Taylor & Francis
Taylor & Francis Group

Expert Opinion on Biological Therapy

ISSN: (Print) (Online) Journal homepage: https://www.tandfonline.com/loi/iebt20

Current evidence on the use of the adalimumab biosimilar SB5 (Imraldi^{TM}): a multidisciplinary perspective

Javier P. Gisbert, Karl Gaffney, David Young, Hans C. Ebbers & Giampiero Girolomoni

To cite this article: Javier P. Gisbert, Karl Gaffney, David Young, Hans C. Ebbers & Giampiero Girolomoni (2022) Current evidence on the use of the adalimumab biosimilar SB5 (Imraldi^{TM}): a multidisciplinary perspective, Expert Opinion on Biological Therapy, 22:2, 109-121, DOI: 10.1080/14712598.2022.2012146

To link to this article: https://doi.org/10.1080/14712598.2022.2012146

Published online: 31 Dec 2021.

EXPERT OPINION ON BIOLOGICAL THERAPY
2022, VOL. 22, NO. 2, 109–121
https://doi.org/10.1080/14712598.2022.2012146

Taylor & Francis
Taylor & Francis Group

DRUG EVALUATION

Current evidence on the use of the adalimumab biosimilar SB5 (Imraldi™): a multidisciplinary perspective

Javier P. Gisbert [a], Karl Gaffney [b], David Young [c], Hans C. Ebbers[d] and Giampiero Girolomoni [e]

[a]Gastroenterology Department, Hospital Universitario de La Princesa, Instituto de Investigación Sanitaria Princesa (IIS-IP), Universidad Autónoma de Madrid (UAM), Centro de Investigación Biomédica en Red de Enfermedades Hepáticas y Digestivas (CIBEREHD), Madrid, Spain; [b]Rheumatology Department, Norfolk and Norwich Hospitals NHS Foundation Trust, Norwich, UK; [c]Department of Gastroenterology, University Hospital Southampton NHS Foundation Trust, Southampton, UK; [d]Biogen Intl. GmbH, Baar, Switzerland; [e]Section of Dermatology and Venereology, Department of Medicine, University of Verona, Verona, Italy

ABSTRACT

Introduction: This review provides an overview of data from trials and real-world studies available for SB5 (Imraldi™) across three main therapeutic areas: rheumatology, gastroenterology, and dermatology.
Areas covered: A literature search for publications on data for SB5 efficacy/effectiveness, safety, and immunogenicity was undertaken.
Expert opinion: Evidence derived from clinical studies suggest that the biosimilar SB5 is a safe and effective alternative to reference adalimumab. Considering that patients suffering from immune-mediated inflammatory diseases such as inflammatory arthritis, inflammatory bowel disease and psoriasis often require long-term biologic treatment, biosimilar medicines (such as SB5) can reduce healthcare costs while increasing access to effective treatments.

ARTICLE HISTORY
Received 16 September 2021
Accepted 25 November 2021

KEYWORDS
Biosimilar; adalimumab; anti-TNF; SB5; Imraldi®; dermatology; gastroenterology; rheumatology; multidisciplinary

1. Introduction

Biological drugs have played a fundamental role in the treatment of immune-mediated inflcammatory diseases over the past 20 years. Increasing healthcare costs in recent years has led to an increase in the demand for more affordable biosimilars. A biosimilar is recognized as a biological drug that is highly similar, with regard to its clinical behavior (including pharmacokinetics, efficacy, safety, and immunogenicity) to a previously approved and existing biologic treatment, referred to as the originator or reference product [1]. As of July 2021, 29 biosimilars have been approved by the US Food and Drug Administration and 76 by the European Medicines Agency (EMA) [2,3].

Adalimumab is a fully human IgG1 monoclonal antibody directed against tumor necrosis factor (TNF), introduced in 2002 and subsequently approved for the treatment of a range of immune-mediated diseases in dermatology (plaque psoriasis and hidradenitis suppurativa), rheumatology (rheumatoid arthritis; RA, juvenile idiopathic arthritis, psoriatic arthritis; PsA, and axial spondyloarthritis; axSpA) and gastroenterology (Crohn's disease and ulcerative colitis) as well as non-infectious uveitis [4]. Adalimumab is recommended as a first-line biologic treatment option for rheumatoid arthritis [5], inflammatory bowel disease (IBD) [6,7] and chronic plaque psoriasis [8].

SB5 (Imraldi™), a biosimilar to reference adalimumab (Humira®), was introduced into the European market at the end of 2018 [9] (Box 1). The decision to use biosimilars such as SB5 in clinical practice represents an opportunity to decrease healthcare costs [10,11] while increasing patient access to effective biological treatments. There is consensus from several European competent authorities that switching patients from the original to a biosimilar medicine or vice-versa is safe and effective and biosimilars can be interchanged for the reference product under the supervision of the treating physician, provided that patients are well informed and adequately followed up and traceability is ensured [12–15]. While biosimilars are approved on a robust and comprehensive data package, including comparative (bio)analytical, pharmacokinetic and clinical efficacy/safety studies, there is a perceived need for long-term real-life data, also in indications not specifically studied pre-authorization. It is recognized that the clinical characteristics of patients included in real-life studies can be different to those enrolled in clinical trials (e.g. age, comorbidities, disease severity and prior and concomitant medication) [16,17] but also that factors such as compliance and nocebo effects could affect outcomes [18,19], especially in patients switching from the originator to the corresponding biosimilar.

The pivotal clinical trial of SB5 was performed in RA patients, but approval by the European Medicines Agency (EMA) for all indications for the reference product was on the basis of extrapolation [20]: that is, the extension of efficacy and safety data originated from an already approved therapeutic indication for which the biosimilar has been clinically

CONTACT Javier P. Gisbert javier.p.gisbert@gmail.com Gastroenterology Unit, Hospital Universitario de La Princesa, Instituto de Investigación Sanitaria Princesa (IIS-IP), Universidad Autónoma de Madrid, Centro de Investigación Biomédica en Red de Enfermedades Hepáticas y Digestivas (CIBEREHD), Diego de León, 62, 28006, Madrid, Spain

tested, to other indications for which the innovator product has been previously approved [21].

Box 1. Drug summary box

Drug name: SB5 (Imraldi^{TM}) adalimumab biosimilar
Phase: Approved in EU, USA, South Korea, Australia, Canada and Switzerland
Indication: rheumatoid arthritis, juvenile idiopathic arthritis, axial spondyloarthritis, psoriatic arthritis, psoriasis, hidradenitis suppurativa, Crohn's disease, ulcerative colitis, and non-infectious uveitis
Pharmacology description/mechanism of action: is a recombinant human monoclonal antibody with specific binding to both soluble and transmembrane forms of tumor necrosis factor (TNF)
Chemical structure: 1330 amino acids 148 kDa monoclonal antibody molecular formula without the N-glycan moiety is C6448H9996N1732O2020S42
Pivotal trials: Shin et al. 2017. A randomized phase I comparative pharmacokinetic study comparing SB5 with reference adalimumab in healthy volunteers. J Clin Pharm Ther. 42:672–678. Weinblatt et al. 2018, Phase III Randomized Study of SB5, an Adalimumab Biosimilar, Versus Reference Adalimumab in Patients with Moderate-to-Severe Rheumatoid Arthritis. Arthritis Rheumatol. 2018;70:40–48.

This review aims to collate evidence on the efficacy/effectiveness, safety, and immunogenicity of SB5 from multiple sources, including trials and real-world studies in immune-mediated inflammatory diseases in the three main settings where adalimumab is prescribed: rheumatology, gastroenterology, and dermatology. A literature search was performed on PubMed/Medline, Science Direct, and Google Scholar using the keywords: 'SB5 or Imraldi' from 2017 to June 2021. Figure 1 shows a flow diagram of the selection process.

