04 group. The immunogenicity of both AVT04 and RP had no clinically significant impact on their efficacy, safety, or pharmacokinetic profiles throughout the study. Significantly, by week 16, 49 patients (25.4%) in the AVT04 group and 184 patients (48.2%) in the RP group developed binding ADAs. Among these, 13 patients (26.5%) in the AVT04 group and 57 patients (31.0%) in the RP group had NAbs.[33]

Another ustekinumab biosimilar (CT-P43) is on the horizon supported by a double-blind, phase 3 randomized trial, where the biosimilar exhibited comparable efficacy to the RP ustekinumab in patients with moderate to severe plaque psoriasis.[34] In this study, a total of 509 patients participated in the treatment phase I (at week 0 and week 4), with 253 receiving the RP drug and 256 receiving CT-P43. Drug administration occurred at both week 0 and week 4, with dosages of 45 mg or 90 mg based on their baseline body weight (≤100 kg or >100 kg). In the treatment phase II, patients were randomly assigned to either continue with the RP drug, switch to CT-P43, or maintain CT-P43 from week 16 to week 40. Drug dosage adjustments were made at week 16 to accommodate any weight changes. Efficacy in the primary endpoint results showed similar improvements in PASI scores across treatment phases. At baseline, the average PASI score was 21.51 in the CT-P43 group and 20.88 in the ustekinumab reference group. By week 12, proportions of patients achieving PASI75 score were 86.05% for CT-P43 and 83.99% for RP. According to the FDA recommended confidence interval for biosimilarity, the average percentage improvements in PASI score at week 12 were 77.93% for the CT-P43 group and 75.89% for the RP group. Under the EMA recommended confidence interval for biosimilarity, these figures were 78.26% and 77.33%, respectively. By week 28, proportions of patients experiencing improvements in their PASI scores were 92.55% in the continued RP group, 95.07% in the continued CT-P43 group, and 92.86% in the switch group. Secondary endpoints included changes in patients' Dermatology Life Quality Index (DLQI) scores. At baseline, patients in the CT-P43 group had a DLQI of 13.2, and those in the RP group had a DLQI of 11.9. By week 12, mean changes from baseline in DLQI scores were −9.7 and −8.5 for CT-P43 and the RP groups, respectively. At week 28, mean DLQI score changes were −10.9, −8.8, and −9.4 for the continued CT-P43 group, continued RP group, and switched to CT-P43 group, respectively.

Regarding immunogenicity, patients in the CT-P43 group had lower positive ADA results compared with the RP in the initial treatment phase (10.2% in CT-P43 vs. 17% in EU-UST RP).[34] By week 28, ADA-positive patients included 26 in the CT-P43 group, 21 in the continued RP group, and 22 who switched to CT-P43. The incidence of adverse events was similar between the groups (158/256 in CT-P43 and 110/253 in RP group during the treatment phase I; 57/253 in the group of continued CT-P43, 38/125 in the group of continued RP and 40/124 in the group of switched to CT-P43 during the treatment phase II) with no TEAE of hypersensitivity or malignancy. Infections occurred with similar frequencies across groups (39/256 in CT-P43 and 35/254 in RP group during the first phase; 14/253 in the group of continued CT-P43, 7/125 in the group of continued RP and 8/124 in the group of switched to CT-P43 during the subsequent phase).

Patient characteristics of these studies are represented in Table 3, while efficacy and safety data are summarized in Table 4.

A summary of the studies available on biosimilars of ustekinumab is presented in Table 5.

Other ustekinumab biosimilar products are currently in various stages of development, progressing through phase I and III clinical trials[41] or awaiting approval. While Uzpruvo® has secured the first approval for a ustekinumab biosimilar in Europe, at least three other biosimilars are on the way to enter the market and increase access to affordable treatment with ustekinumab. Among these, Dong-A ST's DMB-3115[35] and Fresenius Kabi and Formycon's FYB202[36] have had their marketing authorization applications accepted by the EMA for the Stelara biosimilar.

DISCUSSION

Biological drugs have revolutionized the management of individuals with IBD, but they have also had a significant economic impact on healthcare budgets, representing the primary financial challenge in IBD.[6,42] Biosimilars provide an opportunity to improve access to ustekinumab within the constraints of the health care budget. Various cost-analysis studies indicate that transitioning from RP to biosimilars could yield substantial savings for the health care systems by funding broader access to treatments.[43,44,45] In line with this, the cost-effectiveness evaluations of previous biological treatments are expected to be enhanced with the incorporation of biosimilar

TABLE 3 Patient characteristics at baseline from ustekinumab biosimilar trials in other immune-mediated inflammatory diseases.

