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## Review of Adalimumab Biosimilar SB5 in Immune-Mediated Inflammatory Diseases

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REVIEW

# Review of Adalimumab Biosimilar SB5 in Immune-Mediated Inflammatory Diseases

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## ABSTRACT

SB5 is an approved biosimilar of adalimumab, a recombinant monoclonal anti-tumor necrosis factor (TNF) antibody. The approval of SB5 was based on the comparison with reference adalimumab in analytical studies, pharmacokinetic (PK) and immunogenicity assessments, and randomized controlled trials. Efficacy data was primarily obtained in patients with rheumatoid arthritis, and extended to include additional indications such as psoriasis, Crohn's disease, or

ulcerative colitis by extrapolation. Following its approval, additional post-marketing data have been collected comparing SB5 with reference adalimumab. This review summarizes the clinical data on SB5 from randomized controlled trials and provides a comprehensive overview of the available post-approval data. In “real-world” settings, SB5 was as effective as its reference product across different indications and countries, treatment persistence was well maintained throughout studies, and no new safety concerns were identified. In both controlled and “real-world” settings, switching from reference adalimumab to SB5 was not associated with altered efficacy or clinical complications. In post-approval studies, the quality of SB5 was consistent over time, independent of the batch and process changes, and the SB5 autoinjector was preferred over other autoinjectors by both healthcare professionals and patients. Taken together, these data support the use of SB5 whenever reference adalimumab is appropriate and demonstrate that switching from reference adalimumab to SB5 is feasible.

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### Key Summary Points

SB5 is an approved adalimumab biosimilar with equivalent pharmacokinetics and efficacy, and comparable safety and immunogenicity to reference adalimumab demonstrated in randomized controlled clinical trials enrolling patients with rheumatoid arthritis.

“Real-world” evidence confirms the effectiveness and safety of SB5 for the treatment of immune-mediated inflammatory diseases for which reference adalimumab has been approved.

In both controlled and “real-world” settings, SB5 was not associated with reduced efficacy/effectiveness or clinical complications in both naïve and switched patients compared to reference adalimumab.

The quality of SB5 is tightly controlled and consistent over time, and its unique self-injection device is preferred over other autoinjectors by both patients and healthcare professionals.

## INTRODUCTION

Adalimumab is a fully human recombinant immunoglobulin G1 (IgG1) monoclonal antibody that binds to the pro-inflammatory cytokine tumor necrosis factor (TNF) and inhibits its receptor interaction. In the USA, adalimumab is indicated for the treatment of immune-mediated inflammatory disorders such as rheumatoid arthritis (RA), juvenile idiopathic arthritis (JIA), psoriatic arthritis (PsA), ankylosing spondylitis (AS), adult and pediatric Crohn’s disease (CD), adult and pediatric ulcerative colitis (UC), psoriasis (PsO), hidradenitis suppurativa (HS), and uveitis. Approved by the US Food and Drug Administration (FDA) in 2002,

adalimumab has a well-established long-term safety and efficacy profile [1].

In 2016, the main patent for adalimumab (Humira®, AbbVie Inc., North Chicago, Illinois, USA) expired, opening the opportunity to launch biosimilars. With settlement agreements in place, nine adalimumab biosimilars approved by the FDA have been marketed in the USA as of August 2023 (Table 1) [2].

Biosimilars are biological products with equivalent efficacy and comparable safety and immunogenicity to a reference product [3, 4]. Biosimilars undergo stringent regulatory review and their approval requires comprehensive evidence of the similarity to the approved reference biologic. Upon approval, biosimilars may introduce market competition and reduce the cost of medications, thereby expanding patients’ access to effective treatment [5–8].

An approved biosimilar can be designated as an interchangeable biosimilar product if it meets additional requirements outlined by the FDA [9]. An interchangeability designation allows pharmacists to substitute the interchangeable biosimilar for its reference product, or vice versa, without the intervention of the prescribing healthcare professional [10]. This process, commonly referred to as pharmacy-level substitution, is regulated by state pharmacy laws and is similar to how reference drugs are substituted for generic drugs [9]. To date, interchangeable biosimilar products are only available for three different reference products, including adalimumab, which was the second biologic to have an interchangeable biosimilar product [2, 11].

SB5 (Hadlima™ in the USA and Imraldi™ in the European Union (EU), Samsung Bioepis, Republic of Korea) is an adalimumab biosimilar with equivalent pharmacokinetics (PK) and efficacy to its reference product as demonstrated in clinical trials [12–15]. Regulatory approval was granted in the EU in 2017 and in the USA in 2019 on the basis of the “totality of the evidence”. Initially, clinical data was obtained from patients with RA. By extrapolation, the approval was extended to include additional indications such as JIA, PsA, AS, adult and pediatric CD, UC, PsO, and HS (Table 2). In the USA, SB5 has been approved as both low-

**Table 1** FDA-approved adalimumab biosimilars

Proprietary name	Proper name	License type	Applicant	FDA approval date
Abrilada	Adalimumab-afzb	Biosimilar	Pfizer Inc	Nov 15, 2019
Amjevita	Adalimumab-atto	Biosimilar	Amgen Inc	Sep 23, 2016
Cyltezo	Adalimumab-adbm	Interchangeable	Boehringer Ingelheim Pharmaceuticals, Inc	Aug 25, 2017
Hadlima	Adalimumab-bwwd	Biosimilar	Samsung Bioepis Co., Ltd	Jul 23, 2019
Hulio	Adalimumab-fkjp	Biosimilar	Mylan Pharmaceuticals Inc	Jul 06, 2020
Hyrimoz	Adalimumab-adaz	Biosimilar	Sandoz Inc	Oct 30, 2018
Idacio	Adalimumab-aacf	Biosimilar	Fresenius Kabi USA, LLC	Dec 13, 2022
Yuflyma	Adalimumab-atty	Biosimilar	Celltrion Inc	May 23, 2023
Yusimry	Adalimumab-aqvh	Biosimilar	Coherus BioSciences, Inc	Dec 17, 2021

Information taken from <https://purplebooksearch.fda.gov/advanced-search>  
 FDA, Food and Drug Administration

concentration formulation (40 mg/0.8 mL [SB5-LC]) containing citrate and as high-concentration formulation (40 mg/0.4 mL [SB5-HC]) without citrate [16]. Currently, a phase IV study in patients with plaque psoriasis is ongoing aiming to support the granting of an interchangeability designation [NCT05510063] (Fig. 1).

The objective of this review is to aggregate and analyze available data and information on the biosimilarity of SB5 to reference adalimumab (ADL). To this end, the “totality of the evidence” from clinical trials and real-world studies is summarized, an overview of the control measures taken during the last 10 years to ensure the consistency of quality of SB5 is provided, and the unique characteristics of the SB5 autoinjector are explored. This article is based on previously conducted studies and does not contain any new studies with human participants or animals performed by any of the authors.

## STEPWISE APPROACH TO BUILD THE “TOTALITY OF THE EVIDENCE” DEMONSTRATING BIOSIMILARITY

Rather than demonstrating efficacy and safety de novo, biosimilar clinical development programs rely on confirming the similarity between a proposed biosimilar product and its reference product. Critical elements in the biosimilar development program include establishing the key product quality attributes of these complex biopharmaceuticals, demonstrating equivalent PK/pharmacodynamic profiles and clinical efficacy with comparable safety, and immunogenicity profiles to the reference product [17]. Once the “totality of the evidence” supports biosimilarity of the proposed biosimilar to its reference product, regulatory guidance allows for extrapolation of the data to all indications of use for which the reference product is approved, provided there is sufficient scientific justification considering the pathophysiology of each disease [18, 19].

