

An Update Review of Biosimilars of Adalimumab in Psoriasis – Bioequivalence and Interchangeability

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Abstract: Biologic drugs have revolutionized the treatment of psoriasis and other rheumatological diseases. In recent years, many biosimilar agents that are highly similar in structure and function to their originator products have been developed, including the tumor necrosis factor-alpha antagonist adalimumab. The considerably lower cost of these products has greatly cut the economic burden of the patients and increased the accessibility of biologic therapies worldwide. The US Food and Drug Administration and/or the European Medicines Agency have approved eight biosimilars of adalimumab (ABP 501/BI 695501/SB5/GP2017/FKB327/MSB11022/PF-06410293/CT-P17) for the treatment of psoriasis, and others are under review. Given that these agents showed pharmacokinetic, efficacy, safety, and immunogenicity profiles comparable to those of the originator, adalimumab biosimilars were licensed for all indications approved for reference adalimumab based on extrapolation; however, some of the equivalence studies were only conducted in one or two disease populations. This review discusses the bioequivalence of adalimumab biosimilars as demonstrated by various clinical trials, the extrapolation of indications, guidance and policies of the EU and US on interchangeability (nonmedical switching/automatic substitution) between biosimilars and originators, and the real-life practices of switching from reference adalimumab to the respective biosimilars. Further data from real-world studies and post-marketing analyses are needed better to address the efficacy and safety of the transition strategy.

Keywords: biosimilar, adalimumab, psoriasis, guidance of interchangeability, extrapolation of indications

Introduction

The occurrence of biologic medicines has brought a drastic change in the treatment regimens for psoriasis and other chronic rheumatic diseases over the past decades. Many biological agents have been licensed for treating chronic plaque psoriasis. Biologics targeting tumor necrosis factor-alpha (TNF- α) (infliximab, etanercept, and adalimumab), interleukin (IL)-12/23p40 (ustekinumab), IL-23p19 (guselkumab, til-drakizumab, and risankizumab), IL-17A (secukinumab and ixekizumab), and IL-17RA (brodalumab) were among the most commonly used medications in this class. However, the high expense often limits patient access to these medications.¹

A biosimilar, as defined by the European Medicines Agency (EMA), is a biologic agent very similar to another already approved biological drug in the European Union (EU); although there might be minor differences from the originator, the biological properties and clinical performance in terms of pharmacokinetic (PK) and pharmacodynamic (PD) features, immunogenicity, efficacy, and safety should be comparable to the respective originator.² The United States (US) Food and Drug Administration

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(FDA) defines a biosimilar as a biological medicine that has “no clinically meaningful differences” from an already licensed originator.³ The phrase “no clinically meaningful differences” means that the biosimilar should be comparable in terms of purity, safety, efficacy, and clinical immunogenicity to the reference drug. Biosimilars were created to reduce the financial expense of originators, thus allowing wider application of biologic treatment.⁴

Adalimumab (Humira, AbbVie Inc. North Chicago, Illinois, US) is a fully human, recombinant, IgG1 monoclonal antibody⁵ targeting TNF- α . After binding to TNF, adalimumab blocks the interaction of the cytokine with p55 and p75 cell surface TNF receptors, thus inhibiting TNF-related biological reactions.⁶ Results of the REVEAL⁶ study showed that 71% patients from adalimumab group achieved 75% improvement of Psoriasis Area and Severity Index (PASI) score at week 16 compared to that of placebo group (7%). Considering the results of the REVEAL⁶ and CHAMPION trials,⁷ it was approved by the FDA for treating adult psoriasis in 2008 and by the EMA in 2007. Since 2012, adalimumab has become the world's top selling drug, with total sales of 2014 reaching as much as \$12.89 billion.⁸ The tremendous commercial success worldwide makes adalimumab the most appealing target for biosimilar manufacturers. Upon expiration of the patents of Humira in the US in December 2016 and in Europe in October 2018,⁹ several biosimilars gained the approval of regulatory agencies and entered the market.

To date, through the years 2016–2020, the FDA and/or the EMA have approved eight adalimumab biosimilars (ABP 501: EMA 2017, FDA 2016; BI 695501: EMA 2017 (withdrawn 2019), FDA 2017; SB5: EMA 2017, FDA 2019; GP2017: EMA 2018, FDA 2018; FKB327: EMA 2018, FDA 2020; MSB11022: EMA 2019; PF-06410293: FDA 2019, EMA 2020;¹⁰ CT-P17: EMA2020¹¹), for treating chronic plaque psoriasis, and many others are in development (Table 1).

