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ORIGINAL RESEARCH ARTICLE

Safety, Immunogenicity and Interchangeability of Biosimilar Monoclonal Antibodies and Fusion Proteins: A Regulatory Perspective

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Abstract

Background Biosimilars have been used for 15 years in the European Union (EU), and have been shown to reduce costs and increase access to important biological medicines. In spite of their considerable exposure and excellent safety record, many prescribers still have doubts on the safety and interchangeability of biosimilars, especially monoclonal antibodies (mAbs) and fusion proteins.

Objectives The aim of this study was to analyse the short- and long-term safety and interchangeability data of biosimilar mAbs and fusion proteins to provide unbiased information to prescribers and policy makers.

Methods Data on the safety, immunogenicity and interchangeability of EU-licensed mAbs and fusion proteins were examined using European Public Assessment Reports (EPARs) and postmarketing safety surveillance reports from the European Medicines Agency (EMA). As recent biosimilar approvals allow self-administration by patients by the subcutaneous route, the administration devices were also analyzed.

Results Prelicensing data of EPARs (six different biosimilar adalimumabs, three infliximabs, three etanercepts, three rituximabs, two bevacizumabs, and six trastuzumabs) revealed that the frequency of fatal treatment-emergent adverse events (TEAEs), TEAEs leading to discontinuation of treatment, serious adverse events (SAEs), and main immune-mediated adverse events (AEs) were comparable between the biosimilars and their reference products. The availability of new biosimilar presentations and administration devices may add to patient choice and be an emerging factor in the decision to switch patients. Analysis of postmarketing surveillance data covering up to 7 years of follow-up did not reveal any biosimilar-specific adverse effects. No product was withdrawn for safety reasons. This is in spite of considerable exposure to biosimilars in treatment-naïve patients and in patients switched from the reference medicinal product to the biosimilar. Analysis of data from switching studies provided in regulatory submissions showed that single or multiple switches between the originator and its biosimilar versions had no negative impact on efficacy, safety or immunogenicity.

Conclusions In line with previous reports of prelicensing studies of biosimilar mAbs and etanercepts, this study demonstrated comparable efficacy, safety, and immunogenicity compared with the reference products. This is the first study to comprehensively analyze postmarketing surveillance data of the biosimilar mAbs and etanercept. An analysis of more than 1 million patient-treatment years of safety data raised no safety concerns. Based on these data, we argue that biosimilars approved in the EU are highly similar to and interchangeable with their reference products. Thus, additional systematic switch studies are not required to support the switching of patients.

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Key Points

This is the first comprehensive analysis of prelicensing and long-term safety data, as well as immunogenicity and interchangeability data of all biosimilar mAbs and fusion proteins approved before August 2020.

Our study suggests that safety and immunogenicity of biosimilar mAbs and etanercepts and their respective originators approved in the European Union are highly similar and interchangeable.

The present results are in line with theoretical considerations suggesting that highly similar proteins have similar safety and immunogenicity.

Our study, together with previous reports, suggests that concerns regarding immunogenicity upon switches are unfounded. Thus, systematic switch studies are not needed

1 Introduction

Monoclonal antibodies (mAbs) and related fusion proteins have become key therapeutic agents in the treatment of many diseases, and their use is increasing rapidly [1–3]. Compared with conventional therapies, the costs of therapeutic mAbs and fusion proteins are very high, which may restrict the access of patients to optimal therapy for many serious diseases. One of the major drivers of high costs is the lack of sufficient competition in the biologicals market, especially among products that have lost patent and data protection [1, 4–8].

Copies of original biologicals and biosimilars have lowered the costs and increased access to biologicals throughout the EU [8]; thus, biosimilars have the potential to support the sustainability of modern pharmacotherapy [7, 9–11]. The first biosimilar mAb, infliximab (Remsima/Inflectra), was approved for the EU market in 2013. Since then, more than 20 biosimilar mAbs have been licensed in the European Economic Area. The success of biosimilar mAbs is dependent on the willingness of physicians to prescribe biosimilars for their patients. The key aspect of such prescription practice is switching between the originators (reference product) and their biosimilars [7].

