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REVIEW

The 'totality of evidence' and 'extrapolation' of SB17, a ustekinumab biosimilar

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ABSTRACT

Introduction: SB17 is a ustekinumab (UST) biosimilar targeting interleukin-12/23 for treating immune-mediated inflammatory diseases (IMIDs). The development of UST biosimilars like SB17 may help address the high cost of innovator biologics, offering affordable alternatives without compromising efficacy or safety.

Areas covered: This review encompasses the totality of evidence supporting SB17's similarity to UST, its regulatory approval, and indication extrapolation. It also discusses SB17's lower immunogenicity relative to UST.

Expert opinion: The approval of UST biosimilars represents a significant advancement in managing chronic IMIDs including psoriasis, plaque psoriasis, psoriatic arthritis, Crohn's disease, and ulcerative colitis, providing cost-effective, efficacious alternatives. A randomized double-blind 28-week study involving over 500 patients with moderate-to-severe chronic plaque psoriasis demonstrated SB17's equivalence to UST, with more than 80% of patients achieving over 90% improvement in psoriasis severity indices. Treatment-emergent adverse events were comparable between SB17 and UST. Despite their potential to transform clinical outcomes, economic burdens, and drug utilization patterns, the adoption of UST biosimilars faces challenges, including concerns about equivalence and regulatory inconsistencies. Addressing these issues through education, consistent regulatory frameworks, real-world data, and ongoing monitoring is crucial for their successful integration into clinical practice.

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Biosimilar; crohn's disease; psoriasis; psoriatic arthritis; SB17; totality of evidence; ulcerative colitis; ustekinumab

1. Introduction

Ustekinumab (UST) is a fully human immunoglobulin G1 kappa (IgG1κ) monoclonal antibody (mAb) that neutralizes interleukin (IL)-12 and IL-23, two key cytokines involved in the inflammatory processes underlying several chronic immune-mediated inflammatory diseases (IMIDs) [1]. UST targets the common p40 subunit shared by the heterodimeric IL-12 (p35/p40) and IL-23 (p19/p40) cytokines [1]. p40 binds to the IL-12 receptor β1 chain (IL-12 Rβ1) which is shared by cell surface IL-12R complexes (IL-12Rβ1/IL-12Rβ2) and IL-23 receptor (IL-23R) complexes (IL-12Rβ1/IL-23R). By inhibiting the bioactivity of IL-12/23 cytokines, UST effectively disrupts signaling through their respective cell surface cytokine receptors expressed by various immune cells, including T cells and natural killer (NK) cells [2]. UST selectively binds the p40 subunit common to both IL-12 and IL-23, and therefore does not directly alter immune responses driven by other cytokines [2]. Moreover, UST cannot bind to receptor bound p40, and thus UST is unlikely to trigger Fc effector functions such as antibody-dependent cell-mediated cytotoxicity (ADCC) or complement-dependent cytotoxicity (CDC) [2]. These features make UST a highly specific and targeted therapeutic agent in modulating immune responses to IL-12/23.

Initially, innovator UST (Stelara®; Janssen Biotech, US) was approved by the US Food and Drug Administration (FDA) and the European Medicines Agency (EMA) in 2009 for the treatment of moderate to severe plaque psoriasis [3,4] based on its efficacy in reducing the severity of psoriatic lesions and improving patients' quality of life [5,6]. Subsequent approvals expanded its use to other indications, including psoriatic arthritis (PsA) in 2013, Crohn's disease in 2016 [7], and ulcerative colitis in 2019 [3,8]. Thus, UST is a treatment option for a range of chronic IMIDs.

Biologics, including mAbs such as UST, are complex molecules produced by living cells or organisms. This complexity imparts some degree of heterogeneity in the structure and function of biologic agents, which is a critical consideration in biologic development and production [9]. Biosimilars are biologic medical products that are highly similar to an already approved innovator, or 'reference' biologic, with no clinically meaningful differences in

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Article highlights

- SB17, an ustekinumab (UST) biosimilar, is a fully human IgG1κ monoclonal antibody targeting interleukins 12 and 23 approved in 2024.
- SB17 demonstrated biosimilarity to both EU- and US-sourced UST reference product (RP) through analytical characterization across critical quality attributes.
- SB17 demonstrated bioequivalence for the primary pharmacokinetics (PK) endpoints, area under the concentration-time curve from time zero to infinity (AUC_{inf}) and maximum serum concentration (C_{max}) in healthy volunteers.
- A randomized, double-blind, multicenter, phase III study demonstrated that SB17 is clinically biosimilar to UST RP at week 28 in moderate-to-severe plaque psoriasis. After switching from UST RP, SB17 maintained long-term comparable efficacy and safety with UST RP up to Week 52.
- SB17 exhibited a lower immunogenicity profile compared to the UST RP.
- The SB17 prefilled syringe represents a technological advancement in UST delivery, featuring latex-free construction, reduced needle size (29 G), and improved temperature stability.

quality, efficacy, and safety [10]. The regulation of biosimilars is rigorous, involving direct comparative studies to ensure equivalence to the reference product (RP) [10–12]. Approval of biosimilars requires comprehensive evaluations of analytical, preclinical, and clinical data by health authorities such as the FDA and the EMA [10–12].

Biologic medicines provide significant health benefits when used for treatment of chronic IMIDs such as Crohn's disease, resulting in improved clinical remission and mucosal healing, reduced incidence of complications and need for surgical intervention, prevention or delay of disease progression, and enhanced quality of life [13–15]. However, the high cost of innovator biologic therapies is often a significant barrier to patient access [16–18]. Biosimilars reduce this financial burden by providing less costly treatment options without compromising efficacy or safety in clinical practice. The 2024 Association for Accessible Medicines report shows that biosimilars have generated $36 billion in savings in the US since 2015, of which $12.4 billion where in 2023 alone [19]. Biosimilars are often priced more than 40% lower than the originators which consequently also results in a reduction in price of brand prices. Ultimately, the development of biosimilars has increased patient access to biologic therapies, improved therapeutic efficiency, and reduced direct treatment costs [20–23].

SB17 (Pyzchiva® in EU and US, Epyztek® in South Korea; Samsung Bioepis, Republic of Korea) was approved as an UST biosimilar in 2024 by the FDA and the EMA based on the totality of evidence (TOE) [24–26]. The TOE supporting SB17's approval encompasses extensive analytical, preclinical, and clinical data demonstrating its similarity or comparability in terms of quality, efficacy, and safety relative to UST RP [27,28]. Currently, seven UST biosimilars including SB17 have been approved by the US FDA or the EMA (Table 1).

This review aims to provide a focused overview of SB17, centering on the TOE supporting its biosimilarity to UST, including analytical, non-clinical, and clinical studies. The review also addresses the concept of extrapolation and the FDA's interchangeability designation for biosimilars. It further explores the lower immunogenicity observed with SB17, concluding consistency in treatment efficacy. Finally, this review highlights the device features of SB17, which may further enhance patient convenience and adherence and improve their overall treatment experience. This article is based on previously conducted research and does not include new studies with human or animal subjects carried out by the authors.

2. Totality of evidence in SB17 development

2.1. Evidence-based approach to support biosimilarity

The regulatory approval pathways for biosimilars involve detailed and systematic comparability assessments to compile comprehensive evidence demonstrating their biosimilarity to the RP with respect to quality, efficacy, and safety [27,28,40]. This methodology, known as the 'totality of evidence (TOE),' begins with analytical evaluations of chemistry, manufacturing, and control (CMC) along with quality assessments, and then progresses through non-clinical and clinical phases. Analytical characterization is the foundation of biosimilar development and involves comparison of the biosimilar's pharmaceutical quality, primary structure, higher-order structures, post-translational modifications, and biological activity relative to the RP. Biosimilars do not require generation in the same cell line as the RP, which reflects the focus on physical, chemical, and biological characteristics of the biosimilar rather than the manufacturing process in regulatory requirements. Non-clinical *in vitro* and *in vivo* studies assess the biosimilar's toxicity, pharmacokinetics (PK), and pharmacodynamics (PD), and aim to demonstrate the biosimilar's similarity in safety and efficacy relative to the RP in non-human models. Lastly, clinical trials are conducted, with phase I focusing on PK and PD comparisons in healthy volunteers, and phase III assessing efficacy, safety, and immunogenicity in patients with one of the RPs indications, ideally in the indication that would be most sensitive for detecting differences. This stepwise approach ensures a thorough comparison between the biosimilar and its RP, supporting the conclusion of biosimilarity based on the TOE.

2.2. Analytical characterization

To demonstrate that SB17 and UST RP are structurally, physiochemically, and biologically similar, state-of-the-art analytical techniques were used to compare SB17 with the EU and US versions of UST RP [41]. Several critical parameters were evaluated to determine biosimilarity, including physiochemical properties such as purity, product-related impurities, and charge heterogeneity; structural properties such as primary structure, post-translational modifications (PTMs), higher-order structures, and quantity; and functional properties such as fragment antigen binding (Fab)- and fragment crystallizable (Fc)-related biological activities [41].