Some prior articles have reviewed adalimumab biosimilars. Olteanu et al¹² reviewed published and ongoing studies relating to biosimilars targeting TNF- α . They listed three completed trials of adalimumab biosimilars (ABP 501 and BCD-057) and three ongoing trials of adalimumab biosimilars (SB5, M923, and GP2017). However, the results including safety, efficacy and immunogenicity of these trials were not available at the time. The authors concluded that the current situation is very unsatisfactory, which will give clinicians a certain degree of uncertainty in their treatment decisions. In addition, the review was written seven

years ago, there were no adalimumab biosimilars approved by the FDA and the EMA, and the RCTs of adalimumab biosimilars were still ongoing at that time. Discussions about the guidance and policies of various countries on interchangeability, and the real-life practices of switching were missing. Reynolds et al¹⁰ reviewed biosimilars in the treatment of psoriasis, but mainly focused on the safety and efficacy. Extrapolation, interchangeability, and guidance of different societies and countries were not involved. The perspectives on the biosimilars have changed over years, so it is necessary to discuss about these problems that may influence clinicians in their clinical practice.

The purpose of this review is to present the most updated clinical trials' outcomes of adalimumab biosimilars (ABP 501, BI 695501, SB5, GP2017, FKB327, MSB11022, PF-06410293 and CT-P17), extrapolation of indications, guidance and policies in the EU and USA on interchangeability (nonmedical switching/automatic substitution) between these biosimilars and their originators, and the real-life practices of switching from originator adalimumab to respective biosimilars through a narrative review of the existing literature. Additional adalimumab biosimilars that were approved in countries other than the US and the EU are also mentioned.

Methods

The literature review was conducted in the PubMed database to identify English articles related to Phase I PK studies and Phase III randomized clinical trials (RCTs) investigating the safety and effectiveness of adalimumab biosimilars in the treatment of psoriasis or other rheumatic diseases. Each phase III study recruited more than 400 patients from multiple centers, and the efficacy and safety results were analyzed by the full analysis set (FAS) and the safety analysis set (SAS) separately. We extracted data from the corresponding regulatory agencies' approval documents, national registries of biologics or post-marketing surveillance analyses, and we also searched ClinicalTrials.gov to identify unpublished study results relating to adalimumab biosimilars. The search was performed by using the following key words: biosimilar adalimumab, ABP501, BI 695501, SB5, GP2017, FKB327, MSB11022, PF-06410293, CT-P17, psoriatic arthritis (PsA), psoriasis (PsO), rheumatoid arthritis (RA), ankylosing spondylitis (AS), immunogenicity, efficacy, safety, extrapolation of indication, interchangeability, switch, and substitution. The literature review was extended to Feb 28, 2021.

Table I Adalimumab Biosimilars Approved or in Clinical Development for Psoriasis Treatment

Reference Product	Biosimilar	Manufacturer	Phase of Development
Adalimumab	ABP 501	Amgen (USA)	Approved in EU (2017), USA (2016)
	BI 695501	Boehringer Ingelheim (Germany)	Approved in EU (2017, withdrawn in 2019), USA (2017)
	SB5	Biogen/Samsung Bioepis (South Korea)/ Merck (USA)	Approved in EU (2017), USA (2019)
	GP2017	Sandoz (Switzerland)	Approved in EU (2018), USA (2018)
	MSB11022	Fresenius Kabi (Germany)	Approved in EU (2019)
	FKB327	Fujifilm Kyowa Kirin Biologics (Japan)/ Mylan (USA)	Approved in EU (2018), USA (2020)
	PF-06410293	Pfizer (USA)	Approved in EU (2020), USA (2019)
	CT-PI7	Celltrion (South Korea)	Approved in EU (2020)
	CinnoRA	CinnaGen (Iran)	Approved in Iran
	ZRC-3197	Cadila Healthcare (India)	Approved in India (2014)
	BAT1406	Bio-Thera (China)	Approved in China (2019)
	HS016	Zhejiang Hisun Pharmaceutical (China)	Approved in China (2019)
	HLX3	Shanghai Henlius Biotech (China)	Approved in China (2020)
	LBAL	LG Life Sciences (South Korea)/Mochida Pharmaceutical (Japan)	Phase III (completed)
	ONS-3010	Outlook Therapeutics (former Oncobiologics) (USA)	Phase III (completed)
	MYL-1401A	Mylan (USA)	Phase III (completed)
	M923	Momenta Pharmaceuticals (USA)	Phase III (completed)
	BCD-057	Biocad (Russia)	Phase III (completed)
	AVT02	Alvotech Swiss AG (Switzerland)	Phase III (completed)
	DMB-3113	Meiji Seika Pharma (Japan)	Phase I
TUR01	Turgut İlaçları A.Ş.(Turkey)	Phase I	
BMO-2	Mylan (USA)	Phase I	