2. Biosimilarity

Several studies have shown similarity of SB5 to adalimumab in terms of physicochemical and pharmacodynamic properties [9,22–24]. Using *in-vitro* functional assays, Lee et al. characterized the structural, physicochemical, and biological properties of SB5 compared to adalimumab reference product [23,25]. They demonstrated that both SB5 and reference adalimumab had identical primary sequences and were highly similar in terms of secondary and tertiary structure, post-translational modifications, and purity/impurity profile [23]. Furthermore, biological characterization demonstrated that SB5 and reference adalimumab exhibited highly similar TNF binding and

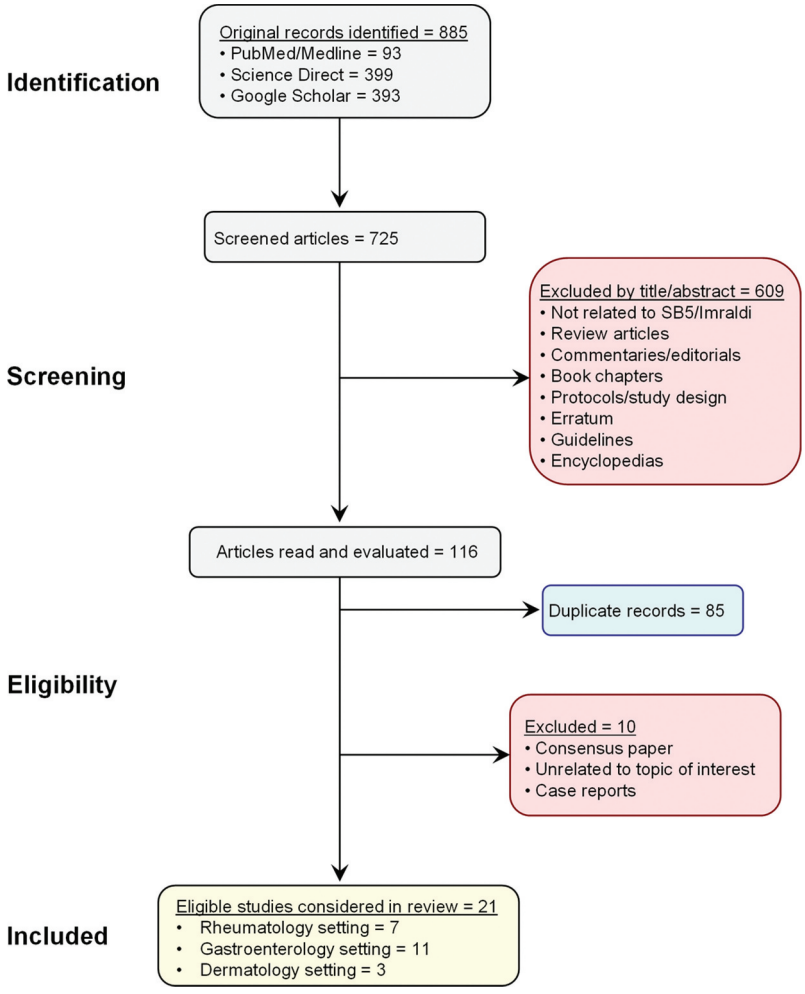

Figure 1. Selection process for studies included in the review. Studies published in languages other than English, editorials, case reports, abstracts, letters, errata, book chapters and reviews were excluded. Duplicate articles as well as congress abstracts superseded by manuscripts, or abstracts of the study that were followed up by more recent abstracts describing the same study population were omitted. Our initial search returned 885 distinct results, of which 116 were considered potentially relevant based on reading their title and abstract. A further 85 records were found to be duplicates and another 10 were excluded leaving a total of 21 studies included in the final evaluation.

neutralizing activity, as well as similar binding of various Fc gamma receptors and Fc-related effector functions (e.g. antibody-dependent cell-mediated cytotoxicity and complement-dependent cytotoxicity) [23,25]. Cytokine release and expression of adhesion molecules were also similar between the two products [25].

3. Pharmacokinetics

In a phase I study, the pharmacokinetic (PK) properties of SB5 (single 40 mg sc) were compared to European Union-sourced reference adalimumab (EU-adalimumab) and United States-sourced reference adalimumab (US-adalimumab) in 189 healthy subjects (63 in each arm) [26]. PK equivalence was demonstrated in this study, as the 90% confidence intervals (CIs) for all primary PK parameters (area under the curve; AUC_{0-t}, $AUC_{0-\infty}$, and C_{max}) were within the predefined margins of 0.8 to 1.25 for all comparisons [26]. The half-life (~350 hours) and clearance rates (~19 ml/h) of SB5 were similar to EU and US-adalimumab [26].The number and kind of treatment-emergent adverse events (AEs) were comparable between the three groups and considered mild to moderate. The incidence of subjects with anti-drug antibodies and the overall incidence of neutralizing antibodies were also similar across the three groups. Goncalves et al. analyzed the cross-reactivity of anti-drug antibodies to reference adalimumab and SB5 in samples taken from patients with IBD treated with reference adalimumab and RA patients treated with SB5 [27]. Antibodies to reference adalimumab and SB5 showed cross-immunogenicity in sera from patients with IBD or RA, supporting shared immune-dominant epitopes.

Evidence from the phase III and real-world studies also showed that trough levels remain unchanged after switching from reference adalimumab to SB5 with little/no development of anti-drug antibodies observed [28–30].

4. Clinical evidence

4.1. Rheumatology setting

Several studies involving SB5 have been undertaken in the rheumatology setting (Table 1).

SB5 demonstrated equivalent efficacy and comparable safety and immunogenicity to reference adalimumab in a randomized double-blind active controlled phase-III trial in RA patients with a follow-up period of 52 weeks [30]. This trial included 542 patients with moderate-to-severe active RA (despite methotrexate therapy), comparing reference adalimumab vs. SB5 for 24 weeks [31], followed by a transition period where patients treated with reference adalimumab were randomized 1:1 to continue reference adalimumab or switch to SB5 and followed for 52 weeks [30]. The primary efficacy endpoint was the proportion of patients achieving a 20% improvement in the American College of Rheumatology Criteria (ACR20 response) at week 24. The SB5 and reference adalimumab groups achieved similar ACR20 response rates (72.4 and 72.2%, respectively). The rate difference was 0.1% (95% CI, −7.83 to 8.13%), which was within the predefined equivalence margin of −15% to 15% [31]. Secondary efficacy endpoints were all comparable [31]. Tolerability and safety for SB5 were also similar to reference adalimumab, with similar severity and frequency of AEs in the reference adalimumab/SB5 switching group and similar antidrug antibody rates [30,31].

In addition to RCTs, data from real-world studies have provided evidence of the effectiveness and safety of SB5 in real-life clinical practice.

Differences in drug survival between originator and biosimilar products in first users were examined from the Swedish Rheumatology Quality register by Di Giuseppe et al. for several products, including 3,117 patients who initiated adalimumab [32]. Of these, 852 patients (27%) initiated on SB5, and no difference was observed in terms of drug survival between originator adalimumab and SB5.

Bruni et al. examined the persistence, predictors of drug interruption and safety following switching from reference adalimumab to SB5 in 172 patients with clinically stable inflammatory rheumatic diseases, comprising RA, PsA and axSpA [33]. The probability of persistence on SB5 was 94.7% at 6 months and 85.1% at 12 months. Baseline corticosteroid use [hazard ratio (HR) 3.21, 95% CI: 1.2–8.64, $p = 0.021$], therapy with nonsteroidal anti-inflammatory drugs (HR 2.9, 95% CI: 1.2–6.7, $p = 0.015$), and baseline corticosteroid dose (HR 1.2, 95% CI 1.03–1.4, $p = 0.022$) were predictors of drug interruption. AEs were found to be in line with existing data. Twenty-four patients stopped SB5. The authors concluded that these real-life data replicate the safety profile of switching from reference adalimumab to SB5 in RA and other rheumatic diseases [30,31].

In the 'PROPER' study, an ongoing real-world pan-European observational study, patients with RA, axSpA, PsA, ulcerative colitis, or Crohn's disease initiated SB5 during routine clinical practice (following at least 16 weeks adalimumab treatment) [34]. Of the 504 patients included in an interim analysis 201 had RA, 169 had PsA, and 134 axSpA. Two hundred and sixteen patients completed 48 weeks of treatment with SB5, 73 patients discontinued SB5, and 8 discontinued the study. The majority of patients showed no meaningful difference in disease score or dose regimen of SB5 by week 48 post-transition.

Nabi et al. examined a total of 1,570 eligible patients from the DANBIO registry with inflammatory arthritis (467 had RA, 321 had PsA and 530 had AxSpA) who were switched from adalimumab to GP2017 (N = 623; 47%) or SB5 (N = 695; 53%) [35]. The retention rate after 1 year for the two biosimilars was 89.5% with 8.5% of GP2017 patients and 12.9% of SB5 patients discontinued respectively. The risk of discontinuation for GP2017 was lower (HR 0.60; 95% CI: 0.42–0.86, $p = 0.005$) and the 6-month remission rate was higher (OR 1.72; 95% CI: 1.25–2.37, $p = 0.001$) compared to SB5. The authors concluded that the observed differences in effectiveness in routine care between these biosimilars may reflect a true difference or may be attributed to differences in excipients or residual confounding [35].

Table 1. Studies evaluating the use of the biosimilar SB5 as first biological agent, or after switching from reference adalimumab to SB5 in the rheumatology setting.