EU biosimilars have had an excellent safety record over the past 15 years of use [12]; however, it has been claimed that 'second generation' biosimilars (mAbs and fusion proteins) may have additional risks [13–15]. Prescriber surveys suggest that while clinicians are generally comfortable in prescribing biosimilars for treatment-naïve patients, there is more hesitancy in switching patients from reference products, especially mAbs, to biosimilars [16–18]. As a result, the uptake of biosimilars is very modest in many European countries [8]. The aim of this report is to review available regulatory documents from the European Medicines Agency (EMA) regarding the safety, immunogenicity, administration devices, and interchangeability of biosimilar mAbs and related fusion proteins, to address the concerns of prescribers.

2 Methods

The data lock point for the analysis of safety, immunogenicity, and interchangeability was 31 July 2020.

The safety, immunogenicity, and interchangeability data of clinical trials were analyzed on the basis of European Public Assessment Reports (EPARs), which are derived from assessment reports of the quality, efficacy, and safety of medicinal products on the basis of documentation that was submitted to the EMA by the manufacturer. These reports are created by two independent assessment teams consisting of multiple European experts in biotechnology, pharmacy, non-clinical testing, clinical pharmacokinetics (PK), pharmacodynamics, and efficacy and safety studies. EPARs are updated periodically to reflect the latest regulatory information on medicines [19]. EPARs of mAbs can be found on the EMA website [20].

Analysis of postmarketing safety data of all authorized biosimilar mAbs and fusion proteins and their reference products was based on the latest Periodic Safety Update Reports (PSURs) and other safety reports submitted to the EMA. PSURs are regularly submitted pharmacovigilance documents intended to provide a comprehensive, concise and critical analysis of the risk–benefit balance of the medicinal product, taking into account new or emerging information from spontaneous adverse event (AE) reports, and pharmacoepidemiological and clinical studies [21, 22].

Periodic Safety Update Single Assessment (PSUSA) reports assess PSURs of medicines containing the same active substances or combinations, even if they are subject to different marketing authorizations and are authorized in different EU Member States.

The included products constitute six product classes based on the international nonproprietary name (INN) of the active substance: adalimumab, bevacizumab, infliximab, rituximab, trastuzumab and etanercept.

PSURs and PSUSAs were retrieved from the EMA PSUR repository. To compensate for the lack of recently updated safety data for trastuzumabs (PSUR cut-off date: September 2018), the assessment history of this product class was

explored in order to retrieve relevant safety information following the PSUR cut-off date. Postmarketing data are presented in aggregated format as they may contain confidential information.

PSURs for biosimilars authorized in 2020 were not yet available for *Amsparity* (adalimumab, EU Marketing Authorization 13 February 2020), *Nepexto* (etanercept, EU Marketing Authorization 20 May 2020), *Zercepac* (trastuzumab, EU Marketing Authorization 27 July 2020) and *Ruxience* (rituximab, EU Marketing Authorization 1 April 2020) [20].

The following postmarketing information was retrieved: (1) estimated cumulative postmarketing patient exposure since the international birth date of the product; (2) main safety data of biosimilar mAbs, including evaluations of possible safety signals; (3) changes to the safety information of products; (4) risk minimization activities for specific safety concerns; and (5) impact of new safety information on the benefit–risk balance of the product.

3 Results

3.1 Safety

3.1.1 Premarketing Safety Data

The efficacy and safety of the biosimilars were investigated in randomized, double-blind clinical trials in therapeutic indications where the therapeutic effect size could be estimated on the basis of previous studies of the originator product. The most sensitive primary efficacy endpoints were selected. All biosimilar mAbs and etanercepts met the predefined equivalence criteria of efficacy (not shown).

The safety profile has been compared between 29 biosimilar mAb products and fusion proteins (adalimumab biosimilars: Amgevita®, Hulio®, Imraldi®, Amsparity®, Halimatoz®, Hefiya®, Hyrimoz®, Idacio®; infliximab biosimilars: Flixabi®, Zessly®, Inflectra®, Remsima®; bevacizumab biosimilars: Mvasi®, Zirabev®; rituximab biosimilars: Ruxience®; Rixathon®, Riximyo®, Blitzima®, Truxima®, Ritemvia®; trastuzumab biosimilars: Ogivri®, Zercepac®, Trazimera®, Ontruzant®, Herzuma®, Kanjinti®; etanercept biosimilars: Benapali®, Nepexto®, Erelzi®) and their reference products (Humira®, Remicade®, Avastin®, MabThera®/Rituxan®, Herceptin®, and Enbrel®) using clinical safety data from the main phase III studies. The licensing of certain products was based on the same clinical documentation (duplicate marketing authorizations), in which case the same product can be marketed under multiple names; thus, there were 23 different development programs [20].