Efficacy, Safety and Bioequivalence Studies

ABP 501

The FDA and the EMA approved the first adalimumab biosimilar ABP 501 in 2016 and 2017, respectively.^{11,13} A phase I study enrolled healthy subjects to evaluate the PK similarity of ABP 501 to adalimumab.¹⁴ Healthy volunteers were randomized into three groups to be treated subcutaneously with 40 mg of ABP 501, US- or EU-sourced adalimumab. The mean serum concentration-time

profiles after a single dose were similar across the three groups. The single doses of ABP501 and adalimumab were shown to be equivalent with respect to the area under the serum concentration-time curve from time 0 (AUC_0) to infinity (AUC_{inf}) and from AUC_0 to terminal concentration (AUC_{last}). The 90% confidence intervals (CIs) for the geometrical mean ratios (GMRs) of C_{max} , AUC_{inf} and AUC_{last} were within the predefined range (0.80–1.25; primary endpoint), demonstrating the equivalence of PK between ABP501 and adalimumab.¹⁴

Papp et al conducted a multicenter, randomized, phase III study to compare the safety and efficacy of ABP 501 with adalimumab in psoriasis.¹⁵ Overall, 350 patients were enrolled, randomized 1:1 into two groups and included in the efficacy analysis; 347 patients (ABP 501 group, $n = 174$; adalimumab group, $n = 173$) were included within the safety analysis. At week 16, the percentage improvement of PASI score in the two groups was 80.9% (ABP 501) and 83.1% (adalimumab). Adverse events (AEs) (67.2% [ABP 501] vs 63.6% [adalimumab]) and antidrug antibody (ADA) incidence (55.2% [ABP 501] vs 63.6% [adalimumab]) were comparable between groups. Safety and immunogenicity remained similar across groups after a single transition at 20 weeks.¹⁵

Another phase III RCT was conducted in patients with RA.¹⁶ In this active comparator-controlled study, 526 patients were randomized, and 494 completed the study. At week 24, the American College of Rheumatology (ACR)-20 response rate was 74.6% in the ABP 501 group and 72.4% in the adalimumab group; the risk ratio (RR) was 1.039, and the 90% CI (0.954–1.133) fell within a predefined margin. The safety profiles were comparable between the two groups. No clinically significant differences were found in AEs or laboratory abnormalities. ADAs tested positive in 38.3% of the ABP501 group and in 38.2% of the adalimumab group.¹⁶ An open-label extension of this study evaluated patients from the former trial who switched to ABP501 at week 26 and those who maintained ABP 501 treatment throughout 68 weeks. The results confirmed the long-term safety and efficacy between groups.¹⁷

BI 695501

BI 695501 gained approval by both the FDA and the EMA in 2017.^{11,13} On 15 January 2019, the EMA withdrew the marketing authorization for BI 695501 in the EU at the request of the manufacturer for commercial reasons.¹⁸ Ninety percent CIs of all primary PK variables (BI 695501 to US-/EU-sourced adalimumab and US- to EU-sourced adalimumab) fell within the predefined margin in the phase I VOLTAIRE-PK study, confirming three-way PK equivalence. The similarity of BI 695501 to US-/EU-sourced adalimumab was further supported by comparison of secondary and additional PK parameters.¹⁹

The phase III VOLTAIRE-RA trial randomized active RA patients with concomitant methotrexate (MTX) to receive BI 695501 or Humira for 24 weeks. Before week 25, patients receiving adalimumab treatment in the first 24 weeks were rerandomized into the adalimumab maintenance group or BI

695501 transition group for another 24 weeks of treatment. The ACR-20 response rates were 67.0% (BI 695501) and 61.1% (adalimumab) at week 12 (90% CI -0.9 to 12.7) and 69.0% (BI 695501) and 64.5% (adalimumab) at week 24 (95% CI -3.4 to 12.5), confirming clinical similarity between the biosimilar BI 695501 and the adalimumab reference product (RP). The percentages of ACR20, ACR50, and ACR70 responders were comparable among the BI 695501 switching group, adalimumab maintenance group and BI 695501 maintenance group at week 48.²⁰ The immunogenicity (ADAs, ADA titers and neutralizing antibodies), safety and tolerability data were similar among the treatment arms. VOLTAIRE-RAext²¹ was an open-label extension of the VOLTAIRE-RA study, which evaluated the long-term efficacy, safety and immunogenicity of BI 695501 in patients who had completed the VOLTAIRE-RA study. Patients from the abovementioned three groups received BI 695501 biweekly for another 48 weeks. The results showed comparable safety, efficacy, and immunogenicity between groups, without identifying any previously unknown side effects of adalimumab.