Baseline patient demographics and disease characteristics	AVT04		CT-P43	
	AVT04 (*N* = 194)	RP (*N* = 387)	CT-P43 (*N* = 256)	RP (*N* = 253)
Age (years), median (range)	41.0 (18–74)	40.0 (18–73)	41.0 (18–74)	41.0 (18–77)
Sex, *n* (%)	Male 107 (55.2)	Male 257 (66.4)	Male 161 (62.9)	Male 173 (68.4)
	Female 87 (44.8)	Female 130 (33.6)	Female 95 (37.1)	Female 80 (31.6)
Involved body surface area (%), mean (SD)	26.02 (13.2)	26.41 (12.3)	26.1 (14.2)	24.3 (13.2)
Time since plaque-type psoriasis diagnosis, mean (SD)	193.4 months (139.9)	201.0 months (136.5)	17.81 years (12.144)	15.56 years (11.560)
PASI score, mean (SD)	22.05 (8.1)	22.22 (7.5)	21.51 (7.939)	20.88 (7.998)
sPGA score, mean (SD)	Moderate 132 (68.0)	Moderate 241 (62.3)	3.2 (0.37)	3.2 (0.38)
	Severe 49 (25.3)	Severe 117 (30.2) 166		
	Very severe 13 (6.7)	Very severe 29 (7.5)		
Use of prior biologic approved for psoriasis treatment, *n* (%)	Yes 15 (7.7)	Yes 29 (7.5)	Yes 38 (14.8)	Yes 44 (17.4)
	No 179 (92.3)	No 358 (92.5)	No 218 (85.2)	No 209 (82.6)

Abbreviations: PASI, Psoriasis Area and Severity Index; RP, reference product; SD, standard deviation; sPGA, static Physician's Global Assessment.

TABLE 4 Efficacy and safety of ustekinumab biosimilars in other immune-mediated inflammatory diseases.

		Efficacy					Safety	
		Primary endpoint	Secondary endpoint					
		Percent improvement in PASI from baseline to week 12 (least square mean)	Area under the effect curve for PASI from baseline through week 12 (mean [SD])	Proportion of patients achieving sPGA responses of clear (0) or almost clear (1) (%)	Change from baseline mean in DLQI scores (SD)	Change from baseline mean in percent BSA (%BSA) affected by chronic PsO (SD)	TEAE (%)	Serious TEAE (%)
AVT04	AVT04	87.3	620.26 (202.956)	78.4 at w12	−12.48 (7.141) at w12	−19.27 (12.377) at w12	34.5 at w16	0 at w16
	RP	86.8	633.19 (199.910)	80.5 at w12	−11.41 (7.928) at w12	−20.11 (13.436) at w12	33.6 at w16	1.8 at w16
CT-P43	CT-P43	78.06 (FDA protocol) 78.41 (EMA protocol)	NA	85.5 at w12	−9.7 (6.74) at w12	NA	37.1 at w12	1.6 at w12
	RP	76.06 (FDA protocol) 77.54 (EMA protocol)	NA	79.4 at w12	−8.5 (6.67) at w12	NA	29.6 at w12	1.6 at w12

Abbreviations: BSA, body surface area; DLQI, Dermatology Life Quality Index; PASI, Psoriasis Area and Severity Index; PsO, plaque psoriasis; RP, reference product; SD, standard deviation; sPGA, static Physician's Global Assessment; TEAE, treatment-emergent adverse events.

prices.[46] Thus, ustekinumab biosimilars have become available as alternative treatment options. Biosimilars are already a game-changer in IBD treatment, being the first choice among TNF alpha inhibitors in both biologic-naïve patients and those previously treated with the RP in several countries.[10,47]

After the patent expiration of the RP, ustekinumab biosimilars will be available. Besides the analytical assessment, ustekinumab biosimilars have unveiled similar data in PK, efficacy, safety, and immunogenicity compared to the RP.[29,37,39,32,33,34] Equivalent immunogenicity of biosimilars is crucial for validating its biosimilarity

TABLE 5 Main characteristics of the studies available on biosimilars of ustekinumab.

	BAT2206	CT-P43	SB17		ABP 654	AVT04	
Phase	**Phase I**	**Phase III**	**Phase I**	**Phase III**	**Phase I**	**Phase I**	**Phase III**
Design	Randomized, double-blinded, 3-arm, parallel-group, single dose study in healthy Chinese male subjects	Randomized, double-blind clinical trial	Randomized, double-blind, 3-arm, parallel group, single dose study in healthy subjects	Randomized, double-blind, multicentre study in patient with moderate-to-severe plaque psoriasis	Randomized, double-blinded, single-dose, 3-arm, parallel-group study in healthy subjects	Randomized, double-blind, 3-arm, parallel group, single dose study in healthy subjects	Randomized, double-blind multicenter study in patient with moderate-to-severe chronic plaque psoriasis
Dose	45 mg (single SC injection)	45 mg or 90 mg (≤100 kg or >100 kg) at week 0 and week 4 and then every 12 weeks at weeks 16, 28, and 40	45 mg (single SC injection)	45 mg SC injection at week 0, 4 and week 16	90 mg (single SCs injection)	45 mg (single SC injection)	45 mg or 90 mg (≤100 kg or >100 kg) at week 0 and week 4 and then every 12 weeks at weeks 16, 28, and 40
N° subjects	270 healthy male subjects (90 in each arm)	509 patients with psoriasis (253 receiving the originator drug and 256 receiving CT-P43).	201 (67 in each arm)	503 patients with psoriasis (249 in SB17, 254 in UST-RP)	238 (79 in ABP 654, 79 in US-UST RP, and 80 in EU- UST RP)	298 (98 in AVT04, 99 in EU-RP and 97 in US-RP)	581 (194 receive AVT04; 387 received RP; patient in RP group were re-randomized at week 16: 192 received AVT04, 189 maintained RP)
Study duration	113 days	Up to 52 weeks	99 days	Up to 28 weeks	112 days	92 days	Up to 52 weeks
Primary endpoint	PK (Ratio of geometric means [%] [90% CI])	Percent change from baseline in PASI at week 12	PK (LS geometric mean of PK parameters [90% CI])	Percent change from baseline in PASI at week 12	PK (Ratio of geometric LS means [%] [90% CI])	PK (Ratio of geometric LS means [%]: Test/ Reference [90% CI])	Percent change from baseline in PASI at week 12
	AUC_{0-inf}		AUC_{inf}	Per protocol set (LS means [SE] 95% CI)	AUC_{0-inf}	AUC_{0-inf}	AVT04 versus EU- UST RP: 87.3% versus 86.8% (CI: −2.14%, 3.01%)
	BAT2206 versus EU-UST RP: 97.90 (91.63, 104.59)	Per protocol set (LS means 90% CI; modified intent-to-treat set; FDA approach) or ±15% (95% CI; for patients only receiving 45 mg doses in treatment Period I; EMA approach)	SB17 versus EU- UST RP: 1.01 (0.93, 1.10)	SB17 (n = 243): 85.7 (2.53)	ABP 654 versus EU- UST RP: 0.94 (0.86, 1.02)	AVT04 versus EU- UST RP: 109.8 (101.5, 118.8)	
	BAT2206 versus US-UST RP: 100.78 (94.34, 107.65)		SB17 versus US-UST RP: 0.99 (0.90, 1.08)	UST-RP (n = 249): 86.3 (2.41)	ABP 654 versus US-UST RP: 1.01 (0.93, 1.10)	AVT04 versus US-UST RP: 103.9 (95.9, 112.6)	
	EU-USR RP versus US-UST RP: 102.94 (96.56, 109.75)		EU-USR RP versus US-UST RP: 1.02 (0.93, 1.12)	Difference (SB17-UST-RP): −0.6 (1–62) [−3.780, 2.579]	US-USR RP versus EU-UST RP: 0.93 (0.85, 1.01)	EU-UST RP versus US-UST RP: 105.7 (97.6, 114.4)	
	C_{max}		C_{max}	Full analysis set [LS means (SE) 95% CI]	C_{max}	C_{max}	