3.1.1.1 Adalimumab Adalimumab biosimilars and the reference product Humira share a very low and similar toxicity profile when tested in rheumatoid arthritis and plaque psoriasis indications (Table 1). There were few fatal treatment-emergent adverse events (TEAEs; range across the studies, 0–0.73%), incidence of very low serious adverse events (SAEs; 1.1–5.2%), and very low frequency of TEAEs leading to drug discontinuation (0.5–5.5%). Immune-mediated toxicity was also low (hypersensitivity: 0–5.3%; injection site reaction: 1.7–14%).

3.1.1.2 Infliximab The safety profiles of the reference product Remicade and its biosimilars were similar in the rheumatoid arthritis indication, including very few fatal TEAEs (range across the studies, 0–0.6%), incidence of low SAEs (5–14%), low frequency of TEAEs leading to drug discontinuation (7.1–15%), low incidence of hypersensitivity incidence and infusion-related AEs incidence (Table 1).

3.1.1.3 Bevacizumab Although not unexpected in this population, the toxicity was quite high in both biosimilar and reference product Avastin-treated patients (non-small cell lung carcinoma indication), including fatal TEAEs (range between the studies, 3.6–6.7%), SAEs (22.3–26.2%), TEAEs leading to drug discontinuation (10.9–18.8%), and immune-mediated AEs (Table 1).

3.1.1.4 Rituximab Overall, the safety profile is similar between each biosimilar and the reference product MabThera in each clinical study with a very low fatal TEAE rate (range across the studies, 0–2.2%) and a low number of TEAEs leading to discontinuation (1–7.4%) (Table 1). However, higher frequencies of SAEs and infusion-related reactions (IRRs) were observed with Rixathon/Riximyo and MabThera (advanced follicular lymphoma indication) compared with the other rituximab biosimilar clinical programs (Ruxience studied in low tumor burden follicular lymphoma; Blitzima, Truxima, and Ritemvia studied in rheumatoid arthritis). The IRR frequency seen in the clinical studies with Rixathon/Riximyo and MabThera seems abnormally high (above 70%), likely due to different definitions for IRR.

3.1.1.5 Trastuzumab While the SAE rates were comparable in each study between each biosimilar and Herceptin, the different clinical programs were associated with differences in the SAE incidence rate (Table 1). For example, the SAE incidence rate for the biosimilars Ogivri, Zercepac and Trazimera, as well as for the reference product Herceptin (in human epidermal growth factor receptor 2 [HER2]-positive metastatic breast cancer clinical programs) were higher than seen in the other biosimilar clinical programs in HER2-positive early breast cancer or locally advanced breast cancer

Table 1 Main safety features in the phase III clinical studies of biosimilars compared with the reference product (data published in the EPAR; data lock point: 31 July 2020)