**Table 2** Highlights of the FDA Prescribing Information of Hadlima (SB5)

## Indications and usage

HADLIMA is a tumor necrosis factor (TNF) blocker indicated for

Rheumatoid arthritis (RA), juvenile idiopathic arthritis (JIA), psoriatic arthritis (PsA), ankylosing spondylitis (AS), Crohn's disease (CD), ulcerative colitis (UC), plaque psoriasis (Ps)

## Dosage (administered by subcutaneous injection)

Rheumatoid arthritis, psoriatic arthritis, ankylosing spondylitis

*Adults:* 40 mg every other week

Juvenile idiopathic arthritis in pediatric patients  $\geq 2$  years of age

10 to < 15 kg (22 to < 33 lbs)—10 mg every other week; 15 to < 30 kg (33 to < 66 lbs)—20 mg every other week;  $\geq 30$  kg ( $\geq 66$  lbs)—40 mg every other week

Crohn's disease

*Adults:* 160 mg on day 1; 80 mg on day 15; and 40 mg every other week starting on day 29

*Pediatric patients 6 years of age and older:* 17 to < 40 kg (37 to < 88 lbs)—80 mg on day 1, 40 mg on day 15, 20 mg every other week starting on day 29;  $\geq 40$  kg ( $\geq 88$  lbs)—160 mg on day 1, 80 mg on day 15, 40 mg every other week starting on day 29

Ulcerative colitis

*Adults:* 160 mg on day 1, 80 mg on day 15 and 40 mg every other week starting on day 29

Plaque psoriasis

*Adults:* 80 mg initial dose, followed by 40 mg every other week starting 1 week after initial dose

## Dosage forms and strengths

## Injection

Single-dose prefilled autoinjector (HADLIMA PushTouch): 40 mg/0.8 mL

Single-dose prefilled glass syringe: 40 mg/0.8 mL

Single-dose glass vial for institutional use only: 40 mg/0.8 mL

Single-dose prefilled autoinjector (HADLIMA PushTouch): 40 mg/0.4 mL

Single-dose prefilled glass syringe: 40 mg/0.4 mL

## Contraindications

None

## Warnings and precautions

*Serious infections:* Do not start HADLIMA during an active infection. If an infection develops, monitor carefully, and stop HADLIMA if infection becomes serious:

*Invasive fungal infections, malignancies, anaphylaxis or serious hypersensitivity reactions, hepatitis B virus reactivation, demyelinating disease, cytopenias, pancytopenia, heart failure, lupus-like syndrome*

## Adverse reactions

Most common adverse reactions ( $> 10\%$ ): infections (e.g., upper respiratory, sinusitis), injection site reactions, headache, and rash

## Drug interactions

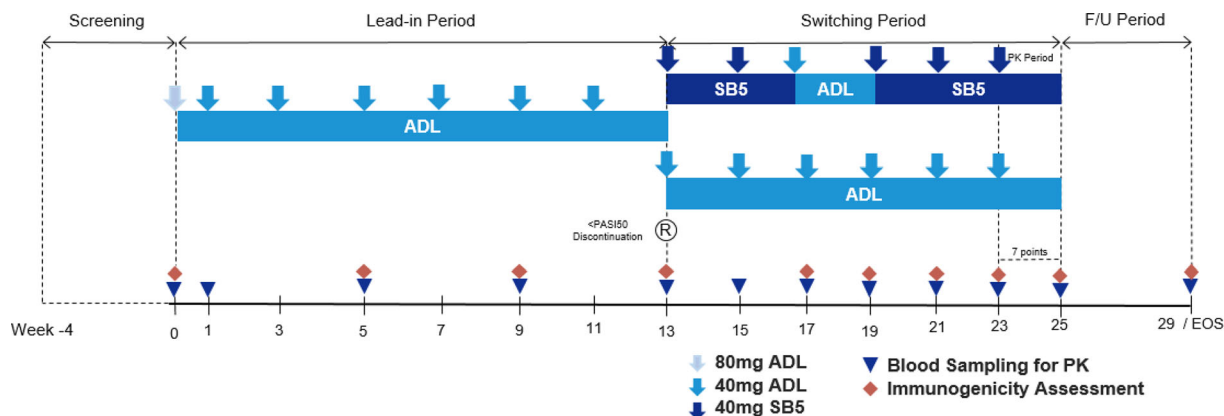
*Abatacept:* Increased risk of serious infection

*Anakinra:* Increased risk of serious infection

*Live vaccines:* Avoid use with HADLIMA

This table is adapted from the FDA Prescribing Information of Hadlima (SB5) revised in December 2022 ([https://www.accessdata.fda.gov/drugsatfda\\_docs/label/2022/761059Orig1s007lbl.pdf](https://www.accessdata.fda.gov/drugsatfda_docs/label/2022/761059Orig1s007lbl.pdf))

FDA, Food and Drug Administration



**Fig. 1** Study design of the SB5 phase IV interchangeability study. ADL, reference adalimumab; EOS, end of study; F/U, follow-up; PASI50, 50% reduction in the Psoriasis Area and Severity Index; PK, pharmacokinetics

The clinical development program of SB5 was built around three randomized controlled clinical trials:

- A randomized, single-blind, three-arm, parallel group, single-dose, PK, clinical equivalence study using the SB5-LC formulation conducted in healthy subjects. In this study, a total of 189 subjects were randomized to either receive SB5, EU-sourced adalimumab (EU-ADL), or USA-sourced adalimumab (US-ADL). Each group featured 63 subjects [15].
- A randomized, double-blind, multinational, 52-week, pivotal, comparative efficacy study using the SB5-LC formulation conducted in patients with moderate to severe RA [12, 13]. A total of 542 patients were initially randomized to SB5 ( $N = 269$ ) or ADL ( $N = 273$ ). After 24 weeks, the patients in the ADL group were re-randomized to either continue ADL ( $N = 129$ ; ADL/ADL) or switch to SB5 ( $N = 125$ , ADL/SB5).
- A randomized, single-blind, two-arm, parallel-group, single-dose, PK, clinical equivalence study in healthy male subjects comparing the SB5-LC and SB5-HC formulations. A total of 188 healthy subjects were randomized (94 subjects in each group) [20].

## Pharmacokinetics

Equivalent PK of SB5 to ADL had initially been demonstrated in the clinical equivalence study

with healthy subjects using the SB5-LC formulation (40 mg/0.8 mL). For all pairwise comparisons, 90% confidence intervals (CI) of the geometric least squares mean (LSMean) ratios of area under the concentration–time curve from time zero to infinity ( $AUC_{inf}$ ; SB5 vs EU-ADL, 0.990 [0.885–1.108]; SB5 vs US-ADL, 1.001 [0.890–1.126]), maximum serum concentration ( $C_{max}$ ; SB5 vs EU-ADL, 0.957 [0.870–1.054]; SB5 vs US-ADL, 0.972 [0.881–1.073]), and AUC from time zero to the last quantifiable concentration ( $AUC_{last}$ ; SB5 vs EU-ADL, 1.027 [0.915–1.153]; SB5 vs US-ADL, 1.025 [0.911–1.153]) were contained within the predefined equivalence margins of 0.8–1.25 [15]. Consistent with these findings in healthy subjects, the pivotal comparative efficacy study successfully confirmed the equivalence in terms of PK in patients with moderate-to-severe RA as trough concentrations ( $C_{trough}$ ) for SB5 and ADL were similar up to week 24 [12]. Furthermore, the SB5-HC citrate-free formulation (40 mg/0.4 mL) showed equivalent PK compared to the initially used SB5-LC citrate-containing formulation (40 mg/0.8 mL) in the dedicated PK clinical equivalence study. The LSmear ratios for  $AUC_{inf}$  and  $C_{max}$  were 0.920 and 0.984, respectively, with the corresponding 90% CIs well within the predefined bioequivalence margins of 0.80–1.25 [20].

## Safety

No clinically meaningful differences in clinical safety of SB5 and ADL were detected in

randomized controlled trials. In the pivotal comparative efficacy study conducted in patients with moderate to severe RA, types and characteristics of the reported treatment-emergent adverse events (TEAEs) were consistent with the known safety profile of ADL. In the SB5 and ADL groups, 35.8% and 40.7% of patients experienced TEAEs up to week 24, respectively. Serious adverse events (SAEs) were reported in three patients (1.1%) treated with SB5 and eight patients (2.9%) treated with ADL. No deaths were reported for patients in the SB5 group, whereas two patients in the ADL group died during the study. Both deaths were considered not to be related to the study drug [12]. Switching from ADL to SB5 at week 24 did not result in an increased number of adverse events (AEs) [13]. In the clinical equivalence study conducted in healthy subjects using the SB5-LC formulation, the number of patients experiencing TEAEs was comparable across treatment groups (SB5, 57.1%; EU-ADL, 46.0%; US-ADL, 61.9%), most TEAEs were considered mild to moderate in intensity, and no discontinuations of study drug due to TEAEs were reported. Two subjects (SB5,  $n = 1$  [1.6%]; US-ADL,  $n = 1$  [1.6%]) had SAEs, but neither event was considered to be related to the study drug [15]. The clinical equivalence study dedicated to the comparison of the SB5-LC and SB5-HC formulations revealed comparable safety profiles for the two different formulations. All TEAEs were mild or moderate in intensity and no patient withdrew from the study because of a TEAE [20]. Overall, the combined safety data from all the studies in the SB5 clinical development program were comparable for SB5 and ADL and for the two different SB5 formulations.