The preliminary results of a phase III study in patients with chronic moderate-to-severe plaque psoriasis showed comparable PASI75 response rates between groups (week 16: 68.2% [BI 695501] vs 70.4% [adalimumab], 95% CI -14.4 to 8.7; week 24: 75.3% [BI 695501] vs 72.4% [adalimumab], 95% CI -8.5 to 12.6).²² Multi-switching between adalimumab and BI695501 in patients with plaque psoriasis was conducted in another completed phase III study named VOLTAIRE-X; however, no results have been reported yet.²³

SB5

SB5 was approved by the EMA in 2017 and by the FDA in 2019.^{11,13} A phase I PK clinical trial comparing SB5 with reference adalimumab in healthy subjects showed comparable results of mean PK parameters across the SB5, EU-adalimumab and US-adalimumab groups.²⁴ The mean values of AUC_{inf} , C_{max} and AUC_{last} were similar between groups, and the 90% CI fell within the prespecified equivalence margin.

The results from a randomized, double-blind, phase III clinical trial comparing the efficacy of SB5 with adalimumab RP in patients with moderate-to-severe RA showed that the ACR-20 response was equivalent between the SB5 group (72.4%) and the adalimumab group (72.2%) at week 24 (95% CI -7.83 to 8.13).²⁵ Overall, the rates of treatment-emergent AEs (TEAEs) were 35.8% (SB5) and 40.7% (adalimumab) up to week 24. The incidence of ADA was also comparable between the SB5 (33.1%) and

adalimumab (32.0%) groups.²⁵ At 24 weeks, patients receiving adalimumab were rerandomized either to continue adalimumab treatment or to switch to SB5 until week 52, while patients receiving SB5 maintained their therapeutic drug throughout the 52 weeks of study. The results revealed comparable safety profiles, effectiveness and incidence of ADAs across groups after transition.²⁶

Currently, no clinical trials have been performed to evaluate the efficacy and safety of this biosimilar in psoriasis populations.

GP2017

The FDA and the EMA approved GP2017 in 2018.^{11,13} A single-center, parallel group, three-arm PK similarity study was conducted in healthy male subjects. The GMRs for C_{max} and AUC_{0-inf} were 1.05 and 1.04 for GP2017/EU-adalimumab and 1.00 and 1.08 for GP2017/US-adalimumab, and the 90% CIs fell within the acceptance range, confirming the PK equivalence between GP2017 and adalimumab. The safety and immunogenicity data showed similarity across groups.²⁷

In a phase III study, patients with psoriasis were randomized to receive GP2017 or adalimumab subcutaneously for 17 weeks. Then, PASI50 responders were rerandomized either to continue their former assigned treatment until week 35 or to shift between GP2017 and adalimumab every 6 weeks.²⁸ At week 35, all patients received the originally assigned treatment at randomization until week 51. The response rates of PASI75 were comparable for GP2017 (66.8%) and adalimumab (65.0%); the 95% CI was -7.46 to 11.15. There was no impact on clinical efficacy after multiple switching between GP2017 and adalimumab. All the efficacy parameters, including PASI50, PASI75, PASI90 and PASI100, were similar across the transition groups and the maintenance groups over time. At 51 weeks, no significant differences with regard to efficacy, immunogenicity, or AEs were identified in switched groups compared to the continued groups.²⁸

Another phase III trial named ADMYRA also revealed similar efficacy of GP2017 to the respective adalimumab originator in patients with methotrexate-resistant RA. There were no statistically significant differences regarding efficacy, safety and immunogenicity profiles among any of the groups.²⁹

MSB11022

The EMA approved MSB11022 in April 2019.¹¹ Three-way PK equivalence for all primary endpoints was demonstrated

in a phase I study comparing MSB11022 with the adalimumab originator in healthy subjects. AEs were comparable across groups, with TEAE incidences of 64.1%, 57.5% and 62.0% among the MSB11022 and US-/EU-adalimumab groups, respectively.