(Continues)

TABLE 5 (Continued)

Phase	BAT2206 Phase I	CT-P43 Phase III	SB17 Phase I	SB17 Phase III	ABP 654 Phase I	AVT04 Phase I	AVT04 Phase III
	BAT2206 versus EU-UST RP: 97.44 (90.64, 104.75)	CT-P43 versus UST RP: 77.93% versus 75.89% (FDA approach)	SB17 versus EU- UST RP: 0.94 (0.86, 1.04)	SB17 (n = 249): 85.7 (2.53)	ABP 654 versus EU- UST RP: 0.95 (0.88, 1.02)	AVT04 versus EU- UST RP: 102.8 (95.5, 110.7)	
	BAT2206 versus US-UST RP: 96.01 (89.32, 103.19)	CT-P43 versus UST RP 78.26% versus 77.33% (EMA approach)	SB17 versus US-UST RP: 0.90 (0.82, 0.98)	UST-RP (n = 254): 86.3 (2.41)	ABP 654 versus US-UST RP: 1.00 (0.93, 1.08)	AVT04 versus US-UST RP: 98.6 (91.5, 106.2)	
	EU-USR RP versus US-UST RP: 98.53 (92.04, 105.47)		EU-USR RP versus US-UST RP: 1.05 (0.96, 1.15)	Difference (SB17-UST-RP): −0.7 (1–60) [−3.849, 2.439]	US-USR RP versus EU-UST RP: 0.94 (0.88, 1.01)	EU-UST RP versus US-UST RP: 104.3 (96.8, 112.4)	
Immunogenicity	Anti-drug antibody (%)	Anti-drug antibody (%)	Anti-drug antibody (%)	Anti-drug antibody (%)	Anti-drug antibody (%)	Anti-drug antibody (%)	Anti-drug antibody (%)
	Assessed on days 10, 15, 29, 57, 85, and 113.	Assessed on treatment period i (W0, W4, W12) and treatment period II (W16, W28, W40) and end of the study (W52).	Assessed on days 1, 29, 71, and 99.	Up to W28.	Assessed at predose and on days 11, 35, and 112.	At day 92.	AVT04 (W16): 25.4
	BAT2206: 26.7	CT-P43: 10.2	SB17: 26.9	SB17: 13.3	ABP 654: 16.7	AVT04: 27.6	UST-RP (W16): 48.2
	EU-UST RP: 14.8	EU-UST RP: 17.0	EU-UST RP: 34.3	UST-RP: 39.4	EU-UST RP: 37.5	EU-UST RP: 48.5	AVT04/AVT04 (EOS): 21.2
	US-UST RP: 18.9		US-UST RP: 34.3		US-UST RP: 38	US-UST RP: 45.4	UST-RP/AVT04 (EOS): 31.5
							UST-RP/UST-RP (EOS): 26.7
Safety	TEAE/SAE (%)	TEAE/Treatment-emergent SAE (%)	TEAE/severe TEAE (%)	TEAE/Treatment-emergent SAE (%)	AE/SAE (%)	TEAE/severe TEAE (%)	TEAE/serious TEAE (%)
	Assessed on days 10, 11, 13, 15, 22, 29, 43, 57, 71, 85, 99, and 113.	Up to w12	Up to day 99.	Up to W28.	Assessed on days 7, 9, 11, 13, 21, 28, 35, 49, 56, 70, 98, and 112.	Up to EOS	AVT04 (W16): 34.5./0
					ABP 654: 28.2/0.0	AVT04: 68.4/2	UST-RP(W16): 33.6/1.8