SB17 was highly similar to UST RP across all assessed attributes with no significant differences [41]. PTMs such as oxidation and deamination were measured at comparative levels between SB17 and UST RP [41]. Higher-order secondary and tertiary protein structures showed comparable

Table 1. Approval status of ustekinumab (UST) biosimilars.

Manufacturer	Distributor	Product Code	EMA Approval Status*	FDA Approval Status*	Proprietary Name (Nonproprietary)	Approved Indications	Reference
Alvotech	Stada[a]/ Teva[b]	AVT04	Approved (Jan 2024)	Approved (Apr 2024)	– EU: Uzpruvo – US: Selarsdi (ustekinumab-aekn)	– EU: PsO, PsA, CD, and pediatric PsO (≥60 kg) – US: PsO, PsA, CD, UC and pediatric PsO and PsA (≥60 kg)	[29,30]
Amgen	Amgen	ABP 654	Approved (Jun 2024)	Approved (Oct 2023)	– EU: Wezenla – US: Wezlana (ustekinumab-auub)	– EU: PsO, PsA, CD, and pediatric PsO (≥6 years) – US: PsO, PsA, CD, UC, pediatric PsO and PsA (≥6 years)	[31,32]
Biocon Biologics	N/A	Bmab 1200	N/A	Approved (Nov 2024)	– EU: Yesintek (pending; approval expected Feb 2025) – US: Yesintek (ustekinumab-kfce)	– US: PsO, PsA, CD, UC, pediatric PsO and PsA (≥6 years)	N/A
BioFactura	CuraTeQ	BFI-751	N/A	N/A	N/A	N/A	[33]
Bio-Thera	Hikma	BAT2206	N/A	N/A	N/A	N/A	N/A
Celltrion	Celltrion	CT-P43	Approved (Aug 2024)	Approved (Dec 2024)	– EU: Steqeyma – US: Steqeyma (ustekinumab-stba)	– EU: PsO, PsA, CD, and pediatric PsO (≥60 kg) – US: PsO, PsA, CD, UC, and pediatric PsO and PsA (≥60 kg)	[34,35]
Dong-A ST/ Accord BioPharma	Intas	DMB-3115	Approved (Dec 2024)	Approved (Oct 2024)	– EU: Imuldosa, Absimky (with UC) – US: Imuldosa (ustekinumab-srlf)	– EU: PsO, PsA, CD, and pediatric PsO (≥60 kg), UC (Absimky) – US: PsO, PsA, CD, UC, pediatric PsO and PsA (≥60 kg)	[36,37]
Fresenius Kabi	Formycon AG	FYB202	Approved (Sep 2024)	Approved (Sep 2024)	– EU: Otulfi, Fymskina (with UC) – US: Otulfi (ustekinumab-aauz)	– EU: PsO, PsA, CD, and pediatric PsO (≥60 kg), UC (Fymskina) – US: PsO, PsA, CD, UC, pediatric PsO and PsA (≥60 kg)	[38,39]
Samsung Bioepis	Sandoz	SB17	Approved (Apr 2024)	Approved (Jun 2024)	– EU: Pyzchiva, Eksunbi (with UC) – US: Pyzchiva (Ustekinumab-ttwe)	– EU: PsO, PsA, CD, and pediatric PsO (≥60 kg), UC (Eksunbi) – US: PsO, PsA, CD, UC, pediatric PsO and PsA (≥60 kg)	[26,42]

*Approval date determined by the first approval date in the case of multiple proprietary names.
[b]For EU.
[c]For US.
Abbreviations: BLA, biologics license application; CD, Crohn's disease; FDA, Food and Drug Administration; EMA, European Medicines Agency; MAA, marketing authorization application; N/A, not available; PsA, psoriatic arthritis; PsO, plaque psoriasis; UC, ulcerative colitis.

spectral overlap between SB17 and UST RP [41]. Product-related impurities, including monomer composition, levels of high molecular weight (HMW) species, and IgG species levels (percentage of intact IgG relative to total protein) were also measured. The monomer composition (min-max [SD]) of SB17 (99.7–99.8% [0.1]) was equivalent to EU UST RP (98.9–99.0% [0.1]) and US UST RP (99.0% [0.0]) [41]. Likewise, HMW species (min-max [SD]) were highly similar (0.2% [0.0], 0.3% [0.0], and 0.3% [0.0] for SB17, EU UST RP, and US UST RP, respectively) [41]. Levels of IgG species (min-max [SD]) were also similar (97.7–98.1% [0.2], 97.9–98.2% [0.2], and 98.0–98.5% [0.3] for SB17, EU UST RP, and US UST RP, respectively) [41]. Charge heterogeneity was measured with or without treatment with carboxypeptidase B (CpB) and Peptide-N-Glycosidase F (PNGase F) [41]. Whereas the spectral overlap between SB17 and UST RP was highly similar following treatment with CpB and PNGase F, without enzyme treatment, SB17 exhibited lower amounts (min-max [SD]) of acidic (10.9% [1.3], 23.3% [2.0], and 23.9% [2.4] for SB17, EU UST RP, and US UST RP, respectively) and basic (4.4% [0.1], 41.3% [1.8], 43.2% [2.9] for SB17, EU UST RP, and US UST RP, respectively) variants, and higher contents of main portion (84.7% [1.4], 35.4% [0.6], 33.0 [0.5] for SB17, EU UST RP, and US UST RP, respectively) [41].

Discrepancies in the amount of acidic and basic variants between the biologics are due to difference in producing cell lines as discussed below and were not clinically meaningful, as SB17 was comparable to UST RP in all critical and non-critical quality attributes related to mechanism of action (MoA) and biological activities (Table 2), including IL-12/23 neutralization and binding, ADCC, CDC, and binding of FcRn, FcRγRIa, FcRγRIIa, FcRγRIIb, FcRγRIIIa, and C1q [41].

Overall, the comprehensive analytical characterization confirmed that SB17 is highly similar to UST RP in structural, physicochemical, biophysical, and biological aspects. Given the similarities, SB17 would be expected to have similar clinical efficacy and safety as UST RP.

2.3. Non-clinical in vivo evidence

Previous non-clinical *in vivo* studies with UST RP indicated no significant human health hazards based on repeated-dose toxicity and developmental and reproductive toxicity studies, including safety pharmacology assessments [4]. For SB17, secondary pharmacology, safety pharmacology, PD drug interaction studies, PK analysis, and *in vivo* toxicology/toxicokinetic studies were not conducted given that the comparative structural analyses, physicochemical analyses, and *in vitro* non-clinical studies and functional assays confirmed biosimilarity [25,41]. Non-clinical *in vivo* data for SB17 are thus expected to be highly similar to those of UST RP [42], which aligns with

Table 2. Summary of biological activity results for SB17 and ustekinumab reference product (UST RP) [41].

	Min-Max [SD, N = 3]		
Quality Attributes	SB17	EU-UST	US-UST
IL-23 neutralization (%)	93–106 [6.8]	83–95 [6.7]	83–106 [11.5]
IL-23 binding (%)	100–102 [1.2]	97–103 [3.2]	97–101 [2.1]
IL-12 neutralization (%)	98–103 [2.5]	97–101 [2.1]	84–105 [11.4]
IL-12 binding (%)	96–99 [1.5]	95–97 [1.0]	95–96 [0.6]
FcRn binding (%)	102–106 [2.1]	110–115 [2.6]	113–115 [1.2]
FcγRIa binding (%)	99–110 [6.1]	111–121 [5.1]	115–121 [3.1]
FcγRIIa binding (%)	99–104 [2.5]	96–103 [3.6]	98–101 [1.5]
FcγRIIb binding (%)	93–103 [5.3]	108–110 [1.0]	102–111 [4.9]
FcγRIIIa binding (%)	98–103 [2.5]	109–112 [1.5]	101–111 [5.3]
C1q binding (%)	101–103 [1.0]	102–105 [1.7]	109–112 [1.5]
ADCC	No Activity	No Activity	No Activity
CDC	No Activity	No Activity	No Activity

Abbreviations: ADCC, antibody-dependent cellular cytotoxicity; C1q, complement component 1q; CDC, complement-dependent cellular cytotoxicity; EU-UST, EU-sourced ustekinumab; Min, minimum; Max, maximum; N, number of experiments; SD, standard deviation; US-UST, US-sourced ustekinumab.
Source: Yang SY, et al. 2024 [41].
Table 2 is reprinted from: Yang SY, Lee C, Hwang K, et al. Characterization for the Similarity Assessment Between Proposed Biosimilar SB17 and Ustekinumab Reference Product Using State-of-the-art Analytical Method. Drugs in R&D. 2024; In press.

guidelines from the FDA and EMA on similar biological medicinal products [27,28,43].

2.4. Phase I clinical study

To assess whether SB17 performs similarly to UST RP, the PK parameters, safety, tolerability, and immunogenicity of SB17 and EU and US versions of UST RP were compared in a randomized, double-blind, three-arm, parallel-group, single-dose phase I trial (NCT02453672) conducted with 201 healthy male patients at a center in France (Figure 1(a)) [44,45]. SB17 and UST RP had similar mean serum concentration-time profiles from the nominal times zero to 2,352 hours (Figure 2(a,b)) and similar PK parameters (Table 3) [45]. PK equivalence independent of body weight was confirmed by analysis of covariance (ANCOVA), as the 90% confidence interval (CI) of the weight-adjusted least squares means (LSMeans) ratios of the area under the concentration-time curve from time zero to infinity (AUC_{inf}) and the maximum serum concentration (C_{max}) were within the predefined bioequivalence margin of 0.8–1.25 and contained 1.00 [45].