In the phase III AURIEL-PsO trial, patients with moderate-to-severe plaque psoriasis were enrolled and assigned to receive MSB11022 or reference adalimumab subcutaneously every other week for 16 weeks, at which point patients receiving adalimumab were rerandomized either to continue adalimumab treatment or to switch to MSB11022 up to week 50, while patients receiving MSB11022 continued with MSB11022 until 50 weeks.³⁰ The percentage of PASI75 responders was 89.7% (MSB11022 group) and 91.6% (adalimumab group) at week 16 (95% CI -7.82-4.07). Profiles of safety and immunogenicity were equivalent between the groups.³⁰

In the multicenter, double-blind, parallel group, phase III AURIEL-RA study, patients with moderate-to-severe methotrexate-resistant RA were randomized into the MSB11022 group or the adalimumab group. At week 12, 79.6% of patients in the MSB11022 group achieved ACR20 and 80.9% of patients in the reference adalimumab group achieved ACR20 (95% CI -10.55-8.04), which was similar between the two groups.³¹ This similarity was maintained up to week 52. No significant differences were identified in efficacy, Dermatology Life Quality Index (DLQI), AE incidence, or immunogenicity among the treatment groups throughout the trial.³¹

FKB327

FKB327 gained approval in the EU in September 2018 and in the US in July 2020.^{11,13} A phase I three-way bioequivalence study confirmed PK similarity between FKB327 and EU- or US-sourced adalimumab.³²

In a phase III equivalence study, patients with moderate-to-severe active RA were randomized to be treated with FKB327 or reference adalimumab for 24 weeks (period 1). Then, in period 2 (an open-label extension study), patients were rerandomized 2:1 to continue with the same study drug or to switch to the other up to week 54.³³ The percentages of patients achieving ACR20 were 74.1% (FKB327 group) and 75.7% (adalimumab group) at week 24 (95% CI -7.9 to 4.7), which was maintained at over 70% of patients up to week 54 in all treatment arms. At week 24, the incidence of ADAs was similar between the groups (57.7% [FKB327] vs 55.5% [adalimumab]), and no notable difference in ADAs was identified between the

maintenance and transition groups in the extension study.³³ In period 3, all patients were given FKB327 for another 46 weeks until week 100.³⁴ The results showed that the long-term (up to 2 years) effectiveness, safety and immunogenicity were comparable between FKB327 and adalimumab, and there was no impact on single- or double-switching treatment.

Currently, no clinical trials have been carried out to evaluate the efficacy of this agent in the psoriasis population.

PF-06410293

PF-06410293 was approved by the FDA in 2019 and by the EMA in 2020.^{11,13}

The PK equivalence study REFLECTIONS B538-07, with 362 healthy volunteers, demonstrated similar PK profiles between PF-06410293 and both EU- and US-sourced adalimumab. The ratios and 90% CIs of all parameters (C_{max} , AUC_{2wk} , AUC_t and AUC_{∞}) fell within the acceptance range of 80–125% and included 100% of the sample.³⁵

In a double-blind, randomized, phase III study (REFLECTIONS B538-02), patients with active RA were assigned to be treated with PF-06410293 or EU-adalimumab. The study was divided into 3 periods with each period lasting 26 weeks. At week 12 (primary endpoint), the ACR20 response rate was 68.7% in the PF-06410293 group and 72.7% in the EU-adalimumab group (95% CI –10.38 to 4.44). The safety, immunogenicity and PK profiles were comparable between groups through the first 26 weeks.³⁶ The clinical comparability of PF-06410293 to EU-adalimumab was further supported by results from period 2.³⁵ The ACR20 in patients who switched from reference adalimumab to PF-06410293 in period 2 was 86.6% at week 26 and 84.3% at week 52. Moreover, ACR20 remained similar throughout the first two periods in the PF-06410293 maintenance group (86.6% [week 26] and 82.7% [week 52]) and the adalimumab maintenance group (84.4% [week 26] and 79.3% [week 52]).³⁵ The ACR20 response rate was consistent in all 3 treatment groups during treatment period 2.

CT-P17

CT-P17 was recently approved by the EMA in December 2020.¹¹

PK equivalence was concluded by a phase I study with 312 healthy subjects. AUC_{0-inf} , AUC_{0-last} , and C_{max} were similar among CT-P17, US- and EU-sourced adalimumab,

with the ratios and 90% CIs of all parameters falling within the predefined acceptance range of 80–125%. The safety, efficacy and immunogenicity profiles were comparable across treatment arms.³⁷

Kay et al conducted a 52-week multicenter, randomized, double-blind, phase III clinical trial (N=648) to evaluate the efficacy of CT-P17 compared with EU-adalimumab and reported results up to week 24.³⁸ Moderate-to-severe RA patients were randomized to receive either CT-P17 or EU-adalimumab 40 mg injection every other week until week 24 (period 1). At week 26, patients receiving EU-adalimumab in period 1 were rerandomized either to transition to CT-P17 or to maintain EU-adalimumab treatment until 48 weeks (period 2). Patients receiving CT-P17 in period 1 continued CT-P17 treatment in period 2. The ACR20, ACR50 and ACR70 response rates at week 24 were 82.7%, 60.2% and 40.7% in the CT-P17 group and 82.7%, 63.6% and 44.4% in the EU-adalimumab group (95% CI –5.94 to 5.94),³⁸ which showed similar therapeutic efficacy between CT-P17 and EU-adalimumab.