Author, year [ref.]	Switch	Study design	Patients (N)	Disease	Follow-up	Key effectiveness, safety and immunogenicity results	Authors' Conclusion
Weinblatt et al. 2018 [31]	Naive	Double blind, RCT, single switch phase III trial	All; 542, SB5; 269, ADL; 273	RA	24 weeks	ACR response rates comparable between SB5 and ADL arms (ACR20 of 72.4% and 72.2% respectively). Comparable trends in DAS28, SDAI, and CDAI across arms. The safety profile was consistent across arms. Proportions of patients with (neutralizing) anti-drug antibodies were similar between arms.	Efficacy was equivalent, and safety and tolerability were comparable between patients treated with SB5 and reference ADL.
Weinblatt et al. 2018 [30]	ADL to SB5	Extension, double blind, RCT, single switch phase III trial	All; 542, SB5; 269, ADL; 273	RA	52 weeks	ACR response rates comparable between SB5 and ADL arms up to 1 year. The safety profile and the incidence of anti-drug antibodies were comparable across treatment groups after transition.	Switching had no treatment-emergent issues such as increased AEs, increased immunogenicity, or loss of efficacy.
Di Giuseppe et al. 2021 [32]	None	National disease registry	ADL; 3,117, SB5; 852	RA	2 years	3117 started adalimumab (27% SB5, 14% ABP 501), and 763 started rituximab (39% GP2013). Patients starting CT-P13 and GP2013 were less likely to be biologic-naïve compared to those starting the originator product.	For IFX, ADL and RIT, survival on drug was similar for the originator and its biosimilar(s).
Bruni et al. 2021 [33]	ADL to SB5	Real-life retro-prospective observational study	SB5; 172	RA, PsA, axSpA	10 months	In patients with different inflammatory rheumatic musculoskeletal diseases followed for 10 ± 3 months, AEs were reported in 37.8% patients with 26.7% showing a clinically defined disease flare. 24 (14%) patients stopped SB5. The probability of persistence on SB5 was 94.7% at 6 months and 85.1% at 12 months and baseline corticosteroid, NSAIDs and corticosteroid dose were predictors of drug interruption.	This study confirmed the high value of SB5 persistence on treatment at 6 and 12 months after switching from adalimumab, with a safety profile in line with the current literature. Further studies are needed to confirm baseline corticosteroid and NSAID use as predictors of SB5 interruption.
Müller-Ladner et al. 2021 [34]	ADL to SB5	Retrospective/ prospective real-world study	SB5; 504	RA, PsA, axSpA	48 weeks	At interim analysis, 201 have RA, 169 have PsA, and 134 axSpA.	The majority of patients showed no meaningful difference in disease score or dose regimen of SB5 by Week 48 post-transition.
Nabi et al. 2021 [35]	ADL to GP2017 vs. SB5	Longitudinal observational study	All; 1318, SB5; 695, GP2017; 623	RA, PsA, axSpA	12 months	The combined 1-year retention rate for the two biosimilars was 89.5%. Compared with SB5, estimated risk of withdrawal for GP2017 was lower (HR 0.60; 95% CI 0.42 to 0.86) and 6 months' remission rate was higher (OR 1.72; 95% CI 1.25 to 2.37).	This head-to-head comparison of GP2017 vs. SB5 following switch from ADL indicated differences in effectiveness in routine care.
Ghil et al. 2018 [52]	SB5 (PFS and AI)	Open-label, single-arm study	PFS and AI; 49	RA	2 and 6 weeks	Mean injection site pain scores were equivalent between PFS and AI immediately (2.3 versus 2.0; 97.5% CI, −0.99, 0.30) and 15–30 minutes post-injection (0.8 versus 0.7; 97.5% CI, −0.47, 0.25). Overall impression of both devices was comparable.	In RA patients, SB5 showed equivalent injection site pain and comparable safety when administered via PFS and AI.

ACR: American College of Rheumatology, ADL: reference adalimumab, ADAb: anti-drug antibody, AE: adverse event, AI: autoinjector device, ASDAS: ankylosing spondylitis disease activity score, axSpA: axial spondyloarthritis, CI: confidence interval, CRP: C reactive protein, DAPSA: disease activity in psoriatic arthritis, DAS: disease activity score, ETN: etanercept, INF: infliximab, NSAIDs: nonsteroidal anti-inflammatory drugs, PFS: pre-filled syringe, PsA: psoriatic arthritis, RA: rheumatoid arthritis, RCT: randomized controlled trial, RIT: rituximab, VAS: visual analogue scale

Table 2. Studies evaluating the use of the biosimilar SB5 as first biological agent or after switching from reference adalimumab to SB5 in the gastroenterology setting.

Author, year [ref.]	Switch	Study design	Patients (N)	Disease	Follow-up	Key effectiveness, safety and immunogenicity results	Authors' Conclusion
Deprez et al. 2021 [38]	ADL to SB5	Prospective, interventional cohort study	SB5; 110	CD, UC	12 months	By 12 months, SB5 was stopped in 5 patients because of high ADAbs at both baseline and at week 8. Nine patients presented with secondary loss of response of whom 3 discontinued treatment with SB5 and the remaining 6 patients received treatment optimization.	ADL trough levels remained within the therapeutic range after switch from originator to SB5. In patients persisting on SB5, no change in disease activity over time was observed, based on both disease activity scores and biochemical parameters.
Lukas et al. 2020 [28]	ADL to SB5	Analysis of prospectively collected registry data	SB5; 93	IBD	0 and 10 weeks	No difference in the disease activity in both switch and originator cohorts between weeks 0 and 10 was observed. No significant differences in CRP and FC concentrations were seen between week 0 and week 10 either in the switch, originator cohort ($p^{>}0.05$). ADL serum trough levels remained stable after the switch. No new safety signals were detected.	Switching IBD patients from the originator ADL to a biosimilar compound (SB5) does not affect treatment efficacy.
Dragoni et al. 2020 [39]	ADL to SB5	Real-life observational study	SB5; 96	IBD	6 months	Maintenance of clinical remission after 6 months of switch was reported in 89/96 (92.7%) patients. CRP significantly increased over time but no difference was observed between the two time points. A comparison of clinical remission persistence over time between ADL and SB5 patients did not reveal any difference.	SB5 was considered safe and effective in maintaining clinical remission after switching from ADL. Injection site reaction is a frequent but usually manageable side effect.
Cingolani et al. 2021 [40]	ADL to SB5 or ABP501	Prospective observational study	ABP501; 55; SB5; 25	IBD	6 months	Stability of clinical activity and FC values ($p = 0.90$ and $p = 0.20$) and a statistically significant decrease in CRP ($p = 0.03$) was observed.	Overall, biosimilar drugs seem to be as effective and safe as the originator.
Tapete et al. 2021 [29]	Naïve* and ADL to SB5	Prospective observational study	SB5; 146 (Naïve 48, switched 98)	CD, UC	12 months	In the naïve cohort, the overall remission rate at 12 months was 60.42%, whereas in the switching cohort it was 89.02%. No differences were found in terms of ADL serum trough levels at baseline, 3, and 6 months after switching. No patient developed ADAbs after the switch.	SB5 seemed effective and safe in IBD, both in the naïve cohort and in the switching cohort.
Koumoutsos et al. 2021 [41]	ADL to SB5	Retrospective analysis of prescriptions database	SB5; 77	IBD	52 weeks	Secondary loss of response at 52 weeks post switch of treatment occurred in 16.8% (13/77) following change to SB5, whereas 12.4% (15/121) patients experienced secondary loss of response to originator drug prior to transition period. 23.3% of patients reported clinical deterioration of symptoms, and 13% (10/77) experienced side effects (mainly pain at the site of injection). 25.3% (18/71) of patients had raised CRP and 36% (17/45) of patients had raised FC.	Biosimilar SB5 was not inferior to originator and patient acceptance was very good due to associated cost savings. While switching to a biosimilar should be performed in patients in remission, up to one-third of patients (25–36%) had biochemical markers suggestive of active disease.
Derikx et al. 2021 [42]	Naïve and ADL to SB5	Observational study	SB5; 481 (256 switched from ADL; 225 naive)	IBD	13 months	70.8% of the SB5-switch cohort remained on SB5 beyond one year. In the SB5-start (naïve) cohort, 81/225 discontinued SB5 resulting in SB5-drug persistence of 60.3% beyond one year. No change in trough levels or disease activity were observed following a switch. A difference in persistence was observed in the switch cohort, but not in the naïve cohort. Injection site pain was the most frequently reported AE.	SB5 is effective and safe in patients commencing treatment with SB5.

Table 2. (Continued).