TABLE 5 (Continued)

	BAT2206	CT-P43	SB17		ABP 654	AVT04	
Phase	Phase I	Phase III	Phase I	Phase III	Phase I	Phase I	Phase III
	BAT2206: 70.0/0.0	CT-P43: 37.1/1.6	SB17: 68.7/0.0	SB17: 48.2/2.4	EU-UST RP: 36.3/1.3	EU-UST RP: 67.7/3	AVT-04/AVT04 (W16–28): 10.9/0
					US-UST RP: 22.8/1.3	US-UST RP: 71.1/1	UST-RP/AVT04 (W16–28): 15.6/0
	EU-UST RP: 70.8/0.0	EU-UST RP: 29.6/1.6	EU-UST RP: 58.2/0.0	UST-RP: 48.8/1.2			UST-RP/UST-RP (W16–28): 15.3/0.5
	US-UST RP: 66.7/0.0		US-UST RP: 67.2/0.0				AVT-04/AVT04 (W28-EOS): 16.8 0.5 UST-RP/AVT04 (W28-EOS): 22.8/0.5
							UST-RP/UST-RP (W28-EOS): 21.2/0.5

Abbreviations: AE, adverse events; EOS, end of the study; EU-UST RP, Ustekinumab reference product from Europe; LS, least square; PASI, Psoriasis area and Severity Index; PK, pharmacokinetics; SAE, serious adverse events; SC, subcutaneous; SE, standard error; TEAE, treatment-emergent adverse events; US-UST RP, Ustekinumab reference product from USA; W, week.

as the presence of ADAs can diminish drug exposure potentially impacting both efficacy and safety.[48] Phase III studies of ustekinumab biosimilars have been conducted in psoriasis and the CD indication has been granted in line with regulatory guidelines; the cumulative experience with anti-TNF biosimilars (more immunogenic molecules than ustekinumab) reinforces that there should be no concerns. It should be noted that studies on biosimilars often begin with dermatological indications due to the earlier approval and longer availability of these drugs in dermatology. Furthermore, demonstrating drug efficacy in dermatology primarily involves assessing clinical outcomes, such as the disappearance of skin lesions. However, evaluating efficacy in IBD is more complex as it involves endoscopic and transmural outcomes. However, real world data can increase the confidence of gastroenterologists when adopting ustekinumab biosimilars to treat CD patients.

To date, there are several advanced drugs available but there is no globally validated therapeutic algorithm for the treatment of patients with moderate to severe CD.[3] TNFα inhibitors are generally considered the first-line therapy as they are safe and effective drugs and biosimilars are available which make them accessible. Nevertheless, in the SEAVUE trial,[49] a randomized, double-blind, parallel-group, active-comparator, phase 3b trial, ustekinumab and adalimumab were equally effective and safe in CD patients. Specifically, among the 386 adult CD patients enrolled, there was no significant difference between the ustekinumab and adalimumab groups in the occurrence of the primary endpoint (clinical remission = CDAI score <150) at week 52 (65% vs. 61%, between-group difference 4%, 95% CI −6 to 14; $p = 0.42$), but there was better safety profile, tolerability and treatment persistence for ustekinumab. Based on these data, ustekinumab could emerge as a leading choice in CD. Given this perspective, the presence of ustekinumab biosimilars could provide significant cost-savings, which ideally could guarantee greater access to treatment and modify the positioning of ustekinumab preferring it as first-line given its ease of administration every 8 or 12 weeks.

Recently, the development of drugs that selectively inhibit interleukin 23 has raised attention toward the choice of the best drug for the management of patients with IBD, that is, risankizumab and mirikizumab. Even though the phase 3 SEQUENCE trial demonstrated that treatment with risankizumab was superior to ustekinumab in achieving endoscopic remission in patients with CD already treated with TNF alpha inhibitors,[50] the double-blinded VIVID-1 study[51] did not reveal differences between mirikizumab and ustekinumab in CD. For this reason, more head-to-head trials are needed to define the positioning of selective IL-23 inhibitors in the treatment algorithm of moderate-to-severe CD. On the other hand, the introduction of lower-cost ustekinumab biosimilars has the potential to broaden access to this therapy for patients with CD, allowing for its utilization in earlier stages.[52] Considering all aspects of efficacy and safety, as well as the significant cost reductions, biosimilars of ustekinumab could be considered as first-line therapy for patients with IBD requiring advanced treatment. The comparable therapeutic benefits and lower cost burden of biosimilars present a compelling case for their use in clinical practice, potentially enhancing accessibility and adherence to treatment regimens while maintaining clinical outcomes.

Importantly, a special situation should be considered when using biosimilars, such as the well-known nocebo effect. The nocebo effect, arising from patient expectations and not from the effect of the treatment itself, can adversely impact the effectiveness of biosimilars, particularly when patients are uninformed about their efficacy and safety.[53] This phenomenon, prevalent among IBD patients switching from the RP to the biosimilar, can diminish quality of life and compromise treatment adherence, ultimately impeding the potential cost-saving benefits of biosimilars.[54] A compassionate and empathetic approach to communication by a multidisciplinary team including physician, nurse, psychologist, and pharmacist plays a vital role in mitigating the nocebo effect,[55] enhancing awareness about biosimilars among both healthcare providers and patients.[56,57]

Figure 1 represents an overview of the advantages and challenges of ustekinumab biosimilars.