Biosimilar	Exposure (patients)	Fatal TEAE	SAE	TEAE leading to discontinuation	Immune-mediated AE		
					Hypersensitivity	Infusion-related AE	Injection site reaction
Adalimumab biosimilars compared with the reference product Humira							
Amgevita	264 pts vs. 262	0%	3.8% vs. 5.0%	1.9% vs. 0.8%	5.3% vs. 3.8%	NA	2.3% vs. 5.0%
Hulio	366 pts vs. 362	0.3% vs. 0%	4.1% vs. 5.2%	3.8% vs. 2.8%	3.8% vs. 1.9%	NA	2.2% vs. 3.9%
Imraldi	268 pts vs. 273	0% vs. 0.73%	1.1% vs. 2.9%	0.7% vs. 3.3%	NP	NA	3.0% vs. 2.9%
Amsparity	597 pts vs. 596	0% vs. 0.3%	4.0% vs. 4.3%	3.7% vs. 4.7%	NP	NA	1.7% vs. 2.0%
Halimatoz/ hefiya/hyrimoz	193 pts vs. 197	0%	1.3% vs. 4.3%	~1.2% vs. ~1.2%	0.4% vs. 0%	NA	6.5% vs. 3.4%
Idacio	221 pts vs. 220	0%	3.6% vs. 2.7%	0.5% vs. 5.5%	2.25% vs. 2.7%	NA	11% vs. 14%
Infliximab biosimilars compared with the reference product Remicade							
Flixabi	290 pts vs. 293	0% vs. 0.34%	10.0% vs. 10.6%	10.3% vs. 8.2%	NP	NP	NA
Zessly	323 pts vs. 326	0.6% vs. 0.6%	5% vs. 6.1%	7.1% vs. 7.4%	13.6% vs. 15.6%	5.9% vs. 6.4%	NA
Inflectra/rem-sima	301 pts vs. 301	0	14% vs. 10%	10.9% vs. 15%	8% vs. 10%[a]		NA
Bevacizumab biosimilars compared with the reference product Avastin							
Mvasi	324 pts vs. 309	4% vs. 3.6%	26.2% vs. 23%	18.8% vs. 17.2%	41% vs. 40.5%[a]		NA
Zirabev	356 pts vs. 358	5.9% vs. 6.7%	22.8% vs. 22.3%	14.6% vs. 10.9%	32% vs. 36.9%[b]	5.3% vs. 6.1%	NA
Rituximab biosimilars compared with the reference product Mabthera							
Ruxience	196 pts. vs. 197	0%	8.7% vs. 7.6%	1.5% vs. 1%	NP	25% vs. 29.9%	NA
Rixathon/rix-imyo	312 pts. vs. 315	1.3% vs. 2.2%	22.8% vs. 20%	7.4% vs. 7%	73.4% vs. 70.5%[c]		NA
Blitzima/trux-ima/ritemvia[d]	161 pts vs. 60 vs. 151	1 death	6.2% vs. 0% vs. 6%	1.9% vs. 1.7% vs. 2.6%	15.5% vs. 20% vs. 5.3%		NA
Trastuzumab biosimilars compared with the reference product Herceptin							
Ogivri	247 pts vs. 246	2.4% vs. 1.6%	39.3% vs. 37%	4% vs. 6.5%	2.4%	6.9% vs. 4.9%	NA
Zercepac	324 pts vs. 325	0.9% vs. 1.8%	24.1% vs. 25.2%	~4.5% vs. ~4.5%	NP	13% vs. 9.8%	NA
Trazimera	349 vs. 353	0.3% vs. 0.8%	20.1% vs. 20.7%	4.6% vs. 3.4%	0.9% vs. 1.4%	9.5% vs. 8.5%	NA
Ontruzant	437 pts vs. 438	0.2% vs. 1.1%	12.8% vs. 13.2%	3.4% vs. 3.2%	NP	8.5% vs. 10%	NA
Herzuma	271 pts vs. 278	0.7% vs. 0.7%	7.7% vs. 11.9%	4.1% vs. 4.7%	NP	11.4% vs. 10.4%	NA
Kanjinti	364 pts vs. 361	0.3% vs. 0%	4.9% vs. 1.4%	0.8% vs. 0.6%	6.9% vs. 5.3%	21.7% vs. 18.8%	NA
Etanercept biosimilars compared with the reference product Enbrel							
Benapali	299 pts vs. 297	0.7% vs. 0%	6% vs. 5.1%	NP	NP	NA	0.7% vs. 5.7%
Nepexto	236 pts vs. 235	0	3.4% vs. 2.1%	1.7% vs. 1.7%	NP	NA	1.3% vs. 7.2%
Erelzi	264 pts vs. 267	0% vs. 0.4%	1.5% vs. 1.1%	1.9% vs. 1.5%	NP	NA	NP

The first number mentioned is always the biosimilar, vs. the RP

AE adverse event, *NA* not applicable, *NP* data not presented in the EPAR, *pts* patients, *SAE* serious adverse event, *TEAE* treatment-emergent adverse event, *vs*. versus the reference product, *EPAR* European Public Assessment Report, *RP* reference product, *IRR* infusion-related reaction, *EU* European Union, *US* United States

[a]Percentage of patients experiencing hypersensitivity and infusion-related AE

[b]Anaphylactic reaction and hypersensitivity

[c]Potential IRR

[d]Compared with the EU—Mabthera and US-Rituxan

(Ontruzant) or HER2-positive early breast cancer (Herzuma and Kanjinti). This difference (average of 27.7% vs. 8.7%) can be explained by the different indication, i.e. study population, selected for the main phase III clinical studies. Otherwise, in all studies, there was a low fatal TEAE rate (range between the studies, 0–2.4%), a low number of TEAEs leading to discontinuation (0.6–6.5%), very low hypersensitivity incidence (0.9–6.9%) and low infusion-related AE incidence rate (4.9–21.7%).

3.1.1.6 Etanercept The etanercept biosimilars and the reference product Enbrel share a very low toxicity profile (rheumatoid arthritis and plaque psoriasis indications): only a few fatal TEAEs (range between the studies, 0–0.7%), very low incidence rate of SAEs (1.1–6% for Benepali), TEAEs leading to drug discontinuation (1.5–1.9%), and injection site reaction (0.7–7.2%) (Table 1).