Others

Many other adalimumab biosimilars are in development or have already been approved in other countries worldwide (Table 1). Table 2 shows the results of some phase III studies, demonstrating comparable efficacy of these biosimilars to RP.

Summary

The above clinical trials showed comparable PK, immunogenicity, efficacy and safety profiles between adalimumab biosimilars and their RP in psoriasis or other rheumatic diseases, which means that these biosimilars are very similar to the reference adalimumab and are promising alternatives. In some phase III clinical trials, there were multiple switches of drugs, the results of efficacy were similar among groups and the safety outcomes did not raise any concern, which allows doctors and patients to choose to use biosimilars with confidence in the real world.

Extrapolation of Indications

Provided that biosimilars are equivalent in structure and clinical performance to originators that have already been approved by regulatory agencies, the approval process for these agents is abbreviated compared to that for novel drugs. Extrapolation, as stated by the EMA, is “a well-established scientific principle which has been used for many years”.² If a biosimilar is highly similar to an RP

Table 2 Efficacy of Adalimumab Biosimilars in Some Phase III Clinical Trials

Biosimilar	Sponsor	Design of the Study	Treatment Regimen	Efficacy
CinnoRA	CinnaGen (Iran)	Randomized, double-blind, active-controlled, non-inferiority trial, N=136 (RA)	Either CinnoRA or adalimumab 40mg SC injection every other week, up to 24 weeks	ACR20, ACR50 and ACR70 response rates at week 12 were 85%, 61% and 28% in CinnoRA group and 76%, 48% and 36% in adalimumab group; ACR20, ACR50 and ACR70 response rates at week 24 were 92%, 77% and 47% in CinnoRA group and 89%, 75% and 53% in adalimumab group ⁵²
ZRC-3197	Cadila Healthcare (India)	Prospective, randomized, double-blind, multicenter, parallel-group, active controlled study, N=120 (RA)	Either ZRC-3197 or adalimumab 40mg SC injection every other week, up to 12 weeks	ACR20, ACR50 and ACR70 response rates at week 12 were 82%, 46% and 14% in ZRC-3197 group and 79.2%, 43.4% and 15.1% in adalimumab group ⁵³
HS016	Zhejiang Hisun Pharmaceutical (China)	Multicenter, randomized, double-blind, parallel, positive controlled study, N=648(AS)	Either HS016 or adalimumab 40mg SC injection every other week, up to 24 weeks	ASAS20 response rate at week 24 was 87.5% in HS016 group and 90.1% in adalimumab group ⁵⁴
M923	Momenta Pharmaceuticals (USA)	Randomized, double-blind, parallel, positive controlled study, N=572(plaque psoriasis)	Part1: Either M923 or adalimumab 80mg SC injection at baseline, then 40mg every 2 weeks from Week 1 to Week 16; Part2: from week 17, patients receiving M923 in PartI continued to receive M923 till week 47; while patients receiving adalimumab in PartI rerandomized into 2 groups, one group continued adalimumab treatment and the other switched between M923 and adalimumab till week 47	PASI 75 response rate at week 16 was 80.1% in M923 group and 79% in adalimumab group; PASI 75 response rate at Week 52 (Follow-Up Visit) was 78.3% in M923 continuous group, 73.8% in transition group, and 78.3% in adalimumab continuous group ⁵⁵

Abbreviations: RA, rheumatoid arthritis; N, total number of case studies; SC, subcutaneous; AS, ankylosing spondylitis; ACR, American College of Rheumatology; ACR20, ACR 20% response; ASAS, Assessment of SpondyloArthritis International Society; ASAS20, ASAS 20% response; PASI, Psoriasis Area and Severity Index; PASI 75, PASI 75% response.

and has comparable PK, PD, immunogenicity, safety and efficacy in one indication, safety and efficacy data could be extrapolated to other indications approved for the RP, which means that clinical trials assessing equivalence can be carried out in a single disease, without trials in other relevant indications, the EMA would approve the product for all indications licensed for the RP.² Based on this principle, adalimumab biosimilars were licensed for all indications approved for reference adalimumab although some of their equivalence studies were only conducted in rheumatic diseases.