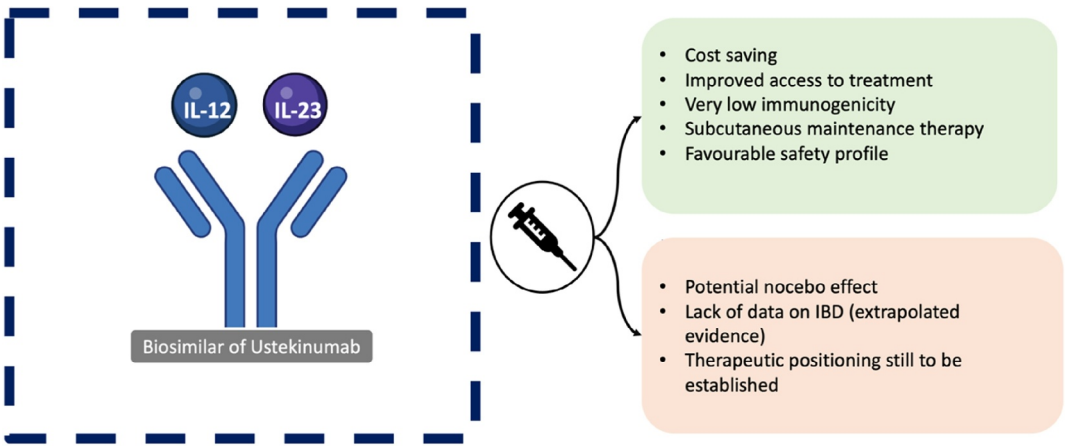

FIGURE 1 Strengths and challenges of biosimilars of ustekinumab. IBD, inflammatory bowel disease.

CONCLUSIONS

Ustekinumab is effective and safe in the treatment of moderate-to-severe CD, but its use is limited due to its high cost. The availability of ustekinumab biosimilars could allow to overcome this limitation, increasing access to therapies and changing drug positioning in the therapeutic algorithm of CD. Real-world studies in the field of IBD are warranted to confirm the long-term safety data of ustekinumab biosimilars and support their widespread use in clinical practice.

AUTHOR CONTRIBUTIONS

Silvio Danese conceived the article. Sarah Bencardino, André Gonçalves, and Ferdinando D'Amico wrote the article and created tables and figures. Mariangela Allocca, Federica Furfaro, Alessandra Zilli, Tommaso Lorenzo Parigi, Gionata Fiorino, Laurent Peyrin-Biroulet, and Silvio Danese critically reviewed the content of the paper and supervised the project. The manuscript was approved by all authors.

ACKNOWLEDGMENTS

This manuscript was supported by Alvotech and STADA. The views and opinions expressed in this article belong solely to the named authors, and do not necessarily reflect those of Alvotech and STADA. Open access funding provided by BIBLIOSAN.

CONFLICT OF INTEREST STATEMENT

S. Bencardino, A. Gonçalves, A. Zilli, T.L. Parigi declares no conflicts of interest. F. D'Amico has served as a speaker for Sandoz, Janssen, Galapagos, and Omega Pharma; he also served as an advisory board member for Ferring, Galapagos, Abbvie, Janssen and Nestlè. M. Allocca received consulting fees from Nikkiso Europe, Mundipharma, Janssen, Abbvie, and Pfizer. F. Furfaro received consulting fees from Amgen, Abbvie, Janssen and Pfizer; L. Peyrin-Biroulet has served as a speaker, consultant and advisory board member for Merck, Abbvie, Janssen, Genentech, Mitsubishi, Ferring, Norgine, Tillots, Vifor, Hospira/Pfizer, Celltrion, Takeda, Biogaran, Boerhinger-Ingelheim, Lilly, HAC-Pharma, Index Pharmaceuticals, Amgen, Sandoz, For-ward Pharma GmbH, Celgene, Biogen, Lycera, Samsung Bioepis, Theravance. G. Fiorino served as a Consultant for AbbVie, Amgen, Celltrion, Ferring, Galapagos, Janssen, Pfizer, Sandoz and Takeda. S. Danese has served as a speaker, consultant, and advisory board member for Schering-Plough, AbbVie, Actelion, Alphawasserman, AstraZeneca, Cellerix, Cosmo Pharmaceuticals, Ferring, Genentech, Grunenthal, Johnson and Johnson, Millenium Takeda, MSD, Nikkiso Europe GmbH, Novo Nordisk, Nycomed, Pfizer, Pharmacosmos, UCB Pharma and Vifor.

DATA AVAILABILITY STATEMENT

No new data were generated or analyzed in support of this research.

ORCID

André Gonçalves https://orcid.org/0000-0001-7984-9522
Gionata Fiorino https://orcid.org/0000-0001-5623-2968
Laurent Peyrin-Biroulet https://orcid.org/0000-0003-2536-6618
Silvio Danese https://orcid.org/0000-0001-7341-1351