Author, year [ref.]	Switch	Study design	Patients (N)	Disease	Follow-up	Key effectiveness, safety and immunogenicity results	Authors' Conclusion
Dignass et al. 2021 [43]	ADL to SB5	Retrospective/ prospective real-world study	SB5; 459	IBD	48 weeks	Of the 459 patients included, 108 had completed 48 weeks on SB5, 45 patients had discontinued SB5, and 10 had withdrawn from study. Disease flare was reported for 29 (6.3%) patients (22 had no subsequent change in biologic treatment; 7 had a change, of whom 5 switched to a different biologic). Twelve patients reported 13 serious AEs, of which 4 were considered to be related to SB5 administration.	The majority of patients showed no meaningful difference in disease activity or SB5 dosing regimen by Week 48 post-transition, and the Covid-19 pandemic seems to have had no impact on SB5 use in this cohort.
Ribaldone et al. 2021 [44]	ADL to ABP501 to SB5	Prospective, single-center observational study	SB5; 61 (of which multiple switch; 43)	CD	6 months	After 6 months 88.5% (54/61) of patients remained on SB5 therapy. The success of the switch (defined as no systemic corticosteroids within 6 months, non-discontinuation of SB5, no dose escalation) was achieved by 82.0% (50/61) of patients. CRP levels >5 mg/L predicted switch failure ($p = 0.03$). Seven patients (11.5%) experienced side effects, compared to one patient (1.6%) in the 6 pre-switch months ($p = 0.03$).	Switching from ABP501 to SB5 did not lead to new safety signals (apart from those reported in literature for this drug class) or loss of efficacy.
Barberio et al. 2021 [45]	Naïve ABP501 or SB5	Multicenter prospective cohort study	ABP501; 54; SB5; 46	CD, UC	6 months	Clinical benefit was achieved by 86.4% and 85.3% after induction and at 6 months, respectively, with no difference between the three treatment groups and an historical propensity matched ADL cohort. After induction, a greater benefit was observed in patients with Crohn's disease vs. UC ($p = 0.004$). All treatments showed a good safety profile, with only 10 patients who needed to stop therapy because of AEs.	ADL biosimilars appeared to be as effective and safe as the originator in patients with IBD representing an excellent opportunity to reduce the costs of biological therapies. However, larger and longer real-life studies are necessary.
De Somer et al. 2021 [54]	ADL to SB5	Prospective, interventional cohort study	SB5: 110	IBD	12 months	An acceptance of switch rate of 79.3% was observed. Fifteen patients reported 22 reasons for refusal; the most common were fear of a flare (N = 8), ease to stay on the originator (N = 4) and absence of trust in biosimilars (N = 3). At 12 months 74.5% of patients were still treated with SB5. The VAS for local discomfort up to 30 minutes after the injection was increased ($p < 0.01$) compared to the originator; this was no longer apparent after 30 minutes.	After being well informed, the majority of patients treated with ADL were willing to switch to SB5. The rate of satisfaction under treatment with SB5 was high and remained stable over time. The most important reasons for discontinuation were AEs. Patients in general reported a higher, temporary, local discomfort within 30 minutes after injection with SB5.

ADL: reference adalimumab, ADAb: anti-drug antibody, AE: adverse event, CRP: C-reactive protein, CD: Crohn's disease, FC: fecal calprotectin, IBD: Inflammatory bowel disease, UC: ulcerative colitis, VAS: visual analogue scale.
*ADL naïve. Ref.; reference

4.2. Gastroenterology setting

No RCTs have examined the efficacy of SB5 in the gastroeneterology setting, the therapeutic indications in IBD are based on extrapolation from RA trial data [20]. This is one of the reasons why real-world data may aid in assuring prescribers on the effectiveness and safety of SB5 in IBD [36,37]. A summary of available real-world studies examining the use of SB5 in the gastroenterology setting is presented in Table 2.

In a prospective observational study performed in Belgium, Deprez et al. evaluated trough levels and disease activity after switching from reference adalimumab to SB5 in 110 patients with IBD [38]. By 1 year, SB5 was stopped in five patients due to high anti-drug antibodies at both baseline and after 8 weeks. Adalimumab trough levels remained within the therapeutic range after switching to SB5. No change in disease activity over time was observed in patients maintaining SB5 treatment, based on both disease activity scores and biochemical parameters.

A retrospective analysis from a single tertiary clinical center in the Czech Republic compared the outcomes in IBD patients (N = 93) who switched to SB5 to a control population (N = 93) treated with reference adalimumab [28]. Disease activity scores were not significantly different between the two groups at week 10 and no significant differences in C-reactive protein and fecal calprotectin from baseline to week 10 between the two cohorts were observed. Adalimumab serum trough levels also remained stable after switching and no new safety signals were observed.

A real-life study performed in Italy by Dragoni et al. evaluated the maintenance of clinical remission in 96 patients with IBD switched from reference adalimumab to SB5 [39]. Clinical remission after 6 months was observed in 89/96 (92.7%) patients and although C-reactive protein significantly increased from baseline to 6 months (from 2.7 ± 2.6 mg/dl to 5 ± 5.8 mg/dl, $p = 0.03$), no difference between the two visits was seen when considering a relevant flare only for C-reactive protein (value above 5 mg/dl). Furthermore, no differences were observed when comparing clinical remission over time between reference adalimumab and SB5 patients and authors considered SB5 safe and effective in maintaining clinical remission after switching from reference adalimumab.

Cingolani et al. evaluated the ability of the adalimumab biosimilar ABP501 (N = 55) and SB5 (N = 25) to maintain clinical and biochemical response after a switch in IBD patients [40]. In both the SB5 and ABP501 groups a stable clinical activity and fecal calprotectin values ($p = 0.20$ and $p = 0.90$) were observed.

In another Italian study based on the TABLET registry, the safety and effectiveness of SB5 in IBD patients was evaluated [29]. The investigators reported that 66.7% of adalimumab-naïve patients (N = 48) and 81.6% of patients who switched from the reference product to SB5 (N = 98) remained on SB5 beyond one year, with remission rates of 60.4% and 72.4% for the adalimumab-naïve group and switch groups, respectively. Overall, 53 (36.3%) IBD patients experienced an AE, and injection site pain was the most common, being significantly more frequent in the switching cohort ($p = 0.001$). Dose escalation was required in four patients (8.33%) in the naïve cohort and in 9 out of 98 patients (9.18%) in the switching cohort. The incidence of serious AEs was low in both adalimumab naïve (N = 2) and SB5-switched groups (N = 1) and no patients developed anti-drug antibodies after the switch.

A retrospective analysis of a prescriptions database in the UK evaluated whether SB5 was inferior to reference adalimumab and assessed efficiency of the IBD service throughout the follow-up process [41]. A total of 121 adalimumab prescriptions were issued and 77 patients were identified as having switched to SB5. Secondary loss of response at 52 weeks following SB5 switch occurred in 16.8% (13/77) of patients, whereas 12.4% (15/121) patients experienced secondary loss of response to adalimumab prior to the transition period. Twenty-three percent of patients reported clinical deterioration of symptoms, and 13% (10/77) changed to a second-line biosimilar due to side effects (mainly injection site pain). Twenty-five percent (18/71) of patients had raised C-reactive protein and 36% (17/45) of patients had raised fecal calprotectin. SB5 was not inferior to referenceadalimumab and patient acceptance was good, due to cost savings. Of note, while switching to a biosimilar should be performed in patients in remission, up to one-third of patients had biochemical markers suggestive of active disease.

In an observational study also performed in the UK by Derikx et al. involving 481 IBD patients long-term outcomes of SB5 following a switch from the adalimumab reference product or after start of SB5, were investigated [42]. It was observed that 70.8% of the SB5-switch cohort remained on SB5 beyond one year and 90/256 (35.2%) discontinued SB5, mainly due to AEs (46/90; 51.1%) or secondary loss of response (37/90; 41.1%). In the SB5-start cohort, 81/225 (36%) discontinued SB5 resulting in SB5-drug persistence of 60.3% beyond one year. No differences in clinical remission, C-reactive protein, fecal calprotectin, and adalimumab trough levels were found between baseline, week 26 and week 52 following switch. Injection site pain was the most frequently reported AE.

Results from the PROPER study restricted to patients with long-standing Crohn's disease have been recently published [43]. Of the 459 patients included in this interim analysis, at the time when data were extracted, 108 had completed 48 weeks on SB5, 45 patients discontinued SB5 treatment and 10 withdrew from the study. Disease flare was reported for 29 (6.3%) patients and twelve patients reported 13 serious AEs, of which only 4 were considered to be related to SB5 administration. However, no meaningful difference in disease activity or SB5 dosing regimen by week 48 post-transition was observed for most patients.

Limited data are available on patients that switched from one biosimilar to another. Ribaldone et al. reported results from a prospective observational study in 61 patients with Crohn's disease that had been originally treated with the adalimumab biosimilar ABP 501 and then switched to SB5 and followed for 6 months [44]. After 6 months, 88.5% (54/61) of patients remained on SB5 therapy. The success (defined as no systemic corticosteroids within 6 months,

Table 3. Studies evaluating the use of the biosimilar SB5 as first biological agent or after switching from reference adalimumab to SB5 in the dermatology setting.