The numbers of treatment-emergent adverse events (TEAEs) were likewise similar across the three treatment groups; 105 TEAEs were reported in 46 (68.7%) patients from the SB17 group, 79 TEAEs in 39 (58.2%) patients from the EU-UST group, and 67 TEAEs in 44 (65.7%) patients from the US-UST group [45]. The most frequently reported TEAEs were headaches (16 TEAEs in 13 [19.4%] patients from the SB17, 19 TEAEs in 15 [22.4%] patients from the EU-UST, and 11 TEAEs in 8 [11.9%] patients from the US-UST group), followed by nasopharyngitis (9 TEAEs in 8 [11.9%] patients from the SB17, 11 TEAEs in 10 [14.9%] patients from the EU-UST, and 7 TEAEs in 7 [10.4%] patients from the US-UST group). Laboratory results, vital signs, and 12-lead electrocardiogram (ECG) parameters likewise showed no clinically significant drug-related changes, with no deaths, serious adverse events (SAEs), severe TEAEs, or study drug-related discontinuations due to TEAEs reported during the study [45]. Taken together, these results in healthy patients confirmed the PK equivalence of SB17 to UST RP.

2.5. Phase III clinical study

To ensure that SB17 performs similarly to UST RP, the efficacy, safety, PK and immunogenicity of the biologics were compared in a randomized, double-blind, two-arm, phase III trial (NCT02754882) conducted with 503 patients with plaque psoriasis at 45 centers from 8 countries (Figure 1(b)) [46,47]. Up to week 28, SB17 and UST RP had similar efficacy, with both drugs reducing percent change from baseline Psoriasis Area Severity Index (PASI) by approximately 85% [46]. The safety profile was comparable between SB17 and UST RP, with very few SAEs, and most of the TEAEs being mild to moderate in severity [46]. One hundred TEAEs with > 5% incidence were reported (46 TEAEs [18.5%] for the SB17 and 54 [21.3%] for the UST-RP group) and included nasopharyngitis (22 TEAEs [8.8%] for the SB17 and 21 [8.3%] for the UST-RP group), COVID-19 (16 TEAEs [6.4%] for the SB17 and 23 [9.1%] for the UST-RP group), and upper respiratory tract infection (10 TEAEs [4.0%] for the SB17 and 13 [5.1%] for the UST-RP group). There were no deaths among patients receiving either SB17 or UST RP. SB17 was biosimilar to UST RP in terms of PK parameters (Figure 2(c)) [46].

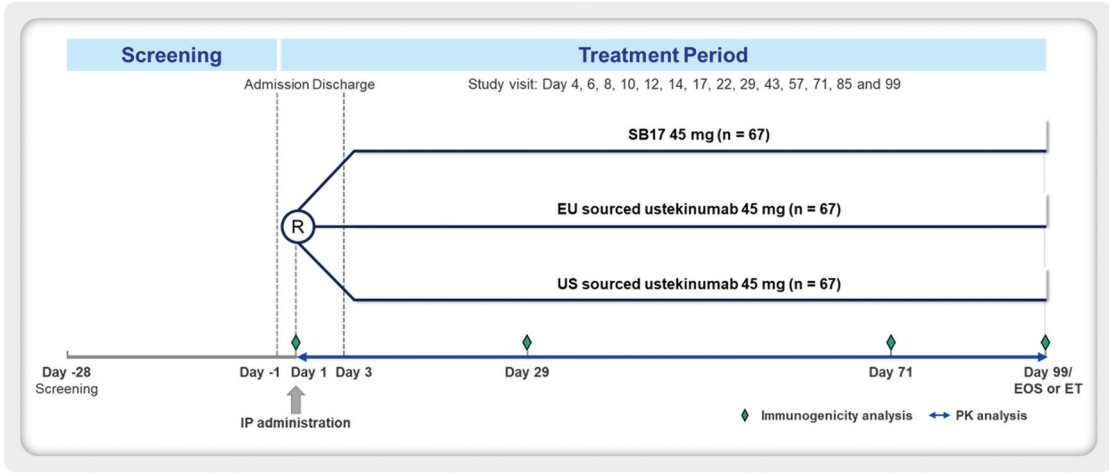
Patients from the phase III study were re-randomized at week 28 into the following groups: continuing SB17 (SB17 +SB17), continuing UST (UST+UST), or switching from UST to SB17 (UST+SB17) [47,48]. The percent change from baseline in PASI at week 52 was comparable between SB17+SB17, UST +UST, and UST+SB17 treatment groups (95.8%, 94.5%, and 95.6%, respectively) [47,48]. During the transition period, the incidence of TEAEs was generally similar across the treatment groups (SB17+SB17: 16.5%, UST+UST: 23.8%, UST+SB17: 13.9%). Collectively, these findings provide clinical evidence supporting the biosimilarity of SB17 to UST RP in the treatment of the target patient population.

3. Immunogenicity of UST biosimilars

3.1. Immunogenicity and clinical implications

The immune system's recognition of therapeutic molecules can lead to the production of anti-drug antibodies (ADAs)

(a)



(b)

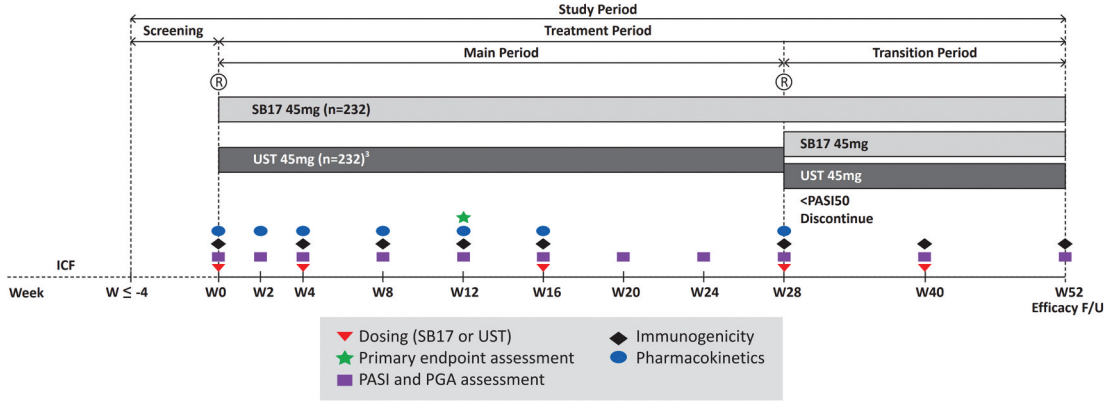


Figure 1. Design of SB17 phase I [44,45] and phase III [46–48] clinical studies. schematic of SB17 phase I and Phase III study designs. (a) Eligible healthy patients were randomized to receive a single dose of 45 mg of SB17, EU-UST, or US-UST on day 1. Patients were observed for 99 days (2,352 hours) post-dose. (b) Patients were randomized to receive either SB17 or UST at week 0, 4, and then every 12 weeks thereafter until week 40. At week 28, the UST RP treatment group was re-randomized in a 1:1 manner to receive either SB17 or UST RP. Patients that received SB17 continued to receive SB17 until week 40, but they followed the randomization procedure in order to maintain blinding. Figure 1(a) is reprinted from abstract 41,531 presented at the American Academy of dermatology association annual meeting 2023 [44], © 2024 American Academy of dermatology association. Written permission received from the author for republication. Figure 1(b) is reprinted from [46], © 2024 the American Academy of dermatology, licensed with CC-BY 4.0.

Abbreviations: EOS, end of study; F/U, follow-up; ICF, informed consent form; IP, investigational product; PASI, psoriasis area and severity index; PGA, physician's global assessment; PK, pharmacokinetics; W, week; ®, randomization; UST, ustekinumab.

which may be neutralizing or non-neutralizing. Neutralizing antibodies (Nabs) specifically bind to regions on therapeutic proteins such that they directly inhibit or nullify their biological activities [49]. On the other hand, non-neutralizing NAbs (NNAbs) bind to therapeutics without compromising their ability to engage their respective antigenic targets, though NNAbs may affect drug clearance and PK [49]. NAb responses can pose serious clinical consequences by reducing the efficacy of therapeutic mAbs and in some cases, necessitating additional dosing or switching drugs for patients. Therefore, understanding and managing immunogenic ADA responses to therapeutic mAbs is crucial to maintaining their effectiveness and ensuring patient safety.