REFERENCES

1. Torres J, Mehandru S, Colombel J-F, Peyrin-Biroulet L. Crohn's disease. Lancet. 2017;389(10080):1741–55. https://doi.org/10.1016/S0140-6736(16)31711-1
2. Roda G, Chien Ng S, Kotze PG, Argollo M, Panaccione R, Spinelli A, et al. Crohn's disease. Nat Rev Dis Primers. 2020;6(1):22. https://doi.org/10.1038/s41572-020-0156-2
3. Torres J, Bonovas S, Doherty G, Kucharzik T, Gisbert JP, Raine T, et al. ECCO guidelines on therapeutics in Crohn's disease: medical treatment. J Crohns Colitis. 2020;14(1):4–22. https://doi.org/10.1093/ecco-jcc/jjz180
4. Skyrizi. European Medicines Agency. 2019. [Online]. Available from: https://www.ema.europa.eu/en/medicines/human/EPAR/skyrizi. Accessed 23 Feb 2024
5. Rinvoq. European Medicines Agency. 2019. [Online]. Available from: https://www.ema.europa.eu/en/medicines/human/EPAR/rinvoq. Accessed 23 Feb 2024
6. van der Valk ME, Mangen MJJ, Leenders M, Dijkstra G, van Bodegraven AA, Fidder HH, et al. Healthcare costs of inflammatory bowel disease have shifted from hospitalisation and surgery towards anti-TNFα therapy: results from the COIN study. Gut. 2014;63(1):72–9. https://doi.org/10.1136/gutjnl-2012-303376
7. Chen B, Nagai S, Armitage JO, Witherspoon B, Nabhan C, Godwin AC, et al. Regulatory and clinical experiences with biosimilar filgrastim in the U.S., the European Union, Japan, and Canada. Oncologist. 2019;24(4):537–48. https://doi.org/10.1634/theoncologist.2018-0341
8. Danese S, Gomollon F. Governing Board and Operational Board of ECCO, 'ECCO position statement: the use of biosimilar medicines in the treatment of inflammatory bowel disease (IBD)'. J Crohns Colitis. 2013;7(7):586–9. https://doi.org/10.1016/j.crohns.2013.03.011
9. Ben-Horin S, Vande Casteele N, Schreiber S, Lakatos PL. Biosimilars in inflammatory bowel disease: facts and fears of extrapolation. Clin Gastroenterol Hepatol. 2016;14(12):1685–96. https://doi.org/10.1016/j.cgh.2016.05.023
10. Parigi TL, D'Amico F, Peyrin-Biroulet L, Danese S. Evolution of infliximab biosimilar in inflammatory bowel disease: from intravenous to subcutaneous CT-P13. Expert Opin Biol Ther. 2021;21(1):37–46. https://doi.org/10.1080/14712598.2020.1811849
11. Ryan C, Thrash B, Warren RB, Menter A. The use of ustekinumab in autoimmune disease. Expert Opin Biol Ther. 2010;10(4):587–604. https://doi.org/10.1517/14712591003724670
12. FDA Approves STELARA® (Ustekinumab) for treatment of adults with moderately to severely active Crohn's disease. JNJ.com. 2016. [Online]. Available from: https://www.jnj.com/media-center/press-releases/fda-approves-stelara-ustekinumab-for-treatment-of-adults-with-moderately-to-severely-active-crohns-disease. Accessed 1 Mar 2024
13. Stelara. European Medicines Agency. 2009. [Online]. Available from: https://www.ema.europa.eu/en/medicines/human/EPAR/stelara. Accessed 23 Feb 2024
14. D'Amico F, Peyrin-Biroulet L, Danese S. Ustekinumab in Crohn's disease: new data for positioning in treatment algorithm. J Crohns Colitis. 2022;16(Suppl 2):ii30–41. https://doi.org/10.1093/ecco-jcc/jjac011
15. Sandborn WJ, Feagan BG, Fedorak RN, Scherl E, Fleisher MR, Katz S, et al. A randomized trial of Ustekinumab, a human interleukin-12/23 monoclonal antibody, in patients with moderate-to-severe Crohn's disease. Gastroenterology. 2008;135(4):1130–41. https://doi.org/10.1053/j.gastro.2008.07.014
16. Sandborn WJ, Gasink C, Gao LL, Blank MA, Johanns J, Guzzo C, 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
17. Feagan BG, Sandborn WJ, Gasink C, Jacobstein D, Lang Y, Friedman JR, 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
18. Sandborn WJ, Rebuck R, Wang Y, Zou B, Adedokun OJ, Gasink C, et al. Five-year efficacy and safety of ustekinumab treatment in Crohn's disease: the IM-UNITI trial. Clin Gastroenterol Hepatol. 2022;20(3):578–90.e4. https://doi.org/10.1016/j.cgh.2021.02.025
19. Danese S, Vermeire S, D'Haens G, Panés J, Dignass A, Magro F, et al. Treat to target versus standard of care for patients with Crohn's disease treated with ustekinumab (STARDUST): an open-label, multicentre, randomised phase 3b trial. Lancet Gastroenterol Hepatol. 2022;7(4):294–306. https://doi.org/10.1016/S2468-1253(21)00474-X
20. Chaparro M, Baston-Rey I, Fernández-Salgado E, González García J, Ramos L, Diz-Lois Palomares MT, et al. Long-term real-world effectiveness and safety of ustekinumab in Crohn's disease patients: the SUSTAIN study. Inflamm Bowel Dis. 2022;28(11):1725–36. https://doi.org/10.1093/ibd/izab357
21. Straatmijer T, Biemans VBC, Hoentjen F, de Boer NKH, Bodelier AGL, Dijkstra G, et al. Ustekinuma b for Crohn's disease: two-year results of the initiative on Crohn and colitis (ICC) registry, a nationwide prospective observational cohort study. J Crohns Colitis. 2021;15(11):1920–30. https://doi.org/10.1093/ecco-jcc/jjab081
22. Iborra M, Beltrán B, Fernández-Clotet A, Iglesias-Flores E, Navarro P, Rivero M, et al. Real-world long-term effectiveness of ustekinumab in Crohn's disease: results from the ENEIDA registry. Aliment Pharmacol Ther. 2020;52(6):1017–30. https://doi.org/10.1111/apt.15958
23. Bermejo F, Jiménez L, Algaba A, Vela M, Bastida G, Merino O, et al. Re-induction with intravenous ustekinumab in patients with Crohn's disease and a loss of response to this therapy. Inflamm Bowel Dis. 2022;28(1):41–7. https://doi.org/10.1093/ibd/izab015