Author, year [ref.]	Switch	Study design	Patients (N)	Disease	Follow-up	Key efficacy, safety and immunogenicity results	Authors' Conclusion
Girolomoni et al. 2020 [46]	SB5 as first biologic or switch from ADL	Real-world evidence (BADBIR registry)	SB5; 769	PsO	1 year	There were 137 discontinuations (17.6%) of SB5 out of 778 treatments and median treatment duration of 12.1 months (IQR: 7.5 months). Based on Kaplan Meier analysis, discontinuation rates of SB5 at 1 year and 2 year were 18.1% and 20.8%, respectively. Common reasons for treatment interruption were adverse events (7.0%) and ineffectiveness (6.8%). Among 14 patients who were switched from reference adalimumab, 14.3% patients interrupted treatment due to adverse events, 14.3% for ineffectiveness, and 1.7% for patient choice.	Treatment with SB5 after 1 year had good long-term persistence in patients with moderate-to-severe psoriasis. Even though data was limited on effectiveness, treatment with SB5 was associated with improvement in PASI as well as DLQI in this cohort.
Di Cesare et al. 2020 [47]	Naïve and ADL to SB5	Retrospective single center analysis	SB5; 23, (naïve; 3, switched; 20)	PsO, PsA	12 weeks	No relevant changes in PASI score were observed in 90% of patients who were switched ADL to SB5. Efficacy was lost in 2 patients. PASI 75 and/or maintenance of previously achieved endpoint were observed in 100% of ADL naïve patients at week 12. In 3/12 patients a worsening of articular symptoms was observed as soon as Week 4 of treatment.	SB5 is well tolerated, safe and effective in the treatment of psoriasis and PsA. However, although limited by the small number of patients treated, our data highlighted the possibility of a progressive loss of response to ADL after switching to SB5 in patients with axial disease.
Ricceri et al. 2020 [49]	Naïve and ADL to SB5	Retrospective observational study	SB5; 11 (naïve; 4, switched; 7)	HS	36 weeks	Efficacy evaluation after 36 weeks revealed rates of clinical remission similar to those before switch in bio-experienced patients and clinical improvement in bio-naïve patients. The incidence of adverse events prior to and after switching did not differ significantly. Pain at injection site reaction was reported in 4/11 patients. No cases of infections were recorded during 9 months of observations.	SB5 demonstrated clinical efficacy similar to that of reference ADL and was generally well tolerated in this population.

ADL: reference adalimumab, AE: adverse event, HS: hidradenitis suppurativa, IQR: interquartile range, PASI: psoriasis area and severity index, PsO: psoriasis, PsA: psoriatic arthritis. Ref.; reference

non-discontinuation of SB5, no dose escalation) of the switch was achieved in 82% (50/61) of patients. C-reactive protein levels >5 mg/l predicted switch failure (p = 0.03). Seven patients (11.5%) experienced side effects, compared to one patient (1.6%) in the 6 pre-switch months (p = 0.03). The authors conclude that switching from ABP501 to SB5 did not lead to new safety signals or loss of efficacy.

Another study performed in Italy by Barberio et al. compared the effectiveness and tolerability between reference adalimumab, ABP501 and SB5 in patients with IBD (ulcerative colitis and Crohn's disease) after induction and after 6 months of treatment using a propensity score-weighted approach [45]. Clinical benefit was achieved by 86.4% (134/155) of patients after induction and 85.3% (116/155) at 6 months, with no difference between treatment groups. All treatments showed a good safety profile, with only 10 patients stopping treatment due to AEs.

4.3. Dermatology setting

No clinical trials have examined the efficacy of SB5 in the dermatology setting and only few real-world studies are currently available (Table 3).

A real-world study in the UK based on data from the British Association of Dermatologists Biologic and Immunomodulators Register evaluated the effectiveness and persistence of SB5 treatment in 769 patients with moderate-to-severe psoriasis up to 1 year [46]. SB5 persistence was maintained in >80% of patients after 1 year. Although data were limited on effectiveness, treatment with SB5 was associated with an improvement in psoriasis area and severity index as well as the Dermatology life Quality Index in this cohort.

Another real-life study performed on psoriasis and PsA patients was recently published by Di Cesare et al. involving 23 patients, who were administered SB5 for at least 12 weeks [47]. All patients had cutaneous plaque psoriasis and almost 61% of patients had PsA, with axial involvement in 5/23 (21.7%) cases. No clinically important changes in psoriasis area and severity index were observed in 90% of patients who switched from adalimumab to SB5 and no safety issues were reported. Six out of twenty-three (26.1%) patients reported discomfort at the site of injection that was mitigated by keeping the syringe at room temperature before injections and improved over time. Overall, SB5 was found to be well tolerated, safe and effective for the treatment of psoriasis and PsA.

There are limited data on the use of SB5 in hidradenitis suppurativa, where adalimumab is the only biologic indicated [48]. In a real-world study conducted in Italy over 36 weeks, the use of SB5 in 11 patients with moderate-to-severe hidradenitis suppurativa was evaluated [49]. No patient interrupted the treatment and after 36 weeks of SB5 therapy. Similar rates of clinical remission to those before switch in bio-experienced patients and clinical improvement in bio-naïve patients were seen. The incidence of AEs prior to and after switching did not differ significantly. Pain at the site of injection was reported in 4/11 (36.4%) patients and no cases of infection were recorded.

4.4. Uveitis

While SB5 is indicated for the treatment of (non-infectious) uveitis [9], there is limited evidence available from clinical studies. A real-world retrospective study performed by Sota et al. examined the effectiveness of SB5 in uveitis at baseline and after 3 months [50]. SB5 biosimilar was effective by reducing uveitis relapses and the occurrence of retinal vasculitis. Furthermore, SB5 improved visual acuity, allowed a significant glucocorticoid-sparing effect and showed an excellent drug retention rate (91.8% at 12 months).

5. Safety/tolerability and patient perception

Comparable safety and tolerability profiles of SB5 and reference adalimumab have been demonstrated from pre-authorization studies [26] as well as a phase III clinical trial [30,31]. Real-world evidence identified some degree of heterogeneity with regard to the tolerability of SB5 across the three therapeutic areas of rheumatology, gastroenterology, and dermatology, particularly with regard to injection site pain [29,47,49].

SB5 is available as a 40 mg solution that is administered by sc injection in a pre-filled syringe/pen [51]. The usability and safety of SB5-pre-filled syringe (PFS) and pre-filled pen (PFP) was assessed in a study by Ghil et al [52]. The mean injection site pain score on a 10-point Likert scale was 2.3 in PFS vs. 2.0 in PFP immediately post-injection and 0.8 in PFS vs. 0.7 in PFP at 15–30 minutes post-injection. At both time points, the score was equivalent between PFS and PFP: the 97.5% CI was (−0.99, 0.30) and (−0.47, 0.25) immediately and 15–30 minutes post-injection, respectively. Overall impression by patients was also similar between PFS and PFP and the overall preference for PFP (56.5%) was higher than PFS (30.4%). The tolerability of the PFP and PFS of SB5 in 190 healthy subjects was evaluated by Shin et al. [53]. One subject in SB5-PFS group experienced a moderate injection site reaction.

In a Belgian study involving 110 IBD patients [54], the vast majority of patients (79.3%) treated with adalimumab were willing to switch to SB5 after being well informed. The rate of satisfaction under treatment with SB5 was high and remained stable over time, while some patients reported a higher, temporary, local discomfort within 30 minutes after injection with SB5 compared to adalimumab reference product.

In another recent phase IV single-center, prospective, randomized, single-blind, cross-over study performed in the UK in 112 adults with Crohn's disease, the patient's perspective on switching between adalimumab and SB5 was evaluated [55]. Prior to switching to SB5, efficacy and AEs were frequent concerns. Trust in the healthcare team was reported to be critical to patient acceptance of biosimilars and important reassurances include a point of contact, education about biosimilars and specific monitoring.

Additional considerations on the decision as to switch treatment and the timing to perform the switch have been addressed in detail elsewhere [56]. In general, the decision to switch should be made on a case-by-case basis depending on the underlying disease, patient characteristics, presence of

comorbidities, originator drug, and the willingness of the patient to switch.

6. Conclusion

Evidence to date derived from the three different therapeutic areas – rheumatology, gastroenterology, and dermatology – do not suggest clinically meaningful differences between SB5 and reference adalimumab in terms of pharmacokinetics, efficacy/effectiveness, safety, or immunogenicity, either in patients who initiated SB5 or patients who switched from adalimumab to SB5.

7. Expert opinion

Based on current evidence, we can conclude that the biosimilar SB5 was approved on the basis of a robust data package [9]. Since its approval, a substantial body of real-world evidence has been generated providing additional assurance that SB5 is as effective and safe in dermatological, gastroenterological, and rheumatic immune-mediated inflammatory diseases as the reference product. Differences in terms of persistence across studies may be partly due to the perception of increased injection site pain [29,42] or potential nocebo effects [33]. Understanding and minimizing injection-site pain following sc injection of adalimumab biologics such as SB5 is important to optimize the injection experience [57]. All biologics, including biosimilars, may differ in terms of product factors on top of other triggers of the multi-factorial pathogenesis of injection site pain. These may be specific to the formulation such as excipients (including buffers), pH, differences in volume or device used (and needle size). There are data that the citrate buffer used for SB5, compared to other buffers such as saline or histidine, may be associated with increased injection site pain, which may be augmented by nocebo effects [57]. Furthermore, patient characteristics such as gender, age, and low body weight can also lead to increased susceptibility to experiencing injection site pain [57]. This reinforces the idea that a close communication between physician and patient when initiating or switching to a biosimilar is key to the successful adoption [19,58].