Overall, based on the proportion of fatal TEAEs, SAEs, TEAEs leading to discontinuation of the investigated product, and immune-mediated AEs (such as hypersensitivity, infusion-related AEs, or injection site reactions), the European-approved biosimilar mAbs and fusion proteins showed a very similar safety profile to the reference products.

3.1.2 Postmarketing Safety

Based on the results of our postmarketing data analysis, the following observations can be made:

- Review of the updated safety profiles of biosimilars and their reference products revealed no significant differences within each product class.
- Recommendations for updates to safety concerns listed in the Risk Management Programs of biosimilars were mainly restricted to harmonization with the Risk Management Program of the reference product. Thus, no new or unexpected adverse effects and no differences in the severity of adverse effects were observed.
- The majority of the investigated safety signals and recommendations of the EMA Pharmacovigilance Risk Assessment Committee (PRAC), were addressed by both the reference product and the biosimilar manufacturers. The signals that led to an update of the product information were regarded as class effects.
- Following regulatory evaluation of the PSUR submissions, there were no instances of a recommendation to suspend or revoke the marketing authorization of any authorized biosimilar mAb or fusion protein.

Values for exposure estimates are based on patient exposure for the cumulative period (from the product international birth date to the latest PSUR submission) and expressed in patient-treatment years (PTYs). The highest patient exposure was obtained for biosimilar tumor necrosis factor (TNF)-α inhibitors, estimated totally at 1,286,578 PTYs (891,545 for infliximabs, 131,418 for adalimumabs, and 263,615 for etanercepts), whereas among anticancer mAbs, significant exposure was only seen for biosimilar trastuzumabs (1387 PTYs). The exposure estimates for the remaining anticancer mAbs were calculated in different ways, which prevented the aggregation of data. These mAbs had significantly lower exposure values, partly because of relatively recent approval and slow launches in EU Member states.

3.2 Administration Devices and Presentations

Table 1 in the electronic supplementary material (ESM) provides a comparison of the presentations and administration devices for the originator and biosimilar products of five mAbs, i.e. adalimumab, bevacizumab, infliximab, rituximab, trastuzumab, and one fusion protein, etanercept.

There are several instances of where certain presentations of the reference product are not available for the biosimilars. For example, while all adalimumab biosimilars are available in prefilled syringes and prefilled pens, not every strength of the reference product is available in these presentations; none of the approved biosimilars are available in the 100 mg/mL presentations and there are no approved biosimilar 80 mg prefilled syringe or prefilled pen presentations. For etanercept, biosimilar presentations are not available for the 10 mg presentation. There are two examples of where subcutaneous presentations of the reference product are not yet available for the biosimilars; the rituximab 1,400 mg vial and the trastuzumab 600 mg vial.

There are also examples of where biosimilars have approved presentations that are not available for the reference product. Several trastuzumab biosimilars are also available as a 420 mg intravenous presentation, which is not available for the reference product. Remsima (infliximab) is available as a 120 mg solution for injection in a prefilled syringe and prefilled pen; these presentations are unique to Remsima and are currently not available for the reference product. The development of this formulation is a line extension after initial marketing approval was granted. The introduction of subcutaneous administration required clinical studies to demonstrate acceptable efficacy and safety. Nevertheless, intravenous, and also subcutaneous, Remsima remains a biosimilar product according to EU law and guidelines. Subcutaneous Remsima would not be viewed as a biosimilar in other legislations (e.g. US, Canada, Japan). This is the first example of an mAb where the biosimilar product allows for subcutaneous self-administration by the patient in the home, whereas the reference product can only be administered intravenously.

Even where the same administration format is available for both the reference product and the biosimilar, there can be minor differences. For example, some prefilled pens require the user to press a button to initiate the injection, while in other cases the injection commences when the pen is pushed onto the skin. There may also be differences in the needle gauge or the presence of latex in the needle cover. Some devices may contain different safety features, for example the presence of a needle guard shield on a prefilled syringe. Prefilled pens may also contain different features

which aid the user in self administration, for example the use of audible or visual cues to indicate when the injection is complete. Regardless of any differences in administration devices between the biosimilar and reference product, dedicated usability studies must be carried out to demonstrate that patients or caregivers can successfully deliver the injection in a consistent manner. Usability studies are assessed as part of the marketing authorization application (MAA) to ensure that administration devices can be used correctly by the intended patient population.