24. Fumery M, Peyrin-Biroulet L, Nancey S, Altwegg R, Gilletta C, Veyrard P, et al. Effectiveness and safety of ustekinumab intensification at 90 mg every four weeks in Crohn's disease: a multicenter study. J Crohns Colitis. 2020;15:jjaa177. https://doi.org/10.1093/ecco-jcc/jjaa177
25. FDA approves first stelara biosimilar, Wezlana. 2023. [Online]. Available from: https://www.centerforbiosimilars.com/view/fda-approves-first-stelara-biosimilar-wezlana. Accessed 1 Mar 2024
26. FDA approves ustekinumab-auub as interchangeable biosimilar to stelara for plaque psoriasis, psoriatic arthritis, and more. 2023. [Online]. Available from: https://www.dermatologytimes.com/view/fda-approves-ustekinumab-auub-as-interchangeable-biosimilar-to-stelara-for-plaque-psoriasis-psoriatic-arthritis-and-more. Accessed 1 Mar 2024
27. Alvotech and Teva announce U.S. FDA Approval of SELARSDI™ (ustekinumab-aekn), biosimilar to Stelara® (ustekinumab). 2024. [Online]. Available from: https://www.tevapharm.com/news-and-media/latest-news/alvotech-and-teva-announce-u.s.-fda-approval-of-selarsdi-ustekinumab-aekn-biosimilar-to-stelara-ust/. Accessed 20 May 2024
28. Uzpruvo. European Medicines Agency. 2024. [Online]. Available from: https://www.ema.europa.eu/en/medicines/human/EPAR/uzpruvo#ema-inpage-item-authorisation-details. Accessed 1 Mar 2024
29. Wu M, Li X, Yang D, Wang M, Zhang H, Li C, et al. Comparison of pharmacokinetic similarity, immunogenicity, and safety of ustekinumab and BAT2206 in healthy Chinese male subjects in a double-blind, randomized, single-dose, parallel-group phase I trial. BioDrugs. 2023;37(1):89–98. https://doi.org/10.1007/s40259-022-00563-5
30. Study details. A study to investigate interchangeability of ABP 654 for the treatment of participants with moderate to severe plaque psoriasis. ClinicalTrials.gov. 2023. [Online]. Available from: https://clinicaltrials.gov/study/NCT04761627?cond=NCT04761627&rank=1. Accessed 2 Mar 2024
31. Study details. A study to investigate ABP 654 for the treatment of participants with moderate to severe plaque psoriasis. ClinicalTrials.gov. 2023. [Online]. Available from: https://clinicaltrials.gov/study/NCT04607980?cond=NCT04607980&rank=1. Accessed 2 Mar 2024
32. Wynne C, Hamilton P, McLendon K, Stroissnig H, Smith M, Duijzings P, et al. A randomized, double-blind, 3-arm, parallel study assessing the pharmacokinetics, safety, tolerability and immunogenicity of AVT04, an ustekinumab candidate biosimilar, in healthy adults. Expert Opin Investig Drugs. 2023;32(5):417–27. https://doi.org/10.1080/13543784.2023.2215426
33. Feldman SR, Reznichenko N, Berti F, Duijzings P, Ruffieux R, Otto H, 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
34. Papp KA, Lebwohl MG, Thaçi D, Jaworski J, Kwiek B, Trefler J, 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
35. Study details. Efficacy, safety, and immunogenicity of subcutaneous DMB-3115 versus Stelara® in patients with moderate to severe chronic plaque psoriasis. ClinicalTrials.gov. 2023. [Online]. Available from: https://clinicaltrials.gov/study/NCT04785326?cond=NCT04785326&rank=1. Accessed 2 Mar 2024
36. Study details. A double-blind study to compare the efficacy, safety, and immunogenicity of the proposed biosimilar ustekinumab FYB202 to Stelara® in patients with moderate-to-severe plaque psoriasis. 2023. ClinicalTrials.gov. [Online]. Available from: https://clinicaltrials.gov/study/NCT04595409. Accessed 2 Mar 2024
37. Jeong H, Kang T, Lee J, Im S. Comparison of SB17 and reference ustekinumab in healthy adults: a randomized, double-blind, single-dose, phase I study. Int J Clin Pharmacol Ther. 2024;62(05):231–40. https://doi.org/10.5414/CP204492
38. 34047.pdf. 2023. [Online]. Available from: https://s3.eu-central-1.amazonaws.com/m-anage.com.storage.eadv/abstracts_congress2023/34047.pdf. Accessed 2 Mar 2024
39. Chow V, Mytych DT, Das S, Franklin J. Pharmacokinetic similarity of ABP 654, an ustekinumab biosimilar candidate: results from a randomized, double-blind study in healthy subjects. Clin Pharmacol Drug Dev. 2023;12(9):863–73. https://doi.org/10.1002/cpdd.1301
40. Danese S, Fiorino G, Raine T, Ferrante M, Kemp K, Kierkus J, et al. ECCO position statement on the use of biosimilars for inflammatory bowel disease-an update. J Crohns Colitis. 2017;11(1):26–34. https://doi.org/10.1093/ecco-jcc/jjw198
41. New and upcoming biosimilar launches.
42. Cohen RD. The pharmacoeconomics of biologic therapy for IBD. Nat Rev Gastroenterol Hepatol. 2010;7(2):103–9. https://doi.org/10.1038/nrgastro.2009.232
43. Berns M, Hommes DW. Anti-TNF-α therapies for the treatment of Crohn's disease: the past, present and future. Expert Opin Investig Drugs. 2016;25(2):129–43. https://doi.org/10.1517/13543784.2016.1126247
44. Dovizio M, Hartz S, Buzzoni C, Redondo I, Nedeljkovic Protic M, Birra D, et al. Real-world treatment patterns and healthcare resource use for ulcerative colitis and Crohn's disease in Italy. Adv Ther. 2024;41(6):2282–98. https://doi.org/10.1007/s12325-024-02840-x
45. Brodszky V, Baji P, Balogh O, Péntek M. Budget impact analysis of biosimilar infliximab (CT-P13) for the treatment of rheumatoid arthritis in six Central and Eastern European countries. Eur J Health Econ. 2014;15(Suppl 1):S65–71. https://doi.org/10.1007/s10198-014-0595-3