The immunogenicity of UST has been closely monitored. Historically, the UST ADA positivity rate was reported as approximately 4–7%, with the majority of patients who were ADA-positive also having neutralizing antibodies (Table 4) [50]. Whereas earlier detection methods for immunogenicity involved enzyme-linked immunosorbent assays (ELISAs), the introduction of more advanced techniques such as electrochemiluminescent (ECL) assays has provided greater detection sensitivity [51,52]. Indeed, changes in sensitivity of analytical techniques may explain the increased ADA positivity rate of UST RP compared to historical data (Table 4). The immunogenicity of UST biosimilars has been analyzed in multiple clinical studies [41,45,46,53–59]. Five UST biosimilars, including SB17, exhibit less immunogenicity with respect to ADA responses compared to UST RP (Table 4). Although the basis for lower immunogenicity has not been elucidated for each biosimilar, for three of the five, this difference could be attributed to the absence or decrease of alpha-galactose (α-Gal) and NGNA glycan structures in the respective biosimilars compared to UST RP.

In the SB17 phase I study, the post-dose (all time) ADA incidences for SB17 and UST RP were 26.9% and 34.3%,

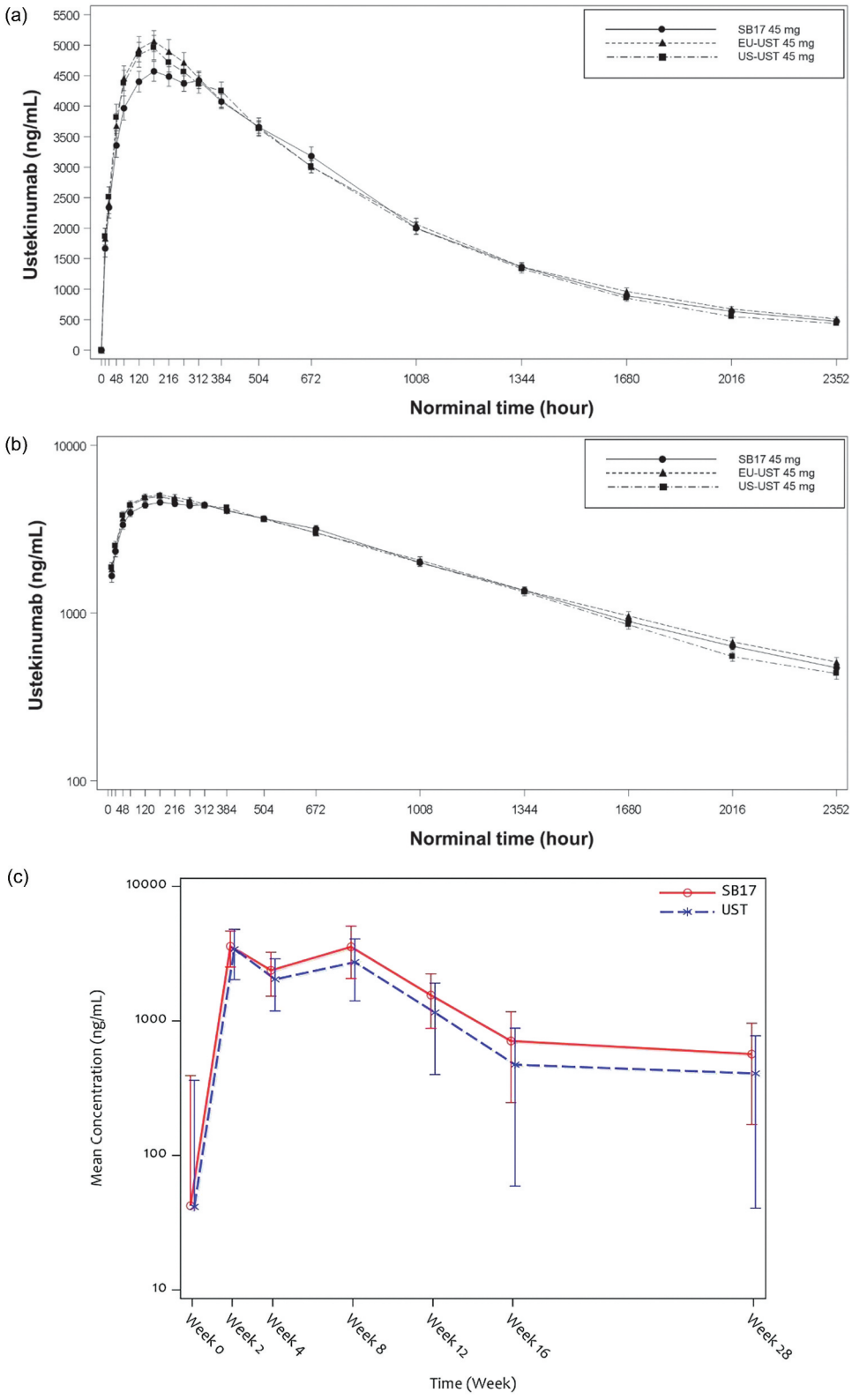


Figure 2. Mean serum concentration-time profiles of SB17 and ustekinumab reference product (UST RP). Mean serum concentration-time profiles (mean ± SD) of USTs. (a) Linear scale of UST concentrations from the phase I study. (b) Semi-logarithmic scale of UST concentrations from the phase I study. (c) Semi-logarithmic scale of UST concentrations from the phase III study from week 0 to week 28 (pharmacokinetic analysis set). For the phase I study (a) and (b), profiles for the three treatment groups (SB17, EU-UST, and US-UST) were similar and overlapped across all comparisons. Weight-adjusted analyses of LSMeans ratios (90% CI) of SB17 vs. EU-UST, SB17 vs. US-UST, and EU-UST vs. US-UST showed that all 90% CIs were within the equivalence margin of 0.8–1.25 and contained 1.0. The results for AUC_{inf} were 1.01 (0.92, 1.11), 1.02 (0.94, 1.12), and 1.00 (0.92, 1.10) for SB17 vs. EU-UST, SB17 vs. US-UST, and EU-UST vs. US-UST, respectively, while the results for C_{max} were 0.93 (0.85, 1.02), 0.96 (0.88, 1.05), and 1.02 (0.94, 1.12), respectively. For the phase III study (c), the PK profiles of SB17 vs. UST were likewise comparable. Figure 2(a,b) are reprinted with permission from [45] © dustri-verlag dr. K. Feistle. Figure 2(c) is reprinted from [46], © 2024 the American Academy of dermatology, licensed with CC-BY 4.0.

Abbreviations: AUC_{inf}, area under the concentration-time curve from time zero to infinity; CI, confidence interval; C_{max}, maximum serum concentration; EU-UST = EU-sourced ustekinumab; SD, standard deviation; US-UST = US-sourced ustekinumab.

Table 3. Summary statistics of pharmacokinetics (PK) parameters [45].

PK parameter	Statistics	SB17 N = 62	EU-UST N = 64	US-UST N = 60
AUC_{inf} (ng×h/mL)	Mean (SD)	5,143,600 (1,401,400)	5,273,000 (1,649,100)	5,116,600 (1,526,800)
	Median (Min – Max)	4,969,900 (2,414,000–8,884,000)	5,305,400 (2,045,000–10,280,000)	4,918,500 (2,118,000–10,200,000)
C_{max} (ng/mL)	Mean (SD)	5,095 (1,498)	5,689 (1,877)	5,420 (1,659)
	Median (Min – Max)	5,045 (2,630–9,030)	5,480 (2,950–13,700)	5,400 (1,590–11,100)
AUC_{last} (ng×h/mL)	Mean (SD)	4,721,000 (1,262,300)	4,853,500 (1,431,100)	4,769,900 (1,336,800)
	Median (Min – Max)	4,642,600 (2,302,000–8,526,000)	4,993,000 (1,974,000–9,786,000)	4,644,100 (1,959,000–9,257,000)
$AUC_{0-264\,h}$ (ng×h/mL)	Mean (SD)	1,044,800 (325,730)	1,148,200 (365,750)	1,117,700 (355,820)
	Median (Min – Max)	1,039,000 (458,500–1,780,000)	1,104,500 (565,500–2,820,000)	1,105,300 (291,500–2,042,000)
t_{max} (h)	Median (Min – Max)	168.000 (48.00–672.00)	168.000 (12.00–504.00)	168.000 (48.00–1,008.00)
V_z/F (mL)	Mean (SD)	7,561.0 (2,312.5)	7,149.3 (1,744.3)	7,240.6 (2,241.5)
	Median (Min – Max)	7,250.2 (2,817–12,910)	6,945.2 (2,825–11,560)	6,941.4 (3,207–17,980)
λ_z (1/h)	Mean (SD)	0.0013891 (0.00084317)	0.0014051 (0.00083473)	0.0013624 (0.00035215)
	Median (Min – Max)	0.0011864 (0.0007264–0.005569)	0.0012144 (0.0007386–0.007060)	0.0012921 (0.0007192–0.002264)
$T_{1/2}$ (h)	Mean (SD)	582.70 (171.00)	563.80 (161.55)	541.07 (134.93)
	Median (Min – Max)	584.24 (124.5–954.2)	571.09 (98.2–938.4)	536.46 (306.1–963.8)
CL/F (mL/h)	Mean (SD)	9.4308 (2.7416)	9.4592 (3.3800)	9.6075 (3.0698)
	Median (Min – Max)	9.0546 (5.065–18.64)	8.4819 (4.378–22.01)	9.1494 (4.411–21.25)
$\%AUC_{extrap}$	Mean (SD)	7.91 (5.00)	7.40 (3.73)	6.32 (3.18)
	Median (Min – Max)	6.41 (1.4–30.2)	6.69 (1.6–18.5)	5.52 (2.2–14.9)

Median and Min-Max range were summarized for t_{max}. Samples with low-speed centrifuge issue were excluded from PK parameters calculation. Refer to Pharmacokinetic evaluation of Results section [45].