### Efficacy

The pivotal clinical equivalence study conducted in patients with moderate-to-severe RA provided data demonstrating the equivalent efficacy of SB5 and ADL. At week 24, the proportions of patients meeting the American College of Rheumatology 20% (ACR20) improvement criteria were 72.4% and 72.2% for SB5 and ADL, respectively, with an adjusted

difference of 0.1% (95% CI 7.83, 8.13). The remission rates of the Disease Activity Score in 28 joints using the Erythrocyte Sedimentation Rate (DAS28-ESR) (SB5, 21.6% [mean change,  $-2.74$ ] vs. ADL, 19.8% [mean change,  $-2.68$ ]) and of the Simplified Disease Activity Index (SDAI) (SB5, 11.0% [mean change,  $-25.98$ ] vs. ADL, 14.4% [mean change,  $-25.00$ ]) confirmed the equivalent efficacy of SB5 and ADL at week 24 [12]. At week 52, 77.8% of patients treated with SB5 and 73.4% of patients treated with ADL achieved an ACR20 response, indicating that the equivalent efficacy of SB5 and ADL was maintained over an extended treatment period. The observed similarity in long-term efficacy up to week 52 between SB5 and ADL was again corroborated by the results of additional efficacy endpoints such as the remission rates of the DAS28-ESR (SB5, 30.4% [mean change,  $-3.05$ ] vs. ADL, 29.0% [mean change,  $-2.92$ ]) and the SDAI (SB5, 22.3% [mean change,  $-29.0$ ] vs. 18.5% [mean change,  $-27.8$ ]). Importantly, switching from ADL to SB5 at week 24 did not result in a reduction of efficacy, with 78.8% of switched patients meeting the ACR20 at week 52. The DAS28-ESR and SDAI remission rates at week 52 were 28.8% (mean change,  $-3.02$ ) and 19.5% (mean change,  $-28.2$ ), respectively, for patients switching from ADL to SB5 at week 24 [13].

### Immunogenicity

An important component of the “totality of the evidence” approach demonstrating equivalence of a biosimilar candidate to its reference product is to demonstrate that there are no clinically meaningful differences in immunogenicity. In each of the clinical studies mentioned above, the immunogenicity profile of SB5 was comparable to that of ADL. In the pivotal comparative efficacy study conducted in patients with moderate-to-severe RA, 33.1% of patients treated with SB5 and 32.0% of patients treated with ADL developed anti-drug antibodies (ADAs) to adalimumab up to week 24 [12]. The incidences of overall ADAs remained comparable across treatment groups up to week 52, including those patients who switched from

ADL to SB5 at week 24 [13]. In the single-dose clinical equivalence study in healthy subjects using the SB5-LC formulation, the overall incidence of ADAs to adalimumab after dosing was 98.4%, 95.2%, and 100.0% in subjects treated with SB5, EU-ADL, and US-ADL, respectively [15]. In the clinical equivalence study comparing single doses of the two different formulations of SB5 in healthy male subjects, the overall incidence of post-dose ADAs was similar for both formulations, with 93.6% of subjects in the SB5-HC group and 94.7% of subjects in the SB5-LC group having detectable ADAs post dose [20].

Overall, the clinical development program of SB5 provides comprehensive data about the equivalence of SB5 and ADL and corroborates the similarity between the two different SB5 formulations.

## REAL-WORLD EVIDENCE

Gathering real-world data (RWD) is an important means to confirm the findings of randomized clinical trials, which are conducted in controlled settings, and to provide data for the extrapolation of the approval of a biosimilar for use in indications held by the reference product. Observational studies have generated RWD that confirm the comparability of the effectiveness and safety of SB5 to that of ADL in both adalimumab-naïve and adalimumab-experienced patients across major indications (Table 3).

### Rheumatologic Diseases

Several observational studies were conducted in patients with rheumatologic diseases such as RA, AS, and PsA, who were treated with SB5 [21–23].

Two observational studies investigated switching from ADL to SB5 [21, 22]. The first (Bruni et al. [21]), which focused on safety, enrolled 172 patients with inflammatory arthritis, including 34 patients with RA, 59 patients with PsA, and 61 patients with AS. All enrolled patients previously had received at least 6 months of treatment with ADL before

switching to SB5. During the follow-up period of up to 18 months, 65 (37.8%) patients reported AEs, most of which were flares of disease activity ( $n = 46$ ). The remainder were infections ( $n = 19$ ), of which one (0.6%) was reported to be an SAE of severe infection requiring hospitalization. The probability of persisting on SB5 treatment was generally high, with 94.7% and 85.1% after 6 and 12 months, respectively [21]. The second (Müller-Ladner et al. [22]), known as the “PROPER Study,” was a 48-week analysis of data from patients with RA, PsA, AS, CD, or UC, who had switched from ADL to SB5. The inflammatory arthritis cohort of this study consisted of 496 patients, who were enrolled at centers across Europe and followed up to week 48 after the switch to SB5. Effectiveness of treatment was maintained throughout the study: the mean DAS28 score of patients with RA was 2.3 at baseline and 2.4 at week 48; the Hannover Functional Ability Questionnaire (FFbH) for patients with RA was 80.0 at baseline and 77.1 at week 48; the Bath Ankylosing Spondylitis Disease Activity Index (BASDAI) for patients with AS was 2.58 at baseline and 2.65 at week 48; and the Psoriatic Arthritis Response Criteria (PsARC) tender joint count (TJC) and swollen joint count (SJC) for patients with PsA were 1.7 and 0.7 at baseline and 1.9 and 0.7 at week 48, respectively. SAEs were reported in 17 patients, of which two were considered to be related to SB5 treatment. Overall treatment persistence was high with 397 (81.5%) of the 487 patients who completed the full 48 weeks of the study having remained on SB5 throughout the study [22].

Another observational study (Parisi et al. [23]) evaluated sequential switching from ADL to the adalimumab biosimilar ABP501 and subsequently to SB5 in 127 patients with RA, PsA, or AS. Disease activity, as measured by DAS28, Disease Activity in Psoriatic Arthritis (DAPSA), or BASDAI remained stable over 3 years. One year after the switch from ABP501 to SB5, 82.1%, 78.7%, and 77.5% of patients with AS, RA, and PsA, respectively, remained on treatment with SB5 [23].