This protocol may raise debate among dermatologists and affect their use of biosimilars in clinical practice. In a survey (2015) of US specialty physicians who already

prescribe biologics, including dermatologists, gastroenterologists, medical oncologists, hematologist-oncologists, rheumatologists, and nephrologists, only 12% of respondents had positive perceptions of the concept of extrapolation and would use a biosimilar for all approved indications.³⁹ In another survey conducted in the US from 2016 to 2017, rheumatologists, dermatologists and gastroenterologists were included. The majority of physicians (70%) knew that if a biosimilar showed that it treats one disease similarly to an originator biologic, the biosimilar may be extrapolated by regulators to treat all the diseases the originator biologic is approved to treat. However, half of the physicians were uncomfortable with biosimilars receiving approval by extrapolation.⁴⁰

Interchangeability with Reference Adalimumab

Interchangeability is defined by the EMA as “replacing an RP with a biosimilar (or vice versa) or replacing one biosimilar with another”, which includes switching and substitution. Switching means the health provider decides to exchange one medicine for another, while substitution refers to replacement at the pharmacy level without intervention of the prescriber.² If switching from an RP to a respective biosimilar (or switching conversely) or between biosimilars only means saving money, this process is also mentioned as nonmedical switching.⁴¹

The responsibilities of the regulation of switching and substitution practices and the designation of interchangeability fall within different EU member states. Healthcare providers should choose carefully before prescribing biosimilars to their patients, taking into account the legal framework, regulations, guidelines and advice in their areas of specialty and the patient’s perspective.² In a 2017 consensus document of the joint task force comprising 25 experts from 8 European countries, the USA and Japan, in recommendation 6, it was considered effective and safe to switch from the originator to the respective biosimilar, but the patient’s perspective should be taken into consideration (evidence level 1b and degree of recommendation A).⁴² To date, national regulatory agencies and authorities have provided multiple guidelines about the practice of use and switching of biosimilars in real life. The Portuguese Society of Rheumatology states that switching from an RP to a more affordable biosimilar is desirable if it is done under a standardized protocol, the prescriber is involved, the patient is well informed and followed-up and the products’ traceability is guaranteed.⁴³ The British Society for Rheumatology (BSR) states in a stricter way that switching from an RP to a biosimilar should be determined on a case-by-case basis until there are more data to support a safe transition. The statement of BSR says that strong monitoring is required in switching, decisions should be made jointly by clinicians and patients, and medications are traceable.⁴⁴ Moreover, automatic substitution without information and consent of the prescriber is unacceptable.⁴⁵

In the US, a designation pathway has been created to evaluate whether a biological product is interchangeable with an RP. According to the Biologics Price Competition and Innovation Act (BPCI Act), an interchangeable product must meet additional standards to demonstrate its

interchangeability.⁴⁵ It is expected to be shown that a proposed interchangeable product can produce the same clinical outcomes as RP in any indications. Switching studies should be carried out, and post-marketing surveillance (real-world observation) data are needed to support interchangeability.⁴⁵ According to the Public Health Service Act (PHS Act) 351(k)(4), a prescribed biological RP may be substituted by an interchangeable biosimilar at the pharmacy level without consulting the health care provider. To date, the FDA has not considered any biosimilar as interchangeable.⁴⁵

Although several phase III RCTs or open label extension studies on switching from reference adalimumab to the respective biosimilars or multiple switching between groups showed comparable safety, efficacy and immunogenicity,^{15,20,21,26} evidence on the nonmedical switching from reference adalimumab to the respective biosimilars in the real-world setting is limited and is mostly based on a few small-scale observational studies with a limited number of subjects, thus seemingly insufficient to recommend this switching procedure. Safety data from real-world practice are available only for SB5. Di Cesare et al⁴⁶ reported a small cohort study of real-life PsO/PsA patients switching from reference adalimumab to SB5. Of 20 switched patients, two experienced loss of efficacy on cutaneous symptoms, with one case leading to SB5 discontinuation and switching to an IL-12/23 antagonist and the other case developing pustular psoriasis. No changes in PASI scores were noticed in 90% of patients who were shifted from adalimumab to SB5. In PsA patients, 9 out of 12 patients maintained PsA symptom remission, while the other 3 patients experienced axial disease flare as soon as 4 weeks, leading to an alternation of concomitant medication in 2 cases and a back-switch to adalimumab originator in the third. Bruni et al⁴⁷ performed a retrospective real-world cohort of rheumatic joint diseases. Eighty-two patients with RA, PsA, juvenile idiopathic arthritis (JIA) and axial spondyloarthritis (axSpA) treated with adalimumab for at least 6 months and in stable condition were enrolled and switched from reference adalimumab to SB5. RA patients experienced stable disease condition, while PsA patients and axSpA patients showed mild disease flares at 3 months. There was minor adjustment in the concomitant medications, with values of all disease activity and disability measures greatly decreasing and being similar from baseline at 6 months. A total of 33.7% and 16.6% of patients reported AEs at 3 months and 6 months, respectively, mostly disease relapse and