Abbreviations: $UC_{0-264\,h}$, AUC from time zero to 264 hours; AUC_{last}, AUC from time zero to the last quantifiable concentration; AUC_{inf}, area under the concentration-time curve from time zero to infinity; C_{max}, maximum serum concentration; CL/F, apparent clearance; EU-UST, EU-sourced ustekinumab; Max, maximum; Min, minimum; N, number of subjects for the assessment parameter; PK, pharmacokinetic; SD, standard deviation; $T_{1/2}$, terminal half-life; t_{max}, time to reach C_{max}; US-UST, US-sourced ustekinumab; V_z/F, apparent volume of distribution during the terminal phase; λ_z, terminal rate constant; $\%AUC_{extrap}$, percentage of AUC_{inf} due to extrapolation from time of last measurable concentration to infinity.

Source: Jeong H, et al. 2024 [45].

Table 4. Immunogenicity of ustekinumab (UST) biosimilars.

Product	UST RP [50]	SB17 [41,45,46]	ABP 654 [53–55]	BFI-751 [56]	AVT04 [57,58]	CTP43 [59]
Cell line	murine myeloma Sp2/0	CHO	CHO	murine myeloma, NS0	murine myeloma Sp2/0	N/A
ADA Incidence in healthy individuals	5.6%	**SB17: 26.9%** EU UST: 34.3% US UST: 34.3%	**ABP 654: 15.4%** EU UST: 36.3% US UST: 38.0%	**BFI-751: 16%** EU UST: 44% US UST: 49%	**AVT04: 36.7%** EU UST: 59.6% US UST: 53.6%	N/A
ADA incidence in psoriasis patients[a]	4.1%	SB17: 13.3% UST: 39.4%	ABP 654: 18.6% UST: 37.1%	N/A	AVT04: 21.2% UST: 26.2%%	CT-P43: 10.2% UST: 17.0%
NAb incidence in psoriasis patients[b]	67%	SB17: 13.7% UST: 35.4%	ABP 654: 8.6% UST: 17.9%	N/A	AVT04: 33.3% UST: 22.9%	CT-P43: 5.9% UST: 7.9%
Analytical methods	ELISA	ECL	ECL	ECL	ECL	ECL
Study publication (year)	Phase I: 2007 Phase II: 2007	Phase I: 2024 Phase III: 2024	Phase I: 2023 Phase III: 2024	Phase I: 2023	Phase I: 2023 Phase III: 2023	Phase III: 2024
Reasons for lower ADA positivity rate	N/A	No presence of NGNA and α-gal in SB17 cell line vs originator SP2/0 cell line	Lack of α-gal and NGNA nonhuman residues in ABP654	Decreased amount of NANA and NGNA in BFI751	N/A	N/A

[a]ADA incidences in psoriasis patients derived from phase II studies with UST RP (Week 52) and from phase III studies with SB17 (Week 28), ABP 654 (Week 28), AVT04 (Week 52), and CTP43 (Week 28).

[b]NAb evaluations were conducted in patients with confirmed ADA-positive results.

Abbreviations: %, percent; α-gal, galactose-α-1,3-galactose; ADA, anti-drug antibody; CHO, Chinese hamster ovary; ECL, electrochemiluminescence; ELISA, enzyme-linked immunosorbent assay; EU, European Union; N/A, not available; NANA, N-acetylneuraminic acid; NGNA, N-glycolylneuraminic acid; Ref, reference; US, United States; UST, Ustekinumab reference product; vs, versus.

respectively [45]. In the phase III study, up to week 28, the ADA incidence was 13.3% for SB17 compared to 39.4% for UST RP [46]. Corresponding with the ADA results, the incidence of NAbs in ADA positive patients up to week 28 was 13.7% for SB17 and 35.4% for UST RP [46]. Following re-randomization at week 28 (Figure 1(b)), the incidence of new onset overall ADAs at week 52 was comparable (5.6%, 6.7%, and 5.1%, between SB17+SB17, UST+UST, and UST+SB17 treatment groups, respectively) [47,48]. Despite the lower immunogenicity of SB17 compared to UST RP, there was no difference in clinical outcomes between SB17 and UST RP treatment groups [46–48]. The primary clinical efficacy outcome at week 12 (percent change in PASI) was likewise comparable when treatment groups were stratified by ADA status (Figure 3) [46]. These

results suggest that while SB17 is less immunogenic, the presence of UST ADAs does not usually impede UST's clinical efficacy in patients with psoriasis. Moreover, SB17 is nonetheless considered biosimilar to UST because the respective ADA-negative subgroups have comparable efficacies (Figure 3) [27,46]. Variability in SB17 and UST RP immunogenicity across different trials may arise from differences in trial design, patient populations, or detection methods and may differ in real-world settings; these issues do not explain the lower immunogenicity of SB17 compared to UST RP observed in head-to-head trials.

3.2. SB17 manufacturing differences and quality attributes

The development of biosimilar mAbs is a complex process that is sensitive to manufacturing conditions. Inherent to the diversity of mAbs is their capacity to acquire PTMs that can affect their binding, effector functions, MoA, immunogenicity, clearance, and bioavailability [60]. PTMs are highly sensitive to manufacturing processes, such as the production cell line type and cell culture conditions, the purification steps, and the raw materials used [61–63]. Furthermore, biosimilar mAb manufacturers typically possess only limited information on the proprietary production processes of the reference mAb, and it is often necessary to change manufacturing processes for several reasons, such as regulatory compliance, increasing production capacity, moving to new facilities, changing raw materials, improving quality control, or optimizing efficiency [61]. Thus, just as different batches of reference mAbs vary [64], candidate biosimilar mAbs are not identical to the reference mAb; minor structural variations in the biosimilar are considered acceptable if the TOE supporting quality, biologic function, and efficacy are maintained [65].

Whereas UST RP is produced using a murine myeloma cell line (Sp2/0) [66], SB17 is produced in Chinese hamster ovary (CHO) cells using a recombinant DNA technology expression system (Table 4) [42]. Although CHO and SP2/0 are prominently used for production of therapeutic mAbs, differences in the cell lines can lead to variations in mAb structure and PTMs, including glycosylation patterns [67]. Glycosylation can impact several protein properties, including stability, susceptibility to protease cleavage, half-life, bioactivity, PK, and immunogenicity [68–70]. A distinct advantage of CHO cells is their capacity to produce mAbs with human-like glycosylation profiles which reduces the risk of introducing immunogenic non-human glycoforms such as the galactose-α-1,3-galactose (α-Gal) epitope [71]. Given that α-Gal epitopes are associated with mAb production in murine cell lines [71,72], and α-Gal has been linked to immune responses like IgE-mediated anaphylaxis [72], α-Gal epitopes should be minimized during therapeutic development. Additional advantages of CHO cells include high protein yield, continuous perfusion capability, and reduced susceptibility to viral contamination [71].

Although cell line-dependent variations in glycosylation are expected, mAb production in disparate cell lines does not preclude demonstration of matching function, inasmuch as mAb production in the same cell line does not guarantee functional biosimilarity [73,74]. In this regard, SB17 and UST RP exhibit distinct glycan profiles (Figure 4) while maintaining biosimilarity in function (Table 2). Whereas SB17 contains the charged glycan *N-acetylneuraminic* acid (NANA), UST RP contains the glycan epitope α-Gal and the charged glycan *N*-glycolylneuraminic acid (NGNA) [41]. Indeed, the absence of α-Gal and NGNA glycan structures in SB17 and other UST biosimilars may contribute to their lower immunogenicity profile compared to UST RP (Table 4). Thus, variations in biosimilar manufacturing do not necessarily impact scientific bridging based on the TOE, as exemplified by the regulatory approval of UST biosimilars (Tables 1 and 4).