Taken together, RWD from patients with inflammatory arthritis confirm the comparability of SB5 with ADL; sequential switching from

**Table 3** Post-approval observational studies of SB5

Reference	Study design and data source	Objective	Patient numbers and indication	Follow-up and treatment persistence	Effectiveness outcomes	Safety outcomes
Rheumatic diseases						
Bruni 2021 [21]	Prospective, observational cohort study conducted in patients who switched from ADL to SB5 at third-level rheumatology centers in Tuscany, Italy	Investigate the persistence on treatment with SB5, identify predictors of SB5 therapy interruption, and the types of AEs reported and their prevalence	Total = 172 PsA = 59 (34.3%), axSpA = 61 (35.5%), RA = 34 (19.8%), JIA = 11 (6.4%), Behçet disease = 5 (2.9%), idiopathic uveitis = 2 (1.2%)	Follow-up: up to 18 months Treatment persistence: 94.7% at 6 months, 85.1% at 12 months	NR	AEs: 65 patients (37.8%) SAE: 1 patient (0.6%)
Müller-Ladner 2022 [22]	Prospective, retrospective, umbrella design, observational study conducted in patients with immune-mediated inflammatory disease who were enrolled at centers in Belgium, Germany, Ireland, Italy, Spain, and the UK, and followed for 48 weeks after switch from ADL to SB5	Provide insights into outcomes of the transition from ADL to SB5 outside the randomized, controlled, clinical trial setting	Total = 496 PsA = 162 (32.7%) axSpA = 127 (25.6%) RA = 207 (41.7%)	Follow-up: 48 weeks Treatment persistence: 80.0% at 48 weeks	PsA PsARC (TJC) mean (95% CI) Baseline: 1.7 [0.7, 2.7] Week 48: 1.9 [0.7, 3.0] PsARC (SJC) mean (95% CI) Baseline: 0.7 [0.4, 1.0] Week 48: 0.7 [0.2, 1.1] axSpA BASDAI mean (95% CI) Baseline: 2.58 [2.2, 3.0] Week 48: 2.65 [2.2, 3.1] RA DAS28 mean (95% CI) Baseline: 2.3 [2.1, 2.5] Week 48: 2.4 [2.2, 2.6] FFbH mean (95% CI) Baseline: 80.0 [73.5, 86.5] Week 48: 77.1 [70.0, 84.1]	SAE: 15 patients (3.0%)

**Table 3** continued

Reference	Study design and data source	Objective	Patient numbers and indication	Follow-up and treatment persistence	Effectiveness outcomes	Safety outcomes
Paris 2022 [23]	Real-life study in patients with clinical diagnosis of RA, PsA, and AS over the observational period (visits: 0, 12, 24, and 36 months)	Evaluate the disease activity trend after multiple switching from ADL to its biosimilars (ABP 501 and SB5 subsequently) in a cohort of patients with inflammatory arthritis	Total = 127 PsA = 52 (40.9%)  AS = 34 (26.8%) RA = 41 (32.3%)	Follow-up: 3-year Treatment persistence: 82.1%, 78.7%, and 77.5% in AS, RA, and PsA at year 1	DAS28, DAPSA, and BASDAI remained stable over the 3 years (only reported with figure)	NR
<b>Inflammatory bowel diseases</b>						
Lukas 2020 [24]	Data on clinical and disease characteristics were retrieved from the Czech Registry of IBD Patients on Biological and Innovative Therapy [CREdIT Registry] in patients with IBD who underwent a non-medical switch from ADL to SB5 at the Clinical & Research Center ISCARE and Charles University in Prague	Evaluate the efficacy of switching from ADL to SB5 in patients with IBD	Total = 93 CD = 80 (86%) UC = 11 (12%) IBD unclassified = 2 (2%)	NR	CD HBI median (IQR) Baseline: 2 [0, 5] Week 10: 2 [0, 5]  UC Partial Mayo median (IQR) Baseline: 2 [0, 4] Week 10: 1 [0, 2]	NR

Table 3 continued

Reference	Study design and data source	Objective	Patient numbers and indication	Follow-up and treatment persistence	Effectiveness outcomes	Safety outcomes
Tapete 2022 [25]	Prospective, observational cohort study in patients with IBD and need adalimumab treatment from November 2018 to January 2019 were included in the Tuscan Adalimumab Biosimilar rEgisTry (TABLET)	Analyze the effectiveness and safety of SB5 both in patients who were adalimumab-naïve (naïve group) and in those who underwent a nonmedical switch from ADL to SB5 after a follow-up of 12 months (switch group)	Naïve (SB5) = 48 CD = 37 (77%) UC = 11 (23%)  Switch (ADL to SB5) = 98  CD = 78 (80%)  UC = 20 (20%)	Follow-up: 12 months Treatment persistence  Naïve (SB5): 95.8%, 81.3%, and 66.7% at 3, 6, and 12 months, respectively  Switch (ADL to SB5): 96.9%, 92.9%, and 81.6% at 3, 6, and 12 months, respectively	Naïve (SB5) [baseline, 3, 6, 12 months] CRP mean, mg/dL (SD): 1.2 [1.51], 1.15 [1.51], 0.36 [0.37], 0.57 [0.96] FC mean, mg/kg (SD): 665 [769], 151 [138], 271 [376], 231 [253] Clinical remission: 81.3%, 72.9%, and 60.4% were in clinical remission at 3, 6, and 12 month, respectively  Switch (ADL to SB5) [baseline, 3, 6, 12 months] CRP mean, mg/dL (SD): 0.8 [1.6], 2.0 [3.1], 0.31 [0.36], 0.75 [115] FC mean, mg/kg (SD): 212 [218], 129 [206], 134 [197], 84 [115] Clinical remission: 97.9%, 86.7%, and 72.4% were in clinical remission at 3, 6, and 12 months, respectively	Overall (naïve and switch) AEs: 53 patients (36.3%)

**Table 3** continued

Reference	Study design and data source	Objective	Patient numbers and indication	Follow-up and treatment persistence	Effectiveness outcomes	Safety outcomes
Derikx 2021 [26]*	Retrospective, observational cohort study in NHS Lothian (Scotland) to investigate the long-term effectiveness and safety of SB5	Investigate long-term outcomes of SB5 in patients with IBD following a switch from ADL to SB5 (switch group) or after start of SB5 (naïve group)	Naïve (SB5) = 225 CD = 175 (78%) UC = 37 (16%)  IBD unclassified = 13 (6%) Switch (ADL to SB5) = 256 CD = 228 (89%) UC = 23 (9%)  IBD unclassified = 5 (2%)	Naïve (SB5) Median follow-up: 18.3 months Treatment persistence: 77.8% at week 26 and 60.3% at week 52  Switch (ADL to SB5) Median follow-up: 13.7 months Treatment persistence: 84.6% at week 26 and 70.8% at week 52	Switch (ADL to SB5) [baseline, week 26, week 52]  Biochemical remission (CRP): 69.9%, 70.7%, and 70.7%  Fecal biomarker remission: 69.6%, 58.3%, and 59.6% Clinical remission: 82.1%, 77.5%, and 75.4%  Switch (ADL to SB5)	Naïve (SB5)  AEs: 39 patients  AEs: 51 patients

Table 3 continued

Reference	Study design and data source	Objective	Patient numbers and indication	Follow-up and treatment persistence	Effectiveness outcomes	Safety outcomes
Psoriasis						
Loft 2021 [28]	Crossover-cohort design conducted in patients from the Biological Treatment in Danish Dermatology (DERMIBIO) registry who switched from ADL to an adalimumab biosimilar (SB5 or GP2017) between November 1, 2018 and May 1, 2019. The comparator cohort included patients treated with ADL with a visit between May 1, 2017 and November 1, 2018	Assess the outcomes following a mandatory nonmedical switch from ADL to adalimumab biosimilars (SB5, GP2017) in patients with psoriasis	ADL = 378 Switch (ADL to SB5 or GP2017) = 348	Follow-up: 12 months Treatment persistence: 95.8%, and 92.1% in ADL patients and 95.7% and 92.0% in switched patients (ADL to SB5 or GP2017) at 6 months and 12 months, respectively	NR	ADL AEs: 18 patients (5%)
			(SB5 = 162; GP2017 = 186)			Switch (ADL to SB5 or GP2017) AEs: 29 patients (9%)

**Table 3** continued

Reference	Study design and data source	Objective	Patient numbers and indication	Follow-up and treatment persistence	Effectiveness outcomes	Safety outcomes
Killion 2023 [29]	Single-center, retrospective cohort study conducted in patients with moderate to severe psoriasis who had switched from ADL to adalimumab biosimilars from 2018 to 2022 (records and databases from the British Association of Dermatologists, Biologic Immunomodulators Register [BADBIR] and the National High Tech Prescribing Hub)	Describe the clinical experience of switching patients from ADL to adalimumab biosimilars (SB5, ABP501) and that of switching back to ADL for those intolerant to biosimilars	Switch (ADL to SB5 or ABP501) = 100 (SB5 = 79; ABP501 = 21)	Treatment persistence: 81% at week 16	Maintenance or improvement in baseline PASI: 91% DLQI: 90%	NR