While biologics have revolutionized the treatment of immune-mediated inflammatory diseases [59–62], the costs of these products may limit access for some patients [63–65].

The availability of biosimilars has had a profound impact economically [11] as well as a therapeutic benefit in terms of increased patient access to an effective biological treatment, and several budget impact models have predicted large-scale cost savings across Europe following biosimilar market entry [10,66–70]. Evidence to date is largely derived from budget impact models and the introduction of biosimilars such as SB5 compared to adalimumab originator appear to consistently offer substantial economic benefit [10,66–70]. Discounts of adalimumab biosimilars up to 90% of the list price have been reported by Moorkens et al. [71]. These price reductions have led to marked decreases in adalimumab expenditure. In Denmark, adalimumab expenditure dropped from over €5.13 million/month to €1.01 million/month while the volume of adalimumab use expanded. Similarly, annual adalimumab expenditure in the UK was reduced by £300 million, following the introduction of biosimilars [71–73].

While these forecasting analyses do provide grounds for cautious optimism, there have been initial concerns from the clinical community [5,8,74,75]. Most of these initial concerns have been overcome, largely thanks to data derived from real-world studies. In some instances, the arrival of biosimilars has increased access of patient populations that were not previously treated with biologics. Recently, a partial review has been performed of the NICE TA375 guideline outlining treatment recommendations for RA in the UK, following the availability of biosimilar versions of adalimumab and etanercept. The committee assessed the cost-effectiveness of the technologies using the original clinical evidence and economic model developed by the assessment group for NICE technology appraisal 375 [76]. The outcome of the review was to also recommend patients with moderate RA to be treated with anti-TNF biologics, whereas this was previously reserved only for patients with severe disease (disease activity score; DAS28 of >5.1) [77].

Updates to treatment guidelines combined with widespread reimbursement policies across Europe [78] have granted a significantly higher number of patients across a wide range of disease settings access to biologic treatment. Current recommendations from the European Crohn's and Colitis Organization (ECCO) include the use of adalimumab, to induce remission in patients with moderate-to-severe IBD who have not responded to conventional therapy [6,7]. The ECCO Position Statement on the Use of Biosimilars for Inflammatory Bowel Disease, published in 2017, states that: 'Switching from the originator to a biosimilar in patients with IBD is acceptable'; and that 'Switching from originator to a biosimilar should be performed following appropriate discussion between physicians, nurses, pharmacists, and patients, and according to national recommendation' [74].

In the dermatology setting, patients with psoriasis are traditionally reported as undertreated [79]. Despite an exhaustive review of clinical practice guidelines conducted in 2017, which seemed to indicate otherwise, the situation in 2020 does not appear to have changed substantially [80]. A recent Expert Opinion paper by leading dermatology experts in Italy reviewed the available evidence on the use of TNF inhibitor biosimilars in moderate-to-severe psoriasis [81]. They concluded that the use of TNF inhibitor biosimilars may represent a first-line systemic treatment for patients with moderate-to-severe psoriasis. Furthermore, a recent review of 60 published studies revealed that patient satisfaction was higher in psoriatic patients receiving biologic treatment compared to those receiving oral therapies, phototherapy, or topicals and adherence was also found to be higher with biologics compared to conventional agents [82,83]. The early use of biologic therapy with TNF inhibitor biosimilars may provide a valuable and sustainable option, with an improved efficacy/effectiveness compared to conventional agents [81]. Moreover, the extensive experience gained with SB5 across therapeutic areas adds to the overall confidence in using biosimilars.

Funding

Medical writing support was provided by Colin Gerard Egan, PhD (CE Medical Writing, SRLS, Pisa, Italy), and funding was provided by Biogen International GmbH, Switzerland.

Declaration of interests

Dr Javier P. Gisbert has served as speaker, consultant, and advisory member for or has received research funding from MSD, Abbvie, Pfizer, Kern Pharma, Biogen, Mylan, Takeda, Janssen, Roche, Sandoz, Celgene, Gilead/Galapagos, Ferring, Faes Farma, Shire Pharmaceuticals, Dr. Falk Pharma, Tillotts Pharma, Chiesi, Casen Fleet, Gebro Pharma, Otsuka Pharmaceutical, and Vifor Pharma. Professor Karl Gaffney has received honoraria for attending advisory boards and delivering educational talks from Abbvie, Celltrion, Lilly, Novartis and UCB, and received research grants from Abbvie, Biogen, Novartis and UCB.

David Young has received support from Sandoz for meeting attendance/travel.

Dr Hans C. Ebbers is an employee of Biogen and owns stock in Biogen. Professor Girolomoni has received personal fees from AbbVie, Abiogen, Almirall, Amgen, Biogen, Boehringer-Ingelheim, Bristol-Meyers Squibb, Eli-Lilly, Fresenius Kabi, Galderma, Genzyme, Leo Pharma, Novartis, OM Pharma, Pfizer, Regeneron, Samsung bioepis and Sanofi. The authors have no other relevant affiliations or financial involvement with any organization or entity with a financial interest in or financial conflict with the subject matter or materials discussed in the manuscript apart from those disclosed.

Reviewer disclosures

One of the peer reviewers of this manuscript declares to have received research grants from Pfizer, AbbVie and BMS. Peer reviewers on this manuscript have no other relevant financial relationships or otherwise to disclose.

ORCID

Javier P. Gisbert http://orcid.org/0000-0003-2090-3445
Karl Gaffney http://orcid.org/0000-0002-7863-9176
David Young http://orcid.org/0000-0003-0102-5739
Giampiero Girolomoni http://orcid.org/0000-0001-8548-0493

References

Papers of special note have been highlighted as either of interest (•) or of considerable interest (••) to readers.

1. Biosimilar and Interchangeable Products. FDA [Internet]. 2019 [Accessed2021 May 15 2021]; : https://www.fda.gov/drugs/biosimilars/biosimilar-and-interchangeable-products.
2. European Medicines Agency [Internet]. European Medicines Agency. [Accessed2019 May 15 2021]. : https://www.ema.europa.eu/en
3. Biosimilar Product Information. FDA [Internet]. 2021 [Accessed2021 July 12 2021]; : https://www.fda.gov/drugs/biosimilars/biosimilar-product-information
4. EMA. Humira [Internet]. European Medicines Agency. 2018 [Accessed2021 June 30 2021]; : https://www.ema.europa.eu/en/medicines/human/EPAR/humira
5. Smolen JS, Rbm L, Bijlsma JWJ, et al. EULAR recommendations for the management of rheumatoid arthritis with synthetic and biological disease-modifying antirheumatic drugs: 2019 update. Ann Rheum Dis. 2020;79:685–699.
(•)European guidelines for the use of biologics in rheumatoid arthritis.
6. Harbord M, Eliakim R, Bettenworth D, et al. Third European evidence-based consensus on diagnosis and management of ulcerative colitis. Part 2: current management. J Crohns Colitis. 2017;11:769–784.
(•)European consensus statement for management of ulcerative colitis.
7. Torres J, Bonovas S, Doherty G, et al. ECCO guidelines on therapeutics in Crohn's disease: medical treatment. J Crohn's Colitis. 2020;14:4–22.
(•)European guidelines for the therapeutic management of Crohn's disease.
8. Nast A, Spuls PI, van der Kraaij G, et al. European S3-Guideline on the systemic treatment of psoriasis vulgaris – update Apremilast and Secukinumab – EDF in cooperation with EADV and IPC. J Eur Acad Dermatol Venereol. 2017;31:1951–1963.
(•)European guidelines for the use of biologics in psoriasis.
9. European Medicines Agency. Imraldi. [Internet]. European Medicines Agency. 2018 [Accessed2021 Jun 29 2021]; : https://www.ema.europa.eu/en/medicines/human/EPAR/imraldi
10. Porter J, Stuart P, Bartsch R, et al. PBI7 cost-effectiveness analysis of Adalimumab biosimilar compared to delayed biologic treatment initiation in patients with rheumatoid arthritis in Germany. Value Health. 2021;24:S15.
11. Rezk MF, Pieper B. Unlocking the value of anti-TNF biosimilars: reducing disease burden and improving outcomes in chronic immune-mediated inflammatory diseases: a narrative review. Adv Ther. 2020;37:3732–3745.
12. Medicines for Europe. Positioning statements on physician-led switching for biosimilar medicines update September 2020 [Internet] Accessed22 May 2021. : https://www.medicinesforeurope.com/docs/M-Biosimilars-Overview-of-positions-on-physician-led-switching.pdf
13. Kurki P, van Aerts L, Wolff-Holz E, et al. Interchangeability of biosimilars: a European perspective. BioDrugs. 2017;31:83–91.
14. Gisbert JP, Chaparro M. Switching from an originator anti-TNF to a biosimilar in patients with inflammatory bowel disease: can it be recommended? A systematic review. Gastroenterol Hepatol. 2018;41:389–405.
15. de Ridder L, Assa A, Bronsky J, et al. Use of biosimilars in pediatric inflammatory bowel disease: an updated position statement of the pediatric IBD Porto Group of ESPGHAN. J Pediatr Gastroenterol Nutr. 2019;68:144–153.
16. Zink A, Strangfeld A, Schneider M, et al. Effectiveness of tumor necrosis factor inhibitors in rheumatoid arthritis in an observational cohort study: comparison of patients according to their eligibility for major randomized clinical trials. Arthritis Rheum. 2006;54:3399–3407.
17. Jørgensen KK, Olsen IC, Goll GL, et al. Switching from originator infliximab to biosimilar CT-P13 compared with maintained treatment with originator infliximab (NOR-SWITCH): a 52-week, randomised, double-blind, non-inferiority trial. Lancet. 2017;389:2304–2316.
18. Kravvariti E, Kitas GD, Sfikakis PP. The role of the Nocebo effect in the use of biosimilars in routine rheumatology clinical practice. Mediterr J Rheumatol. 2019;30:63–68.
19. Pouillon L, Socha M, Demore B, et al. The nocebo effect: a clinical challenge in the era of biosimilars. Expert Rev Clin Immunol. 2018;14:739–749.
20. Ben-Horin S, Casteele NV, Schreiber S, et al. Biosimilars in inflammatory bowel disease: facts and fears of extrapolation. Clin Gastroenterol Hepatol. 2016;14:1685–1696.
21. Biosimilar medicines: overview [Internet]. European Medicines Agency. 2018 [cited Accessed2021 June 30 2021]; cited: https://www.ema.europa.eu/en/human-regulatory/overview/biosimilar-medicines-overview
22. Nayoung L Biosimilarity between Humira® and the biosimilar candidate SB5 in product quality [Internet]. ACR Meeting Abstracts. [cited 2021 Jun 30]; Available from: https://acrabstracts.org/abstract/biosimilarity-between-humira-and-the-biosimilar-candidate-sb5-in-product-quality/
23. Lee N, Lee JJ, Yang H, et al. Evaluation of similar quality attribute characteristics in SB5 and reference product of Adalimumab. MAbs. 2018;11:129–144.
24. Park D, Yun J, Hwang S-J, et al. Evaluation of physicochemical and biological stability of 36-months-aged SB5 (Adalimumab biosimilar) for 4 weeks at room temperature. Adv Ther. 2019;36:442–450.