4. Extrapolation of SB17 clinical data across indications

4.1. Regulatory basis for extrapolation

'Extrapolation' is a foundational concept applicable to biosimilars in regulatory science that is recognized and implemented by major health authorities such as the FDA and EMA, the European Crohn's and Colitis Organization (ECCO), and the Italian Group for the study of Inflammatory Bowel Disease (IGIBD) [27,40,75,76]. Having demonstrated biosimilarity to its RP, the clinical data obtained for a biosimilar in one approved indication may be extrapolated to additional therapeutic indications of the RP. Thus, extrapolation may support the approval of a biosimilar in an additional indication without confirmatory clinical trials of the biosimilar in each of those indications. The basis for extrapolation is rooted in a thorough understanding of the TOE. The agencies require substantial evidence that the biosimilar's characteristics are consistent across the extrapolated indications, and importantly, that the clinical data supporting the primary indication are robust. Extrapolation across different indications is usually granted case by case, which may differ between different agencies. For example, the biologics infliximab is approved for the treatment of a multitude of inflammatory diseases, including psoriasis, psoriatic arthritis, Crohn's disease, and ulcerative colitis. While the FDA, EMA, and Korean agency approved the biosimilar Remsima/Inflectra across all indications of the RP, Health Canada and the ECCO voiced concerns regarding the approval for inflammatory bowel diseases due to differences between the biosimilar and RP [77]. These issues were addressed by the TOE which ultimately resulted in the approval of the biosimilar for three additional indications [78]. Furthermore, a thorough evaluation of the TOE is required in order to alleviate potential concerns with extrapolation, especially when extrapolating across indications that follow different dosing or treatment schemes. Differences in dosing regimens can affect drug exposure, metabolism, and clearance and thus, a biosimilar can only be safely extrapolated to other indications when the PK/PD profile aligns with the one of the reference product. Similarly, a robust assessment of immunogenicity is required to address concerns arising from the risk of ADAs due to administering higher doses or more frequent dosing. This comprehensive framework requested by

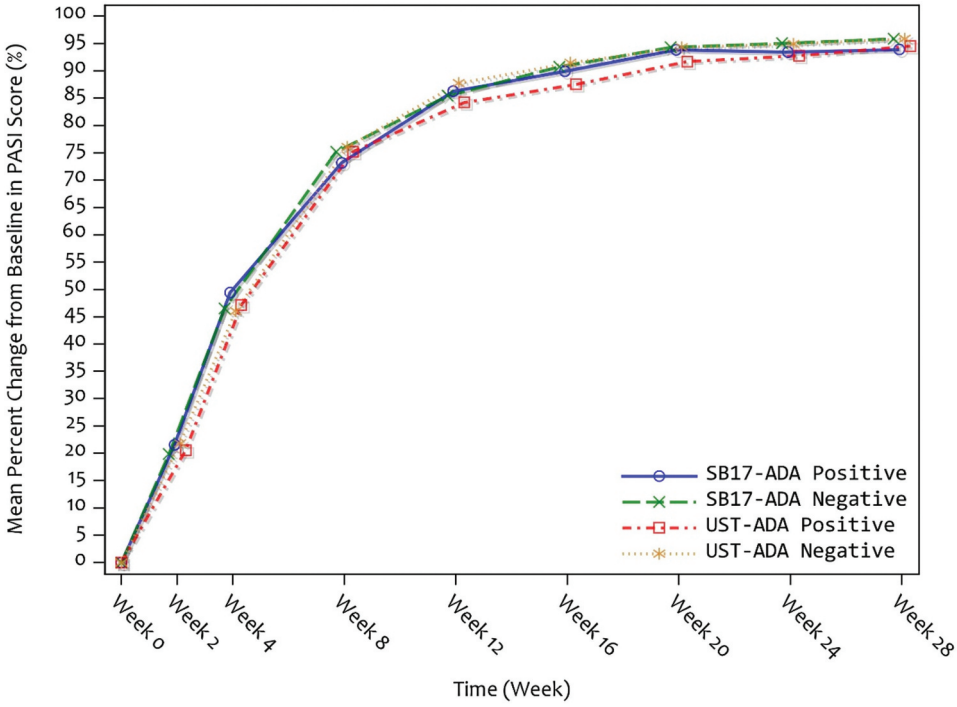


Figure 3. Percent change of PASI from baseline subgrouped by anti-drug antibody (ADA) status up to week 28. Mean percent change from baseline in patients' PASI scores up to week 28 stratified by ADA positivity or negativity. Reprinted from [46], © 2024 the American Academy of dermatology, licensed with CC-BY 4.0.
Abbreviations: ADA, anti-drug antibody; PASI, psoriasis area severity index; UST, ustekinumab.

regulatory authorities ensures that biosimilars can be confidently used across multiple therapeutic areas, thereby enhancing patient access to effective and affordable treatments.

4.2. Mechanism of action and extrapolated indications of SB17

SB17 targets IL-12 and IL-23 cytokines, which are primarily produced by activated dendritic cells, macrophages, and other antigen presenting cells in response to pathogens or other immune signals [79,80]. Whereas IL-12 promotes the differentiation of naive CD4+ T cells into T helper 1 (T_H1) cells and drives their activation, IFN-γ production, proliferation, and survival, IL-23 supports the survival and expansion of T helper 17 (T_H17) cells, which produce IL-17A, IL-17F, and IL-22 [2,79,80]. Dysregulation of IL-12/23 signaling pathways in T_H1/T_H17 cells is central to the development of chronic inflammation and pathology observed in numerous chronic IMIDs [2,81,82]. The clinical effects of UST in these disease settings can therefore be attributed to its selective binding of the common p40 subunit, disrupting signaling via IL-12 and IL-23 receptors, and preventing heightened activation of T_H1/T_H17 cells [1,2]. Clear evidence of the role of IL-23 in the pathogenesis of psoriasis, PsA, and inflammatory bowel disease (IBD) is provided by the genetic linkage between the genes encoding IL-23's two subunits and its receptor with these IMIDs [83–86]. Thus, the MoA of UST provides a basis for the extrapolation of SB17 from psoriasis as its primary indication to its additional approved indications, which include PsA, Crohn's disease, and ulcerative colitis [1].

4.3. Primary indication of psoriasis for ustekinumab and SB17 evaluations

Psoriasis was the first approved indication for UST RP in 2009 [3] and has led to an extensive accumulation of clinical trial data and real-world evidence (RWE) on UST's safety, efficacy, and long-term outcomes in treating psoriasis. This wealth of data has provided a deep understanding of psoriasis pathogenesis, patient responses to treatment, and potential side effects, offering a solid foundation for further comparative analysis of SB17. Furthermore, from a practical standpoint, psoriasis affects a significant portion of the population worldwide [87]; and the assessment of psoriasis severity is noninvasive, utilizing a well-established index (PASI) that can detect and differentiate between the effects of treatment regimens with high sensitivity. This enhances the feasibility, analysis sensitivity and objectivity, and statistical power of clinical trials for both UST and its biosimilars. Comparative testing of biosimilars and their corresponding RPs in the disease that is the most sensitive for detecting differences further supports extrapolation to other approved indications [88].

UST is commonly administered as a monotherapy in patients with psoriasis and IBD, without the concurrent use of immunosuppressive drugs such as methotrexate, which is frequently administered to reduce the production of ADAs against TNF-inhibitor mAbs. The monotherapy setting is ideal and has several clinical implications [40]. Specifically, using UST alone enables a clear assessment of its safety and efficacy. Additionally, studying UST in a monotherapy setting ensures that immunogenic responses are not suppressed and can be directly attributed to UST. For example, concomitant treatments like methotrexate,

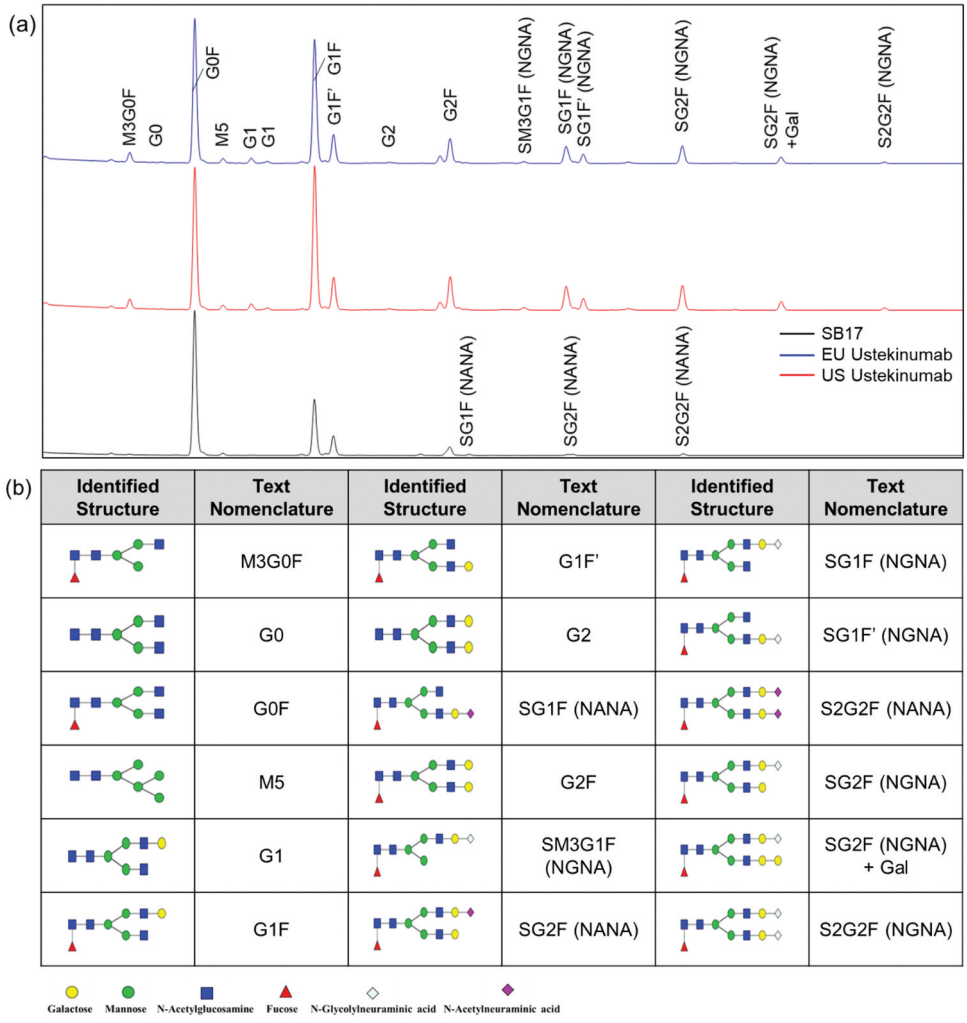


Figure 4. *N*-glycan profiles of SB17 and ustekinumab reference product (UST RP). A: *N*-glycan profiles of SB17, reference EU UST, and reference US UST were compared by HILIC-FLD using 2-AB labeling. B: schematic of identified glycan information relevant to SB17 and UST RP. Reprinted with permission from [30], © 2025 Yang et al., licensed with CC-BY-NC.