46. Kim H, Alten R, Avedano L, Dignass A, Gomollón F, Greveson K, et al. The future of biosimilars: maximizing benefits across immune-mediated inflammatory diseases. Drugs. 2020;80(2):99–113. https://doi.org/10.1007/s40265-020-01256-5
47. D'Amico F, Solitano V, Magro F, Olivera PA, Halfvarson J, Rubin D, et al. Practical management of biosimilar use in inflammatory bowel disease (IBD): a global survey and an international delphi consensus. J Clin Med. 2023;12(19):6350. https://doi.org/10.3390/jcm12196350
48. Shankar G, Arkin S, Cocea L, Devanarayan V, Kirshner S, Kromminga A, et al. Assessment and reporting of the clinical immunogenicity of therapeutic proteins and peptides-harmonized terminology and tactical recommendations. AAPS J. 2014;16(4):658–73. https://doi.org/10.1208/s12248-014-9599-2
49. Ustekinumab versus adalimumab for induction and maintenance therapy in biologic-naive patients with moderately to severely active Crohn's disease: a multicentre, randomised, double-blind, parallel-group, Phase 3b trial. Lancet. 2022;399(10342):2200–11. PubMed. [Online]. Available from: https://pubmed.ncbi.nlm.nih.gov/35691323/. Accessed 2 Mar 2024
50. Thomas H. UEG week 2023. Lancet Gastroenterol & Hepatol. 2023;8(12):1076. https://doi.org/10.1016/S2468-1253(23)00371-0
51. Jairath V, Sands BE, Bossuyt P, Farraye F, Ferrante M, Hisamatsu T, et al. OP35 efficacy of mirikizumab in comparison to ustekinumab in patients with moderate to severe Crohn's disease: results from the phase 3 VIVID 1 study. J Crohn's Colitis. 2024;18(Supplement_1):i62–4. https://doi.org/10.1093/ecco-jcc/jjad212.0035
52. Solitano V, D'Amico F, Fiorino G, Peyrin-Biroulet L, Danese S. Biosimilar switching in inflammatory bowel disease: from evidence to clinical practice. Expert Rev Clin Immunol. 2020;16(10):1019–28. https://doi.org/10.1080/1744666X.2021.1826311
53. Pouillon L, Socha M, Demore B, Thilly N, Abitbol V, Danese S, et al. The nocebo effect: a clinical challenge in the era of biosimilars. Expert Rev Clin Immunol. 2018;14(9):739–49. https://doi.org/10.1080/1744666X.2018.1512406
54. Pouillon L, Danese S, Hart A, Fiorino G, Argollo M, Selmi C, et al. Consensus report: clinical recommendations for the prevention and management of the nocebo effect in biosimilar-treated IBD patients. Aliment Pharmacol Ther. 2019;49(9):1181–7. https://doi.org/10.1111/apt.15223
55. D'Amico F, Pouillon L, Argollo M, Hart A, Fiorino G, Vegni E, et al. Multidisciplinary management of the nocebo effect in biosimilar-treated IBD patients: results of a workshop from the NOCE-BIO consensus group. Dig Liver Dis. 2020;52(2):138–42. https://doi.org/10.1016/j.dld.2019.11.004
56. Colloca L, Finniss D. Nocebo effects, patient-clinician communication, and therapeutic outcomes. JAMA. 2012;307(6):567–8. https://doi.org/10.1001/jama.2012.115
57. D'Amico F, Solitano V, Peyrin-Biroulet L, Danese S. Nocebo effect and biosimilars in inflammatory bowel diseases: what's new and what's next? Expert Opin Biol Ther. 2021;21(1):47–55. https://doi.org/10.1080/14712598.2020.1817374

How to cite this article: D'Amico F, Bencardino S, Gonçalves A, Allocca M, Furfaro F, Zilli A, et al. Unlocking hope: the future of ustekinumab biosimilars in Crohn's disease treatment. United European Gastroenterol J. 2024;1–15. https://doi.org/10.1002/ueg2.12682