(••)One of the first studies to demonstrate physicochemical and biological properties of SB5 compared to adalimumab.

25. Lee JJ, Yang J, Lee C, et al. Demonstration of functional similarity of a biosimilar Adalimumab SB5 to Humira®. Biologicals. 2019;58:7–15.
(••)One of the first studies to demonstrate functional similarity of SB5 compared to adalimumab.
26. Shin D, Lee Y, Kim H, et al. A randomized phase I comparative pharmacokinetic study comparing SB5 with reference Adalimumab in healthy volunteers. J Clin Pharm Ther. 2017;42:672–678.
(••)First study to demonstrate similar pharmacokinetics of SB5 compared to adalimumab in healthy individuals.
27. Goncalves J, Myung G, Park M, et al. SB5 shows cross-immunogenicity to Adalimumab but not infliximab: results in patients with inflammatory bowel disease or rheumatoid arthritis. Therap Adv Gastroenterol. 2019;12:1756284819891081.
28. Lukas M, Malickova K, Kolar M, et al. Switching from originator Adalimumab to the biosimilar SB5 in patients with inflammatory bowel disease: short-term experience from a single tertiary clinical centre. J Crohns Colitis. 2020;14:915–919.
29. Tapete G, Bertani L, Pieraccini A, et al. Effectiveness and safety of nonmedical switch from Adalimumab originator to SB5 biosimilar in patients with inflammatory bowel diseases: twelve-month follow-up from the TABLET registry. Inflamm Bowel Dis. 2021;Feb 11;izab027 doi:10.1093/ibd/izab027.
30. Weinblatt ME, Baranauskaite A, Dokoupilova E, et al. Switching from reference Adalimumab to SB5 (Adalimumab biosimilar) in patients with rheumatoid arthritis: fifty-two-week phase III randomized study results. Arthritis Rheumatol. 2018;70:832–840.
(••)Pivotal phase III trial examining efficacy and safety of SB5 after switching from adalimumab in patients with moderate-to-severe rheumatoid arthritis.
31. Weinblatt ME, Baranauskaite A, Niebrzydowski J, et al. Phase III randomized study of SB5, an Adalimumab biosimilar, versus reference Adalimumab in patients with moderate-to-severe rheumatoid arthritis. Arthritis Rheumatol. 2018;70:40–48.
(••)Pivotal phase III trial examining efficacy and safety of SB5 versus adalimumab in patients with moderate-to-severe rheumatoid arthritis.
32. Di Giuseppe D, Bower H, Delcoigne B, et al. Pos0601 differences in drug survival between originator and biosimilar products among first users of each molecule. Ann Rheum Dis. 2021;80:535.
33. Bruni C, Gentileschi S, Pacini G, et al. Switching from originator Adalimumab to biosimilar SB5 in a rheumatology cohort: persistence on treatment, predictors of drug interruption and safety analysis. Ther Adv Musculoskelet. 2021;13:1759720X211033679.
34. Müller-Ladner U, Gaffney K, Jadon D, et al. AB0204 The proper study: interim analysis of a PAN-EU REAL-World study of SB5 biosimilar following transition from reference Adalimumab in patients with rheumatoid arthritis, axial spondyloarthritis, or psoriatic arthritis. Ann Rheum Dis. 2021;80:1126–1127.
35. Nabi H, Georgiadis S, Loft AG, et al. Comparative effectiveness of two Adalimumab biosimilars in 1318 real-world patients with inflammatory rheumatic disease mandated to switch from originator Adalimumab: nationwide observational study emulating a randomised clinical trial. Ann Rheum Dis. 2021;80:1400–1409.
36. Fiorino G, Ruiz-Argüello MB, Maguregui A, et al. Full interchangeability in regard to immunogenicity between the infliximab reference biologic and biosimilars CT-P13 and SB2 in inflammatory bowel disease. Inflamm Bowel Dis. 2018;24:601–606.
37. Chaparro M, Garre A, Guerra Veloz MF, et al. Effectiveness and safety of the switch from Remicade® to CT-P13 in patients with inflammatory bowel disease. J Crohns Colitis. 2019;13:1380–1386.
38. Deprez N, De Somer T, Baert D, et al. P281 Evaluation of trough level and disease activity after switch from Adalimumab originator to biosimilar in patients with inflammatory bowel disease. J Crohn's Colitis. 2021;15:S314–S315.
39. Dragoni G, Pieraccini A, Bagnoli S, et al. P620 maintenance of clinical remission with SB5 biosimilar after switch from Adalimumab originator: real-life experience of a tertiary referral centre. J Crohn's Colitis. 2020;14:S515–S515.
40. Cingolani L, Barberio B, Zingone F, et al. Adalimumab biosimilars, ABP501 and SB5, are equally effective and safe as Adalimumab originator. Sci Rep. 2021;11:10368.
41. Koumoutsos I, Cowperthwaite S, Glover S, et al. P122 Switching from originator Adalimumab to biosimilar SB5(Imraldi) – IBD service assessment and needs. Gut. 2021;70:A105–A105.
42. Derikx LAAP, Dolby HW, Plevris N, et al. Effectiveness and safety of Adalimumab biosimilar SB5 in IBD: outcomes in originator to SB5 switch, double biosimilar switch and bio-naieve SB5 observational cohorts. J Crohns Colitis. 2021;June 5;jjab100 doi:10.1093/ecco-jcc/jjab100.
43. Dignass A, Gisbert J, Freudensprung U, et al. P469 The PROPER study: interim analysis of a pan-European real-world study of SB5 Adalimumab biosimilar after transition from reference Adalimumab in patients with Crohn's disease. J Crohns Colitis. 2021;15:S459–S460.
44. Ribaldone DG, Tribocco E, Rosso C, et al. Switching from biosimilar to biosimilar Adalimumab, including multiple switching, in Crohn's disease: a prospective study. J Clin Med. 2021;10:3387.
45. Barberio B, Cingolani L, Canova C, et al. A propensity score-weighted comparison between Adalimumab originator and its biosimilars, ABP501 and SB5, in inflammatory bowel disease: a multicenter Italian study. Therap Adv Gastroenterol. 2021;14:17562848211031420.
46. Girolomoni G Real-world data of SB5 (Adalimumab biosimilar) treatment in patients with psoriasis from the British Association of Dermatologists Biologic and Immunomodulators Register (BADBIR) [Internet]. 29th Annual meeting of the European Academy of Dermatology and Venereology Sep 23-27, 2020 Vienna, Austria. . . . : https://pharmacievirtualcongress.com/wp-content/uploads/2020/10/Free-Communications-programme.pdf
47. Di Cesare A, Tronconi G, Fastame TM, et al. SB5 Adalimumab biosimilar in the treatment of psoriasis and psoriatic arthritis. Dermatol Ther. 2020;33:e13435.
48. Kimball AB, Okun MM, Williams DA, et al. Two phase 3 trials of Adalimumab for Hidradenitis Suppurativa. N Engl J Med. 2016;375:422–434.
49. Ricceri F, Rosi E, Di Cesare A, et al. Clinical experience with Adalimumab biosimilar imraldi in hidradenitis suppurativa. Dermatol Ther. 2020;33:e14387.
50. Sota J, Gentileschi S, Vitale A, et al. Effectiveness of SB5, an Adalimumab biosimilar, in patients with noninfectious Uveitis: a real-life monocentric experience. Asia Pac J Ophthalmol [Internet]. 2021 [cited 2021 Jul 6];Publish Ahead of Print. Available from: https://journals.lww.com/apjoo/abstract/9000/effectiveness_of_sb5,_an_adalimumab_biosimilar,_in.99701.aspx
51. Electronic Medicines Compendium. Biogen biosimilars. Imraldi 40 mg solution for injection in pre-filled pen [Internet] Accessed4 July 2021. Available from: https://www.medicines.org.uk/emc/product/9594/smpc#gref
52. Ghil J, Zielińska A, Lee Y. Usability and safety of SB5 (an Adalimumab biosimilar) prefilled syringe and autoinjector in patients with rheumatoid arthritis. Curr Med Res Opin. 2019;35:497–502.
53. Shin D, Lee Y, Kang JW, et al. AB0308 A phase I pharmacokinetic study comparing pre-filled pen and pre-filled syringe of SB5, an Adalimumab biosimilar in healthy subjects. Ann Rheum Dis. 2016;75:1005–1006.
54. De Somer T, Deprez N, Baert D. European Crohn´s and Colitis Organisation - ECCO - P396 acceptance of switch, patient satisfaction and adverse events after switch from Adalimumab originator to biosimilar SB5 in patients with inflammatory bowel disease in a real-life setting [Internet]. [cited 2021 Oct 25]; Available from: https://www.ecco-ibd.eu/publications/congress-abstracts/item/p396-acceptance-of-switch-patient-satisfaction-and-adverse-events-after-switch-from-adalimumab-originator-to-biosimilar-sb5-in-patients-with-inflammatory-bowel-disease-in-a-real-life-setting.html.