Table 3 continued

Reference	Study design and data source	Objective	Patient numbers and indication	Follow-up and treatment persistence	Effectiveness outcomes	Safety outcomes
Girolomoni 2022 [30]	Prospective observational study in patients with psoriasis receiving SB5 between Jun 01, 2019 and Aug 31, 2021. Patients were identified from the British Association of Dermatologists, Biologic Immunomodulators Register (BADBIR)	Analyze 3-year follow-up data of SB5 from BADBIR	Näive (SB5) = 1043 Switch (ADL to SB5) = 16	Mean follow-up: 19.3 months Treatment persistence: 79.7%, 73.5%, and 72.1% at 1, 2, and 3 years	Patients with baseline PASI < 10 Median PASI (IQR) Baseline: 0.9 (1.8) 1 year: 0.5 (2.7) Patients with baseline DLQI < 10 Median DLQI (IQR) Baseline: 6.5 (6.0) 1 year: 2.0 (4.0) Patients with baseline PASI ≥ 10 Median PASI (IQR) Baseline: 17.3 (9.5) 1 year: 2.2 (5.9) Patients with baseline DLQI ≥ 10 Median DLQI (IQR) Baseline: 19.0 (8.0) 1 year: 0.0 (4.0)	NR
Hidradenitis suppurativa						

**Table 3** continued

Reference	Study design and data source	Objective	Patient numbers and indication	Follow-up and treatment persistence	Effectiveness outcomes	Safety outcomes
Ricceri 2020 [31]	Retrospective observational study performed in hidradenitis suppurativa adalimumab-naïve patients who started SB5 and in patients who were switched from ADL to SB5	Evaluate efficacy and safety of SB5 in hidradenitis suppurativa	Naïve (SB5) = 4 Switch (ADL to SB5) = 7	Follow-up: 36 weeks No patient had to interrupt the treatment	Naïve (SB5) IHS4 mean (SD) Baseline: 18.5 [11.3] Week 36: 11.2 [5.4] HiSCR (% achieved): 100% DLQI mean (SD) Baseline: 13 [6.2] Week 36: 10.5 [5.2] Switch (ADL to SB5)	Incidence of AEs prior to and after switching did not differ significantly
Uveitis						
Fabiani 2019 [33]	Retrospective study in non-infectious uveitis undergoing the switch from anti-TNF $\alpha$ originator to biosimilar biologic	Identify any change in the control of ocular inflammatory manifestations among patients with non-infectious uveitis switching from an originator to a corresponding anti-TNF $\alpha$ biosimilar	SB5 = 20 patients (33 eyes)	NR	No SB5-specific effectiveness outcome	No SB5-specific safety outcome

Table 3 continued

Reference	Study design and data source	Objective	Patient numbers and indication	Follow-up and treatment persistence	Effectiveness outcomes	Safety outcomes
Sota [34] 2021	Retrospective, nonrandomized study in patients with refractory noninfectious uveitis treated with SB5	Evaluate the efficacy of SB5 in noninfectious uveitis	SB5 = 26 patients (47 eyes)	Median follow-up: 16.5 months  Treatment persistence: 91.8% at 12 and 20 months	BCVA mean right eye (SD) Baseline: 7.64 [3.69] Last follow-up: 8.89 [2.54]  BCVA mean left eye (SD) Baseline: 7.34 [3.51] Last follow-up: 8.95 [2.44]	No new ocular complications emerged during the treatment with SB5

ADL, reference adalimumab; AE, adverse event; AS, ankylosing spondylitis; axSpA, axial spondyloarthritis; BASDAI, Bath Ankylosing Spondylitis Disease Activity Index; BCVA, best-corrected visual acuity; CD, Crohn's disease; CI, confidence interval; CRP, C-reactive protein; DAPSA, Disease Activity in Psoriatic Arthritis; DAS28, Disease Activity Score 28; DLQI, Dermatology Life Quality Index; FC, fecal calprotectin; FFBh, Hannover Functional Ability Questionnaire; HBI, Harvey-Bradshaw Index; HISCR, Hidradenitis Suppurativa Clinical Response; IBD, inflammatory bowel disease; IHS4, International Hidradenitis Suppurativa Severity Score System; IQR, interquartile range; JIA, juvenile idiopathic arthritis; NR, not reported; PASI, Psoriasis Area Severity Index; PsA, psoriatic arthritis; PsARC, Psoriatic Arthritis Response Criteria; RA, rheumatoid arthritis; SAE, serious adverse event; SD, standard deviation; SJC, swollen joint count; TJC, tender joint count; TNF, tumor necrosis factor; UC, ulcerative colitis

\*Biochemical remission [CRP  $\leq$  5 mg/L], fecal biomarker remission [fecal calprotectin  $\leq$  250  $\mu$ g/g], and clinical remission [Crohn's disease HBI  $\leq$  4; ulcerative colitis  $\leq$  1]

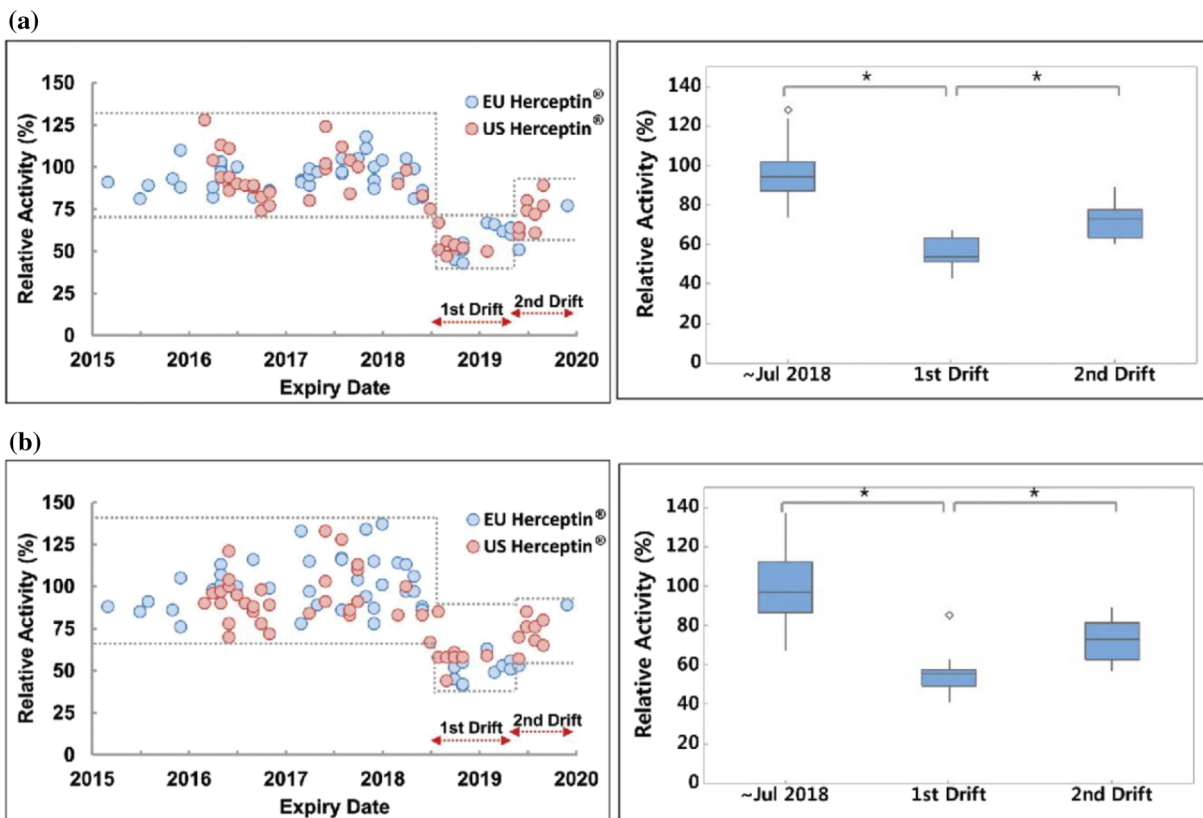
ADL to another adalimumab biosimilar and subsequently to SB5 revealed similar effectiveness of SB5 after two switches with that after a single switch. Effectiveness and safety data in these observational studies are consistent with those of randomized clinical trials, and no new safety concerns were identified.

### Inflammatory Bowel Diseases

The effectiveness and safety of SB5 has also been confirmed in patients with inflammatory bowel diseases (IBDs), CD, and UC in several observational studies [24–26].