Abbreviations: 2-AB, 2-aminobenzamide; HILIC-FLD, hydrophilic interaction liquid chromatography with fluorescence detection; RP, reference product; UST, ustekinumab.

commonly used in patients with inflammatory arthritis, may reduce ADA production, thereby making the treated population less sensitive for detecting differences in immunogenicity. Nonetheless, methotrexate has not been shown to effectively decrease ADA formation against UST in patients with PsA [89].

In consideration of the practical aspects of studying psoriasis and the use of UST as a monotherapy, all approved and proposed UST biosimilars (Table 1) have conducted their pivotal trials in psoriasis patients. This uniform approach highlights and benefits from the sensitivity of psoriasis for biosimilar evaluations. The established understanding of psoriasis pathogenesis and treatment response enables precise evaluations of biosimilarity in critical areas. Importantly, because the same IL-12/23 signaling pathways disrupted by UST in psoriasis also underlie the pathogenesis of PsA, Crohn's disease, and ulcerative colitis, the TOE supporting biosimilarity in psoriasis trials can support extrapolation to other indications. The effective MoA of UST in these conditions, combined with extensive clinical trial data and regulatory guidance, ensures that the extrapolated indications of SB17 are scientifically and clinically valid.

4.4. Interchangeability of ustekinumab biosimilars

The FDA and EMA used to differ significantly in their approach to interchangeability of biosimilars. Historically, the FDA required switching studies or studies intended to support a demonstration that a biosimilar is interchangeable with a RP in order to deem the product as interchangeable in the US. While pharmacy regulations vary by state within the US, the interchangeability designation by the FDA generally implies that the product can be substituted for the reference product without consulting the prescriber. Based on updated scientific practices and experiences gained since the first interchangeability guidance issues in 2019, the FDA has dispensed with the requirement for dedicated switching studies in an update to the guidance in 2024 [90]. The agency states that its change in approach is based on the following considerations: First, the risk in terms of safety concerns or inferior efficacy has proven insignificant following switching between RP and biosimilar. Second, advanced analytical tools can now accurately evaluate the properties of a biologic, often with greater sensitivity than switching studies. Consequently, the FDA now deems a statement discussing how the existing data

package supports the FDA's designation of interchangeability sufficient. While some experts criticize the new approach, many do welcome the update to the guideline, as it may further simplify the access to biosimilars. Additional switching studies, that are often redundant in light of the rigorous comparability studies, increase developmental costs and extend the time to market, which both negatively impact patients' access to affordable treatment options. Furthermore, the regulatory distinction between 'biosimilarity' and 'interchangeability' may create misconceptions among healthcare providers, leading them to believe that biosimilars without a dedicated interchangeability label to be less effective or safe. Of the seven UST biosimilars approved by the FDA only Wezlana (ustekinumab-auub) received the interchangeability status due to dedicated switching studies [91]. A provisional determination of interchangeability was granted for SB17 [92] and Selarsdi (ustekinumab-ttwe) [93] indicating the FDA's confidence in the biosimilars' ability to perform equivalently to the RP across multiple indications based on the TOE and without clinical switching studies.

In the EU, once a biosimilar is approved by the EMA, it is considered interchangeable with its RP, and no additional switching studies are required to confirm interchangeability [94]. The EMA regards the demonstration of biosimilarity as sufficient for interchangeability but leaves the decision on automatic substitution without prescriber consultation to member states. This reflects the agency's view that switching between biosimilars and RPs (and between different, varying batches of the reference product) is a common and well-accepted practice in clinical settings across Europe [94]. Thus, while the FDA requires additional data for a biosimilar to be labeled interchangeable, the EMA considers all EU-approved biosimilars interchangeable by default without requiring further studies.

5. Further convenience of SB17

5.1. Device features of SB17 and ustekinumab reference product

UST RP and SB17 have both been approved in two different presentations of administration, i.e. the 130 mg/26 mL solution vial for intravenous infusion and pre-filled syringe (PFS) of 45 mg/0.5 mL and 90 mg/1 mL and and 45 mg/0.5 mL solution vial subcutaneous injections [26,66,95]. The SB17 PFS is indicated exclusively for pediatric or adolescent patients with a body weight exceeding 60 kg. Importantly, the PFS presentation offers distinct advantages, such as the potential for enhanced safety and patient satisfaction during treatment administration. The SB17 PFS has been designed to streamline the drug administration process for patient and healthcare professionals (HCPs), with several significant improvements over the UST PFS (Figure 5), including multiple usability aspects which may contribute to an improved patient experience.

The SB17 PFS is latex-free (Figure 5). Although latex allergies in patients with psoriasis receiving regular biologics injections are infrequently reported, latex allergies are common in medical practice [96]. The average prevalence of latex allergy worldwide is 9.7%, 7.2%, and 4.3% among healthcare workers, susceptible patients, and the general population, respectively [97]. Furthermore, latex hypersensitivity reactions can pose serious health risks for those affected [96,97]. Ensuring that the SB17 PFS is latex-free mitigates any potential latex specific allergic reactions, thus potentially broadening its usability among a diverse patient population.

An additional advantage of the SB17 PFS is its thinner needle size compared to the UST-RP PFS (29 G vs 27 G; Figure 5). This modification may improve patient comfort as thinner needles are associated with reduced pain and discomfort during injection [98]. This may contribute to a less daunting administration process for patients who require life-long continuous biologic injections, such as those with psoriasis and other IMIDs. Moreover, the psychological barrier associated with needle size can significantly influence a patient's willingness to adhere to treatment regimens [99,100], and thus a thinner needle may also enhance compliance.

Another important feature of the SB17 PFS is the inclusion of a needle safety guard (Figure 5), as needle safety is a paramount concern in clinical settings as well as for home administration. Needle-stick injuries pose a risk of infection transmission [101] and can be a source of anxiety for both

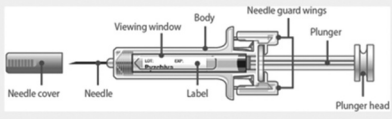
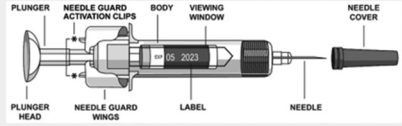
Product	SB17	UST RP
Illustration		
Needle Size	29G	27G
Latex Free	Yes	No
Needle Safety Guard	Yes	Yes

Figure 5. Pre-filled syringe (PFS) features of SB17 [42] and ustekinumab reference product (UST RP) [66]. key device features of the SB17 PFS and the UST PFS are compared.
Abbreviations: G, gauge; PFS, pre-filled syringe; RP, reference product; UST, ustekinumab..

patients and HCPs. Therefore, the needle safety guard in the SB17 PFS helps diminish accidental needle-stick injuries, potentially providing an additional layer of safety and protecting patients and HCPs who may handle the PFS.

Collectively, the design features of the SB17 PFS – latex-free material and thinner needle size – may enhance administration convenience, safety, and comfort for patients and HCPs. In consideration of these design attributes, the SB17 PFS may also improve patient adherence to prescribed UST treatment regimens.

5.2. Extended stability and enhanced flexibility of the SB17 pre-filled syringe

The stability and storage conditions of biologics are important factors that influence their usability and patient adherence. The UST RP PFS has specific storage requirements; according to the product information [4], once the UST RP PFS has been removed from refrigeration and stored at room temperature (RT) (up to 30°C), it cannot be returned to the refrigerator. This limitation presents several challenges. For HCPs who forget to use or are unable to use the PFS within the stipulated time frame, there is a risk of waste. Moreover, the rigidity of this storage requirement may be logistically inconvenient to HCPs or patients who travel or have unpredictable schedules, as they must ensure the UST RP PFS is used promptly within the 30-day window once removed from refrigeration.