55. Young D, Latter S, Harvey J, et al. P585 IBD reference and biosimilar Adalimumab cross over study (iBaSS): a mixed methods clinical trial of patients transitioning between originator and biosimilar Adalimumab. Qualitative findings from an interim analysis presenting the patient perspective. J Crohn's Colitis. 2021;15:S537–S538.
56. Moots R, Azevedo V, Coindreau JL, et al. Switching between reference biologics and biosimilars for the treatment of rheumatology, gastroenterology, and dermatology inflammatory conditions: considerations for the clinician. Curr Rheumatol Rep. 2017;19:37.
57. St Clair-Jones A, Prignano F, Goncalves J, et al. Understanding and minimising injection-site pain following subcutaneous administration of biologics: a narrative review. Rheumatol Ther. 2020;7:741–757.
58. Barbier L, Ebbers HC, Declerck P, et al. The efficacy, safety, and immunogenicity of switching between reference biopharmaceuticals and biosimilars: a systematic review. Clin Pharmacol Ther. 2020;108:734–755.
59. Kuek A, Hazleman BL, Östör AJK. Immune-mediated inflammatory diseases (IMIDs) and biologic therapy: a medical revolution. Postgrad Med J. 2007;83:251–260.
60. Côté-Daigneault J, Bouin M, Lahaie R, et al. Biologics in inflammatory bowel disease: what are the data? United European Gastroenterol J. 2015;3:419–428.
61. Curtis JR, Singh JA. The use of biologics in rheumatoid arthritis: current and emerging paradigms of care. Clin Ther. 2011;33:679–707.
62. Rich SJ, Bello-Quintero CE. Advancements in the treatment of psoriasis: role of biologic agents. J Manag Care Pharm. 2004;10:318–325.
63. Nurmohamed MT, Dijkmans BAC. Efficacy, tolerability and cost effectiveness of disease-modifying antirheumatic drugs and biologic agents in rheumatoid arthritis. Drugs. 2005;65:661–694.
64. Pillai N, Dusheiko M, Burnand B, et al. A systematic review of cost-effectiveness studies comparing conventional, biological and surgical interventions for inflammatory bowel disease. PLoS One. 2017;12:e0185500.
65. van der Velde G, Pham B, Machado M, et al. Cost-effectiveness of biologic response modifiers compared to disease-modifying antirheumatic drugs for rheumatoid arthritis: a systematic review. Arthritis Care Res (Hoboken). 2011;63:65–78.
66. Aladul M, Fitzpatrick R, Chapman S. The effect of new biosimilars in rheumatology and gastroenterology specialities on UK healthcare budgets: results of a budget impact analysis. Res Social Adm Pharm. 2019;15(3): 310–317.
67. Jha A, Upton A, Dunlop WCN, et al. The budget impact of biosimilar Infliximab (Remsima®) for the treatment of autoimmune diseases in five European countries. Adv Ther. 2015;32:742–756.
68. Brodszky V, Rencz F, Péntek M, et al. A budget impact model for biosimilar infliximab in Crohn's disease in Bulgaria, The Czech Republic, Hungary, Poland, Romania, and Slovakia. Expert Rev Pharmacoecon Outcomes Res. 2016;16:119–125.
69. Aubrey P, Waker M, Levysohn A, et al. PBI9 evaluation of the cost saving potential of introducing Adalimumab biosimilars for the treatment of all licensed adult Adalimumab indications in Ireland. Value Health. 2019;22:S48.
70. Barbado G, Waker M, Levysohn A, et al. PBI21 evaluation of the cost saving potential of introducing an Adalimumab biosimilar for the treatment of all licensed adult Adalimumab indications in Spain. Value Health. 2019;22:S50.
71. Moorkens E, Godman B, Huys I, et al. The expiry of Humira® market exclusivity and the entry of Adalimumab biosimilars in Europe: an overview of pricing and national policy measures. Front Pharmacol. 2020;11:591134.
72. Jensen TB, Kim SC, Jimenez-Solem E, et al. Shift from Adalimumab originator to biosimilars in Denmark. JAMA Intern Med. 2020;180:902–903.
73. NHS England. NHS set to save record £300 million on the NHS's highest drug spend [Internet]. [cited 2021 Oct 29]; cited: https://www.england.nhs.uk/2018/11/nhs-set-to-save-record-300-million-on-the-nhss-highest-drug-spend/
74. Danese S, Fiorino G, Raine T, et al. ECCO position statement on the use of biosimilars for inflammatory bowel disease-an update. J Crohns Colitis. 2017;11:26–34.
(•)European guidelines for the use of biosimilars in inflammatory bowel disease.
75. Halimi V, Daci A, Ancevska Netkovska K, et al. Clinical and regulatory concerns of biosimilars: a review of literature. Int J Environ Res Public Health. 2020;17:5800.
76. NICE. Adalimumab, etanercept, infliximab, certolizumab pegol, golimumab, tocilizumab and Abatacept for moderate rheumatoid arthritis after conventional DMARDs have failed (partial review of TA375) [ID2710] [Internet]. NICE; [cited 2021 Jul 13]; Available from: https://www.nice.org.uk/guidance/indevelopment/gid-ta10586
77. NICE. Adalimumab, etanercept, infliximab and Abatacept for treating moderate rheumatoid arthritis after conventional DMARDs have failed (partial review of TA375) [Internet] Accessed18 May 2021. Available from: https://www.nice.org.uk/guidance/ta715/documents/final-appraisal-determination-document
78. Vogler S, Schneider P, Zuba M, et al. Policies to encourage the use of biosimilars in European countries and their potential impact on pharmaceutical expenditure. Front Pharmacol. 2021;12:1479.
79. Horn EJ, Fox KM, Patel V, et al. Are patients with psoriasis undertreated? Results of National Psoriasis Foundation survey. J Am Acad Dermatol. 2007;57:957–962.
80. Cohen AD, Wu JJ, Puig L, et al. Biosimilars for psoriasis: worldwide overview of regulatory guidelines, uptake and implications for dermatology clinical practice. Br J Dermatol. 2017;177:1495–1502.
81. Gisondi P, Geat D, Conti A, et al. TNF-α inhibitors biosimilars as first line systemic treatment for moderate-to-severe chronic plaque psoriasis. Expert Rev Clin Immunol. 2020;16:591–598.
82. Florek AG, Wang CJ, Armstrong AW. Treatment preferences and treatment satisfaction among psoriasis patients: a systematic review. Arch Dermatol Res. 2018;310:271–319.
83. Dommasch ED, Lee MP, Joyce CJ, et al. Drug utilization patterns and adherence in patients on systemic medications for the treatment of psoriasis: a retrospective, comparative cohort study. J Am Acad Dermatol. 2018;79:1061–1068.e1.