In one study (Lukas et al. [24]), 93 patients with IBD who switched from ADL to SB5 were compared to 93 patients who continued treatment with ADL. There were no clinically meaningful differences between SB5 and ADL in disease activity, PK, safety, and immunogenicity. At weeks 0 and 10, the levels of C-reactive protein (CRP) and fecal calprotectin of patients treated with SB5 were comparable to those of patients treated with ADL, reflecting similar disease activity in the two cohorts. Both CD activity as measured by the Harvey-Bradshaw Index (HBI) and UC activity as measured by the partial Mayo score were similar among patients treated with SB5 to those of patients treated with ADL.  $C_{\text{trough}}$  levels at week 0 (SB5, 14.2  $\mu$ g/mL vs. ADL, 14.8  $\mu$ g/mL) and at week 10 (SB5, 13.0  $\mu$ g/mL vs. ADL, 13.7  $\mu$ g/mL) were comparable, confirming similarity of the PK profiles of SB5 and ADL, which had previously been observed in randomized controlled trials. Throughout the study, observed AEs were comparable for patients treated with SB5 and ADL, and two patients in each cohort tested positive for ADAs. Of note, more patients in the SB5 cohort reported injection site pain during drug administration compared to the ADL cohort, and the median visual analogue scale (VAS) score for SB5 injections (3 [1; 5]) was higher than that for ADL injections (0 [0; 0]) [24].

A second observational study (Tapete et al. [25]) assessed the effectiveness and safety of SB5 in a cohort of patients with IBD who were in stable remission and who switched from ADL to



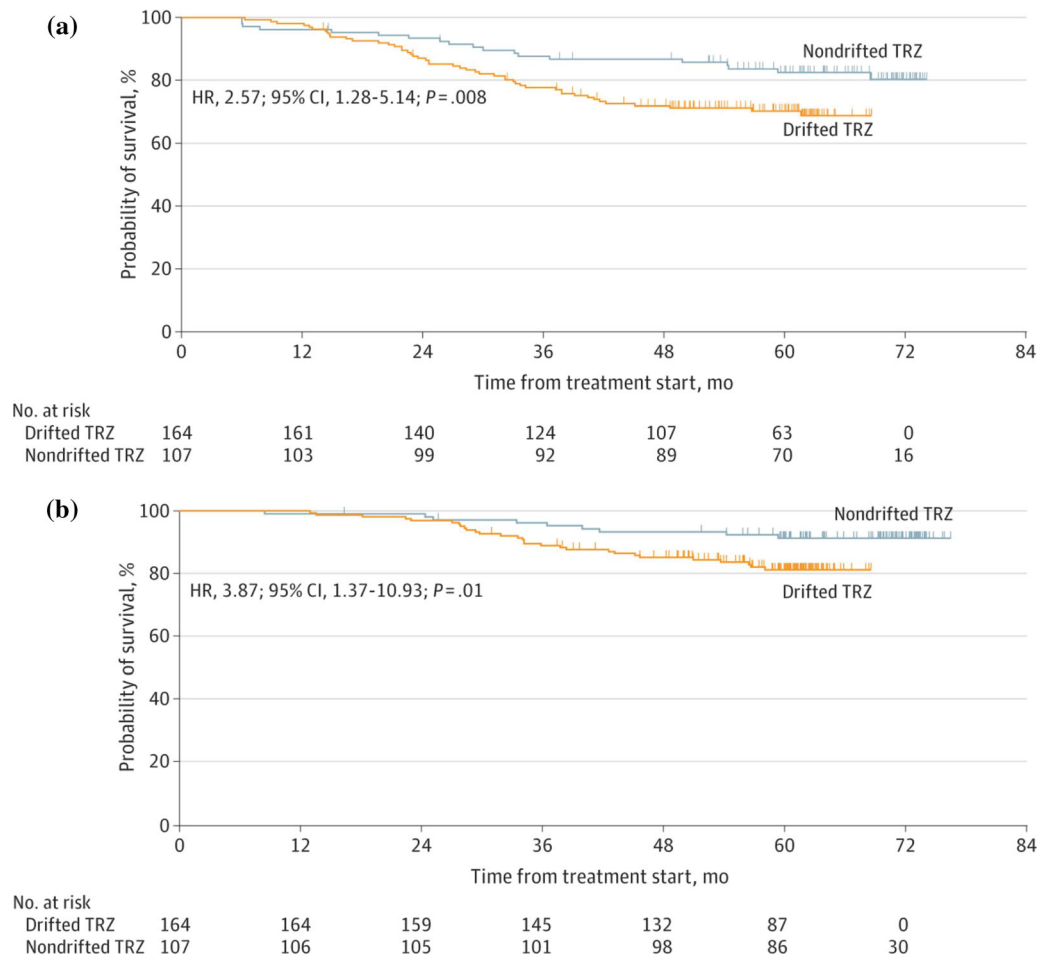
**Fig. 2** Trend of biologic activities of Herceptin®. **a** Relative FcγRIIIa binding activity of Herceptin® ( $n = 98$ ); **b** relative ADCC activity of Herceptin® ( $n = 102$ ). Dotted line shows the min–max range of expiry date before August 2018, 1st drift and 2nd drift periods. Boxplot shows the interquartile range, median and outlier

(◇). Statistical significance was assessed with one-way ANOVA ( $*P \leq 0.05$ ); ADCC, antibody dependent cell-mediated cytotoxicity; ANOVA, analysis of variance; FcγRIIIa, Fc gamma receptor IIIa. The figure and caption have been adapted from Kim et al. [36]

SB5 (switching cohort) and in a cohort of patients with IBD who initiated SB5 treatment without receiving prior treatment with ADL (naïve cohort) [25]. In the naïve cohort, 66.7% (32/48) patients reached the 12-month follow-up, at which time 60.4% (29/48) of patients were in clinical remission. Loss of response was the most common reason for discontinuation. Throughout the study, mean fecal calprotectin (baseline, 665 mg/kg; month 12, 231 mg/kg) and CRP (baseline, 1.2 mg/dL; month 12, 0.57 mg/dL) levels decreased. In the switching cohort, 81.6% (80/98) reached the 12-month follow-up with an overall remission rate of 74.5% (73/98). No statistically significant differences in fecal calprotectin and CRP levels were observed throughout the study. Of the 146

patients in both cohorts, 53 (36.3%) reported AEs. The most common AE was severe injection site pain (24.7%), which was reported more frequently by patients in the switching cohort. Excluding injection site pain, the AE profiles of the two cohorts were otherwise comparable. In 17 of the patients in the switching cohort,  $C_{trough}$  and ADA levels were measured before the switch from ADL to SB5 and at 3 and 6 months after switching and were similar [25].

Another retrospective observational study (Derikx et al. [26]) conducted in a cohort of 481 patients with IBD in the National Health Service (NHS) Lothian (Scotland) analyzed the effectiveness and safety of SB5 in a switched cohort ( $n = 256$ ) and a naïve cohort ( $n = 225$ ) [26]. The median follow-up duration was 13.7 months for



**Fig. 3** Event-free survival and overall survival among patients receiving reference TRZ, by ADCC status. **a** Event-free survival by ADCC status, drifted TRZ vs non-drifted TRZ. **b** Overall survival by ADCC status, drifted TRZ vs non-drifted TRZ. Tick marks represent censored patients. HRs with corresponding 95% CIs and  $P$  values were estimated using a stratified Cox proportional hazards regression model. Non-drifted TRZ, patients who

were never exposed to any vials from a drifted TRZ lot during the neoadjuvant period. Drifted TRZ, patients who were exposed to at least one vial from a drifted TRZ lot during the neoadjuvant period. ADCC, antibody-dependent cell-mediated cytotoxicity; CI, confidence interval; HR, hazard ratio; TRZ, trastuzumab reference product. The figure and caption have been adapted from Pivot et al. [37]

the switched cohort and 8.3 months for the naïve cohort. Treatment persistence was similar in both cohorts, with 35.2% (90/256) and 36% (81/225) of patients discontinuing SB5 in the switched and naïve cohort, respectively. AEs and loss of response were the main reasons for discontinuing SB5 in both cohorts. The median CRP and fecal calprotectin levels, HBI, and partial Mayo scores were similar throughout the study period in patients who switched from ADL to SB5. In the naïve cohort, 22% (40/182)

of the patients who underwent therapeutic drug monitoring developed ADAs. Similar proportions of patients in the switched cohort had ADAs before (10.1% [21/207]) and after (10.5% [27/256]) switching to SB5. In the naïve cohort, the median  $C_{\text{trough}}$  level measured 3 months after SB5 initiation was 9.4  $\mu\text{g/mL}$ . Although several patients in the switched cohort underwent dose adjustments,  $C_{\text{trough}}$  levels remained stable throughout the observational period ( $C_{\text{trough}}$  before switching, 10.1  $\mu\text{g/mL}$ ;  $C_{\text{trough}}$

before week 52, 7.8 µg/mL). SB5 dosing was suspended or discontinued because of AEs experienced by 17.3% (31/225) of patients in the naïve cohort and by 19.9% (51/256) of patients in the switched cohort. Infections ( $n = 17$ ) were the AEs most commonly reported in the naïve cohort, whereas injection site pain ( $n = 34$ ) was the AE most commonly reported in the switched cohort [26].