mild infections. Two patients discontinued SB5, and one of them back-switched to reference adalimumab. The authors concluded that their real-life data confirmed the safety of switching from reference adalimumab to SB5 in RA and the possibility of applying this procedure in axSpA and PsA patients, further supporting that switching to biosimilars is desirable in the treatment of inflammatory rheumatologic diseases. Another real-life practice⁴⁸ with data collected from the DERMBIO registry in Denmark enrolled 43 psoriasis patients who were switched under surveillance from reference adalimumab to GP2017 and revealed that although there was no significantly notable impact on PASI scores and DLQI after switching, 39.5% of patients had increased AE rates, which were mainly pruritus, flares and headache.

Conclusion

According to the principle of extrapolation, data from certain indication studies may be extrapolated to other indications that have already been approved for reference drugs. Eight adalimumab biosimilars showing PK, safety, efficacy and immunogenicity profiles comparable to those of adalimumab originators have been approved by the FDA, the EMA or health regulatory agencies worldwide. Therefore, biosimilars seem to be favorable alternatives to originator biologics, and on a wider scale, have the potential to lower the disease costs and increase the accessibility of biologic therapies. However, scientists have pointed out some concerns on issues with respect to extrapolation of indications and interchangeability. For the former issue, the EMA has defined it as a “well-established scientific principle”. Biosimilar manufacturers should provide bioequivalence data, including the mechanisms of action, PK, safety, efficacy, and immunogenicity, to support extrapolation. The FDA, through the BPCI Act, has created an abbreviated licensure pathway to provide the public with easier access to more economic biological products. The latter issue does not seem to be supported by adequate scientific evidence until now. Although there were several randomized controlled switching studies and some small-scale real-world transition studies of reference adalimumab and the respective biosimilars showing comparable safety and efficacy, and the consensus-based recommendations suggesting that a single switch from an originator to its biosimilar is safe and effective with the patient’s perspective considered, but the transposition of these results to real-life practice still seems debatable. It is well known that patients treated in clinical trials differ greatly from

those in real-world practice. In a clinical trial, participants are strictly selected with limited concomitant diseases, as an analysis from the German biologics register RABBIT (Rheumatoid Arthritis: Observation of Biologic Therapy) showed that merely 21–33% of the registered patients would have been qualified for RCTs.⁴⁹ In addition, data from post-marketing registries showed that patients switching from originators to their biosimilars have a slightly higher discontinuation rate than historical data show in the real-world setting.^{50,51} Thus, further data from controlled switching studies are needed to better address the efficacy and safety of the transition strategy. Although there are some remaining concerns, experts of the International Psoriasis Council advocate that dermatologists take an active role in the development of biosimilar prescribing policies to improve access to biosimilar drugs for psoriasis patients.¹

A limitation of this review is that only a small number of clinical trials were conducted specifically to evaluate biosimilars in psoriasis populations and that only a few real-world observational studies on switching from reference adalimumab to the respective biosimilars have been published to date. More well-designed prospective studies and real-life observational cohorts in patients with psoriasis are needed to support the equivalence between biosimilars and their originators and the transition between the two in achieving desirable clinical results in this patient population. Clear guidance from medical regulatory authorities and data from post-marketing monitoring registries will also be helpful for the confidence of switching for both physicians and patients. Finally, the biosimilar drugs currently on the market are all TNF- α inhibitors. There are some ongoing clinical trials of ustekinumab biosimilars. After ustekinumab biosimilar, which is an IL-12/23p40 inhibitor, enters the market, doctors and patients will have more choices when a patient loses efficacy on a biologic agent and intends to switch to a biosimilar that does not target TNF- α . At the same time, monitoring of switching from one biosimilar to another (or from an RP to a biosimilar) targeting different inflammatory factors and post-marketing clinical trials are needed to ensure this practice.

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Disclosure

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