In comparison, the SB17 PFS offers enhanced stability and flexibility in its storage conditions, significantly alleviating some of the challenges associated with the UST RP PFS. By the FDA's label the SB17 PFS can be returned to the refrigerator once within one month of being stored at RT (up to 30°C) [42]. By the EMA's label, it may be stored at RT (up to 30°C) for a maximum single period of up to 1 month and can be put back in the refrigerator [42]. This feature allows HCPs to better manage PFS storage without the pressure of a strict 30-day usage deadline. For instance, if an HCP removes the SB17 PFS from the refrigerator but then experiences a change in plans, they can re-refrigerate without compromising efficacy. This flexibility may lead to more cost-effective and practical treatment administration coinciding with reduced waste, as HCPs are less likely to encounter situations where they must discard unused SB17 PFS packages due to storage constraints.

6. Conclusions

The development of biologic medications such as mAbs has revolutionized the treatment of numerous diseases [102,103], but poses challenges due to mAbs' complex structures and inherent production variability [60–63]. These variations can lead to difference between mAb production batches and between biosimilars and their RPs [104], which contributes to concerns among HCPs regarding the performance of biosimilars [105]. Understanding that variations also exist between different batches of RP may help alleviate HCPs concerns. Regulatory agencies like the FDA and EMA require a systematic, stepwise approach to demonstrate biosimilarity. This includes rigorous analytical, functional, and clinical evaluations, referred to as the TOE, to ensure that biosimilars match their RPs in terms of molecular structure, biological function, and clinical efficacy. In alignment with this stepwise TOE approach, extensive evaluations confirmed the biosimilarity of SB17 and UST. These comprehensive assessments support SB17's extrapolation across all approved indications and ensure that SB17 provides a reliable treatment alternative for patients and HCPs.

7. Expert opinion

In the treatment of psoriasis, newer IL-23p19 [106,107] and IL-17 [108–112] inhibitors are more effective than UST in head-to-head trials and network meta-analyses [113,114]. As a result, these newer therapeutic agents have largely supplanted UST, especially in markets where their cost is also lower. However, UST may still remain a preferred option for patients with psoriasis, particularly those with concomitant IBD or PsA [115]. Furthermore, UST may also be favored for patients with advanced heart failure or ischemic heart disease, where anti-TNF agents are contraindicated [115]. In IBD treatment, it has not been clearly elucidated whether dual inhibition of IL-12/23 with p40 inhibitors is superior or equivalent to selective inhibition of IL-23 with p19 inhibitors [116]. The SEQUENCE study demonstrated superior efficacy of risankizumab (IL-23p19 inhibitor) over UST in Crohn's disease patients previously exposed to anti-TNFs [117]. However, the VIVID-1 study failed to show superiority of mirikizumab (IL-23p19 inhibitor) over UST in Crohn's disease [118]. The less frequent administration of UST compared to risankizumab and mirikizumab may be appealing to patients who opt to prioritize dosing convenience [119,120]. Additionally, IL-17 inhibitors have no proven clinical effect in IBD treatment and can even worsen disease status [121]. Therefore, UST remains a valuable therapeutic option in psoriasis, PsA and IBD due to its considerable objective efficacy, similar subjective efficacy, and favorable safety profile. By offering comparable efficacy and safety at lower costs, biosimilars such as SB17 can enhance treatment options and improve outcomes for a wider range of patients [20–23].

Adalimumab biosimilars targeting TNF are often used as first-line therapies due to their efficacy in treatment of IMIDs and cost advantage [122]. However, in patients with psoriasis, IL-12/23-specific UST biosimilars exhibit comparable efficacy to adalimumab with a better safety profile and fewer special precautions [114,123,124]. Additionally, the SEAVUE study of biologic-naive patients with Crohn's disease demonstrated that both UST and adalimumab monotherapies were highly effective in this population, with no difference in the primary outcome between the drugs [125]. Moreover, UST exhibits efficacy in anti-TNF refractory pediatric patients with ulcerative colitis [126], supporting the notion that select patient subsets may preferentially respond to UST. A cost-effective approach to managing psoriasis and anti-TNF refractory IBD could therefore involve using UST biosimilars as an earlier (or initial) treatment option among biologics. Patients who do not achieve adequate improvement with an UST biosimilar could then be transitioned to adalimumab or newer, more expensive agents (e.g. IL-23p19 or IL-17 inhibitors). This stepwise

approach could improve overall patient access to biologic treatments by making initial therapies more affordable, thereby increasing the number of patients who can receive timely and effective management for IMIDs or freeing healthcare resources for other needs.

The recent approval of UST biosimilars is likely to impact practice patterns and the surrounding dynamics, including treatment guidelines, therapeutic utility, effectiveness, and economics. With the availability of less costly UST biosimilars, treatment guidelines may evolve to more favorably recommend and adopt them as earlier options in treatment plans, particularly in resource-constrained settings. This may help to improve patient outcomes by controlling disease progression sooner and more effectively. Additional real-world data (RWD) reporting on UST biosimilar use in PsA and IBD will be important to confirm the comparable efficacy extrapolated from clinical trials.

Despite these potential benefits, several factors may hinder the adoption of UST biosimilars in clinical practice. Healthcare providers may be hesitant to use UST biosimilars initially for UST-naïve patients or switch from the UST innovator due to concerns about equivalence in efficacy, safety, or immunogenicity. The nature of biosimilars of not being exact copies of the originator may lead to hesitation in prescribing them, especially for complex or chronic conditions like IMIDs. Many physicians may prefer to rely on well-established treatment options due to familiarity and the extensive clinical data supporting their long-term use. However, knowing that extensive data support the biosimilarity of the biosimilar, often more comprehensive than the data available for the current batch of the innovator product, may help to alleviate these concerns. Furthermore, biosimilar uptake may be influenced by region-specific differences in biosimilar initiatives and policies [127] or by differences in tendering of biosimilars in disparate practice settings [128]. Likewise, patients familiar or previously treated with the UST innovator might be reluctant to switch to a UST biosimilar due to potential negative perceptions regarding treatment outcomes [129]. From a logistical perspective, inconsistent regulatory policies across regions and complex reimbursement processes could delay the adoption of UST biosimilars [130]. On the reimbursement side, biosimilars often face pricing and market access challenges that limit their uptake. Payers and healthcare systems may be locked into exclusive contracts with originator biologic manufacturers, which offer rebates and discounts that make it financially unappealing to switch to biosimilars. Additionally, complex reimbursement structures, including different coding and billing processes for biosimilars, create administrative burdens that discourage healthcare providers from prescribing them. Some insurers require additional documentation or step therapy protocols before approving biosimilar use, further delaying access [131]. Ultimately, addressing these issues will be critical to realize the full potential of UST biosimilars in the clinic.

To overcome these challenges of negative perception and regulatory inconsistency, practical steps must be implemented. Production of RWD and educating HCPs and patients on the safety, efficacy, and cost benefits of UST biosimilars may be helpful [132]; understanding that biologics cannot be duplicated, even by the innovator company, is paramount. Audience-appropriate training programs and informational campaigns [133] may help to build confidence and facilitate smoother transitions from the UST innovator to UST biosimilars.

Continued research and innovation in the field of UST biosimilar medicines may further enhance the treatment of psoriasis, IBD, PsA, and other chronic IMIDs. The SB17 PFS represents a significant technological advancement in UST delivery, given its latex-free construction, smaller needle size, and enhanced temperature stability. Ustekinumab pre-filled pens (PFPs) represent a significant step forward in UST delivery [4]. The development of SB17 PFPs will provide an additional user-friendly option for subcutaneous self-administration. To further optimize the use of UST biosimilars, additional research is required to identify disease-specific factors associated with greater likelihood of patient responsiveness to biologic treatment [134]. Indeed, higher IL-23A gene expression is associated with greater likelihood of remission following UST treatment in Japanese patients with IBD [135]. Moreover, a differential response to UST therapy has been identified in HLA-Cw6+ patients with psoriasis, with a higher proportion of HLA-Cw6+ patients achieving PASI 75/90 responses at weeks 12 and 24 [136]. Whereas UST induction therapy is efficacious in Korean patients with Crohn's disease [137], further study is warranted to better understand the implications of the genetic heterogeneity that exists between European and East Asian populations with respect to Crohn's disease susceptibility [138]. Likewise, given that PsA occurs in 20–30% of patients with psoriasis [139], uncovering the genetic variants specific to PsA but not psoriasis susceptibility may better inform UST treatment strategies. Such precision medicine approaches will facilitate pre-identification of subpopulations of patients that are most likely to benefit from UST therapy, which may enhance treatment outcomes and reduce healthcare expenses. Collectively, such research and technological advancements related to UST biosimilars may increase biosimilar adoption in clinical practice and improve disease management by both HCPs and patients.

Over the next five to ten years, the field of biologic therapy for psoriasis, IBD and related conditions is expected to evolve significantly. UST biosimilars will likely be recommended earlier in the line of biologic treatment due to their effectiveness, safety, convenience, and cost-effectiveness, leading to broader patient access and improved disease management. Treatment guidelines will incorporate UST biosimilars more prominently, with defined protocols for switching between the innovator biologic and biosimilars based on RWE. Improved pharmacovigilance monitoring systems and RWD collection on UST biosimilar use will ensure ongoing safety and efficacy evaluations, addressing immunogenicity and other concerns.

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