Overall, observational studies confirm the clinical equivalence of SB5 and ADL in patients with IBD. Switching from ADL to SB5 was not associated with clinical complications and did not affect treatment success. Injection site pain was the only AE that was observed more frequently among patients switching from ADL to SB5 compared to patients continuing treatment with ADL [24–26]. Multiple factors related to the product formulation, such as pH, volume and excipients, or to the injection process might contribute to injection site pain [27]. The observational studies described in this review were conducted with SB5-LC which contains citrate. In a clinical equivalence study that compared the SB5-LC and SB5-HC formulations, the incidence of injection site reactions in the SB5-HC group was lower than that in the SB5-LC group (4 subjects [4.3%] vs. 10 subjects [10.6%]) [20].

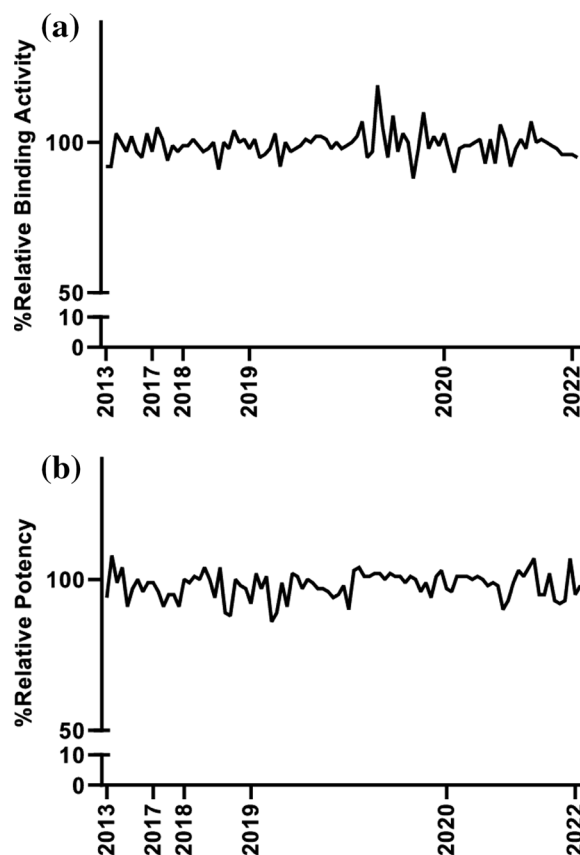
### Psoriasis and Hidradenitis Suppurativa

Three observational studies evaluated the treatment of PsO with SB5 [28–30], and a small case series reported use of SB5 to treat HS [31].

The first study (Loft et al. [28]) assessed the outcome of mandatory nonmedical switching from ADL to an approved adalimumab biosimilar (either SB5 or GP2017) in patients with psoriasis. A cohort of patients who switched from ADL to an adalimumab biosimilar ( $n = 348$  [SB5,  $n = 162$ ; GP2017,  $n = 186$ ]) was compared to a cohort of patients who did not switch treatment and remained on ADL throughout the follow-up duration ( $n = 378$ ). The primary outcome was the 1-year drug retention rate, which was similar between the two cohorts (biosimilar cohort, 92.0% [95% CI 89.0%; 94.9%] vs. ADL cohort, 92.1% [95% CI 89.4%;

94.8%]). Similar proportions of patients discontinued treatment in the biosimilar cohort (8% [28/248]) and in the ADL cohort (7.9% [30/378]), most commonly because of insufficient effect or AEs. A larger proportion of patients who switched from ADL to an adalimumab biosimilar reported AEs ( $n = 29$  [9.1%]) than did those who remained on ADL ( $n = 18$  [5.0%]). Disease activity and Dermatology Life Quality Index (DLQI) remained unchanged throughout the study period in both cohorts. No clinically meaningful difference was detected between the adalimumab biosimilars SB5 and GP2017 [28].

The second study (Killion et al. [29]) was a single-center retrospective cohort study that analyzed 100 patients with moderate to severe PsO who had switched from ADL to either of the adalimumab biosimilars SB5 or ABP501.



**Fig. 4** Biological activities in SB5 batches. **a** Fluorescence resonance energy transfer (FRET)-based competitive inhibition binding assay. **b** Cell-based NFκB-luc reporter gene assay. The figure and caption have been adapted from Lee et al. [38]

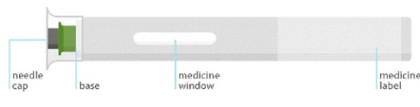
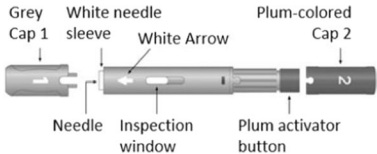
After 16 weeks of follow-up, 81% of patients were still being treated with a biosimilar, whereas 19% of patients had switched back to ADL because of AEs. Among patients who continued treatment with SB5 at week 16, 91% of patients had improvements in Psoriasis Area and Severity Index (PASI) and 90% had improvements in DLQI compared to baseline. Patients who switched back to ADL experienced resolution of the AE or loss of efficiency that caused them to discontinue the biosimilar [29].

Another observational study (Girolomoni et al. [30]) enrolled 1059 patients with PsO who were treated with SB5 from the British Association of Dermatologists Biologic and Immunomodulators Register (BADBIR); 1043 patients were adalimumab naïve and 16 patients were switched from ADL to SB5. The persistence rates of SB5 at years 1, 2, and 3 were 79.7%, 73.5%, and 72.1%, respectively. Median PASI and DLQI improved from baseline to year 1. The most common reasons for SB5 discontinuation were inefficacy (10.6%) followed by AEs (9.9%) [30].

HS is a chronic, relapsing inflammatory skin condition for which currently available conventional synthetic drugs are ineffective in treating severe forms of the disease. The introduction of biologic drugs to treat HS revolutionized the management of this condition. Since adalimumab is the only biologic agent approved to treat HS, the availability of adalimumab biosimilars should expand patients' access to this medication [32]. In a case series (Ricceri et al. [31]) of 11 patients with moderate to severe HS, the four adalimumab-naïve patients experienced clinical improvement when treated with SB5. Clinical remission rates did not change over 36 weeks in the seven patients who switched from ADL to SB5, and the incidence of AEs was not affected by switching from ADL to SB5 [31].

Taken together, the available observational studies conducted in patients with inflammatory dermatologic diseases reveal no clinically meaningful differences in efficacy or safety of SB5 compared to its reference product, and corroborate that switching from ADL to SB5 is not associated with a significant increase in AEs or loss of efficacy.

**Table 4** Comparison of pen device features of SB5 and ADL

Product	SB5	ADL
Illustration		
Operation step	2 step	4 step
Button-free operation	Yes	No
Needle size	29G	27G (LC), 29G (HC)
Latex free	Yes	No (LC), Yes (HC)
Grip surface (Slip Prevention)	Yes	No
Grip shape	Square	Round
Audible indicator	Initiation	Yes
	Completion	No

The illustration of SB5 shows SB5 LC. SB5 HC has smaller medicine window compared to SB5 LC with the same device features

ADL, reference adalimumab; HC, high concentration; LC, low concentration

## Uveitis

Two observational studies reported that SB5 is an effective and safe treatment for uveitis that reduces rates of relapse and improves or preserves visual acuity in both adalimumab-naïve patients and those that have switched from ADL to SB5 [33, 34].

One retrospective study (Sota et al. [34]) assessed the clinical outcomes of SB5 in 26 adalimumab-naïve patients with uveitis. In 47 studied eyes, the rate of uveitis relapses decreased from 121/100 patient-years during the year before SB5 initiation to 4/100 patient-years during the first year of treatment with SB5. By the end of the follow-up (median duration 16.50 months), uveitis was inactive in all but one studied eye. The mean ( $\pm$  SD) letter score of best-corrected visual acuity (BCVA) increased significantly from baseline ( $7.7 \pm 3.41$ ) to the last follow-up ( $8.9 \pm 2.46$ ), while the mean ( $\pm$  SD) daily dosage of co-administered glucocorticoids decreased from  $18.33 \pm 10.33$  to  $5.75 \pm 2.29$  mg/day. Two subjects discontinued SB5 treatment, resulting in a drug retention rate of 92% at both 12 and 20 months of follow-up. One patient reported an injection site reaction, which was considered to be a mild AE [34].

The other observational study (Fabiani et al. [33]) reported the outcome of switching from ADL to SB5 in 20 patients with uveitis (33 eyes). In patients treated with ADL, ocular flares occurred in three patients during the 12 months before switching to SB5. But, after the switch, no patient treated with SB5 experienced an ocular flare. Disease activity did not increase significantly after switching from ADL to SB5. No patient treated with SB5 experienced an ocular flare and no patient experienced an SAE after switching from the ADL to SB5 [33].

## CONSISTENCY OF PRODUCT QUALITY

Whereas small molecules are manufactured by chemical synthesis, biologic medications are produced by living organisms. Since there is variation among proteins manufactured in living cells, biologics from different production

lots differ from one another (lot–lot variation) [35]. Monitoring and minimizing lot–lot variations is necessary to ensure the effectiveness and safety of the biological product. In a clinical study of SB3, a biosimilar of the anti-human epidermal growth factor receptor 2 (HER2) antibody trastuzumab, different lots of reference trastuzumab (Herceptin®, TRZ) varied in efficacy [36]. Analysis of physicochemical and biological properties of lots of TRZ using state-of-the-art methods revealed two sequential drifts in the levels of afucosylated and high mannose N-glycans, which affected Fc gamma receptor 3a (Fc $\gamma$ RIIIa) binding activity and antibody-dependent cell-mediated cytotoxicity (ADCC) activity [36] (Fig. 2). In a comparative efficacy clinical trial with SB3, these downward drifts of ADCC among the lots of TRZ reduced event-free survival and overall survival of patients with breast cancer [37] (Fig. 3).

SB5 has undergone process changes since production started, such as transfer of manufacturing sites and the introduction of a new formulation. The quality attributes of SB5 have been tightly controlled and monitored since production started. Between 2013 and 2022, the purity, charge variants, and functional activities of 93 batches of SB5 drug product have been analyzed. The TNF binding activity and TNF neutralizing potency, which have a direct effect on the efficacy of adalimumab, ranged from 86% to 108% (mean  $\pm$  SD,  $99 \pm 4\%$ ) and from 88% to 119% (mean  $\pm$  SD,  $98 \pm 4\%$ ), respectively, across different SB5 batches. None of the batches showed a relevant drift in biological activity (Fig. 4). Overall, critical quality attributes of all analyzed batches of SB5 were consistent over time and well within the acceptable ranges of variation that had been agreed upon with regulatory agencies [38].

## DEVICE FEATURES

The SB5 pen device has design attributes that differ from those of the ADL pen. The SB5 pen device has a square shape with rounded edges and a nonslip surface. Its needle gauge (29G) is small to reduce injection pain. The initiation mechanism does not require pressing a button,

an audible indicator “clicks” at the start and end of dose administration, and an enlarged medication viewing window allows the patients to confirm that injection is complete (Table 4) [1, 16]. The SB5 pen device was compared to the ADL pen and the reference etanercept (Enbrel®, ETN) MyClic® pen in two survey studies, which were conducted in Germany and the UK, each of which enrolled nurses ( $N = 101$ ) and patients ( $N = 151$ ) [39]. The first study compared the SB5 and ADL pens whereas the second study compared the SB5 and ETN pens. Patients had a confirmed diagnosis of RA, PsA, axial spondyloarthritis, UC, or CD, and were required to have been self-injecting ADL for more than 3 months at the time of screening. Nurses were eligible to participate if they had extensive experience with autoinjector devices and at least 1 year of experience as practicing nurse/nurse practitioner, rheumatology specialist nurse, or gastroenterology specialist nurse. To compare the different autoinjector devices, participants were given show cards providing instructions for use of the autoinjectors before being allowed to handle training versions of the respective pen devices [39].

In the first study, most patients (78%) and nurses (85%) preferred the SB5 pen over the ADL pen. The main attributes prompting preference of the SB5 pen were convenient and easy to use/inject/handle (nurses, 60%; patients, 63%), fits well and does not slip in hand (nurses, 43%; patients, 40%), has an initiation mechanism that requires no thumb trigger button (nurses, 41%; patients, 30%), has a large and visual control that is suitable for hearing-impaired patients (nurses, 42%; patients, 27%), has a double click that is suitable for visually impaired patients (nurses, 49%; patients, 38%), and requires removal of only one cap (nurses, 34%; patients, 33%). Most participants preferred the SB5 pen to the ADL pen because of its ease of use, ease of grip, ease of dose administration, and feedback after administering a full dose. Notably, 87% of nurses would recommend the SB5 pen over the ADL pen, and 79% of patients would choose the SB5 pen over the ADL pen to continue treatment [39].

The SB5 pen was also preferred over the ETN pen by 79% of patients and 86% of nurses in the

second study. The main attributes prompting preference of the SB5 pen were convenient and easy to use/inject/handle (nurses, 45%; patients, 65%), fits well and does not slip in hand (nurses, 57%; patients, 51%), and has an automatic start that requires no thumb trigger button (nurses, 45%; patients, 27%). Its ease of use, ease of grip, ease of dose administration, ease of assessing clarity, feedback after administering a full dose, and audio signals made the SB5 pen the preferred option over the ETN pen. Overall, 81% of nurses would recommend the SB5 pen over the ETN pen, and 79% of patients would choose the SB5 pen over the ETN pen to continue treatment [39].

## LIMITATIONS

The primary focus of this review was to aggregate, analyze, and present available data about SB5. Studies were identified for inclusion by searching PubMed using the keywords “SB5,” “Imraldi,” “Hadlima,” or “Adallice” in combination with “adalimumab biosimilar.” However, because it is not a systematic review, studies were not evaluated for the quality of their methodology as a criterion for inclusion or exclusion from this review. Thus, as with other narrative reviews, the authors’ selections of studies to include or exclude influenced the conclusions.

## CONCLUSION

SB5 is an adalimumab biosimilar with similar quality attributes, PK, efficacy, safety, and immunogenicity to ADL. Although injection site pain was the most common AE after switching from ADL to citrate-containing, low concentration SB5 (SB5-LC), the availability of citrate-free, high concentration SB5 (SB5-HC) is expected to reduce the rate of injection site pain. Both patients and healthcare professionals have preferred the SB5 autoinjector over other autoinjectors. Overall, available data support that SB5 is both safe and effective in clinical practice across immune-mediated inflammatory diseases for which adalimumab is indicated.

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**Author Contribution.** Jonathan Kay, Raymond K. Cross Jr, Steven R. Feldman, Younjin Park, Stephen B. Hanauer conceived the article, Younjin Park performed the literature search and data analysis, Jonathan Kay, Raymond K. Cross Jr, Steven R. Feldman, Younjin Park, Stephen B. Hanauer drafted and/or critically revised the work. All authors read and approved the final version.

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**Data Availability.** Data sharing is not applicable to this article as no datasets were generated or analyzed during the current study.

#### **Declarations**

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**Ethical Approval.** This article is based on previously conducted studies and does not contain any new studies with human participants or animals performed by any of the authors.

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