In summary, all strengths of the reference product are usually available for the approved biosimilars; however, there are some exceptions that need to be taken into account upon switching. There are also some differences in the administration devices, especially devices for subcutaneous administration, which may allow for increased patient choice and convenience. In usability studies, all administration devices were shown to be appropriate for use. Postmarketing safety surveillance does not suggest device-related problems. Nonetheless, there may be a need for patient training when switching between products that use different administration devices.

3.3 Immunogenicity

As stated in the guideline on immunogenicity assessment of therapeutic proteins (EMEA/CHMP/BMWP/14327/2006 Rev 1), the evaluation of immunogenicity is based on integrated analysis of immunological, PK, pharmacodynamic, and clinical efficacy and safety data [23]. Comparative immunogenicity studies are required in the development of biosimilars and were presented in the EPARs for all products [24], representing 23 development programs (see ESM Table 2).

3.3.1 Antidrug Antibody (ADA) Assay Methodology

Immunogenicity testing of the biosimilar and the reference product were conducted during both the phase I and phase III clinical trials for all products (ESM Table 2). In all cases, ADA testing was carried out with an assay using the active substance of the biosimilar product as antigen (i.e. single assay approach) and a standardized sampling schedule within a particular study.

In most instances, electrochemiluminescence (ECL), with direct/indirect bridging format, was used to detect ADAs. The ECL format may have been preferred because it has a comparatively high tolerance to the interference of the active substance in samples and also typically reliably detects low affinity antibodies.

For neutralizing antibodies (nAbs), mostly competitive ligand binding assays were used, as these are typically sensitive and relatively easy to standardize.

3.3.2 Relative Immunogenicity of Biosimilars and their Reference Products

3.3.2.1 Adalimumab Adalimumab biosimilars and the reference product Humira share a high intrinsic immunogenicity, with ADA positivity being well above 50% for healthy volunteers (HVs), and above 30% in patient studies (Table 2). NAbs were reported as a percentage of all ADA-positive patients. NAb positivity ranged between 18 and 82.5% for HVs and between 9 and 80% for patient studies, depending on the assays used.

For each product studied, the immunogenicity ranges were highly comparable between the originator and the biosimilar.

3.3.2.2 Infliximab Infliximab biosimilars and the reference product Remicade share a high intrinsic immunogenicity, with ADA positivity being well above 12% for HVs and above 48% in patient studies (Table 2). The neutralizing capacity was reported as nAb positivity ranging between 19.6% and 85.7% for HVs and above 79% for patient studies, depending on the assays used.

For each product studied, the immunogenicity ranges were highly comparable between the originator and the biosimilar.

3.3.2.3 Bevacizumab Bevacizumab biosimilars and the reference product Avastin share a low intrinsic immunogenicity, with no ADAs measured in HVs and only 1.3–3.3% positivity for ADA in patient studies (Table 2). The neutralizing capacity was low at 0–0.9%. For each product studied, the immunogenicity ranges were highly comparable between the originator and the biosimilar.

3.3.2.4 Rituximab Rituximab biosimilars and the reference product MabThera share a low or high intrinsic immunogenicity depending on the patient population studied and whether/which concomitant medication is administered (Table 2). ADA positivity was observed to be as low as 0.4–0.7% when studied in lymphoma patients, and as high as 23–28% when studying rheumatoid arthritis patients. The neutralizing capacity was low at $<4\%$.

For each product studied, the immunogenicity ranges were regarded as comparable between the originator and the biosimilar.

3.3.2.5 Trastuzumab Trastuzumab biosimilars and the reference product Herceptin share a low intrinsic immunogenicity, with no ADAs measured in HVs and only 0.3–1.4% positivity for ADA in patient studies (Table 2). The neutralizing capacity was low at below 1%.

Table 2 Main immunogenicity features in the phase I/PK clinical studies of biosimilars compared with the reference product (data published in the EPAR; data lock point: 31 July 2020)

Biosimilar	HVs/patients Phase I PK study	Pts with ADA-positive samples at any time (BS vs. EU vs. US)	Pts with nAb-positive samples at any time (BS vs. EU vs. US)	Patients Phase III study	Pts with ADA-positive samples at any time (BS vs. RMP)	Pts with nAb-positive samples at any time (BS vs. RMP)
Adalimumab biosimilars compared with the reference product Humira						
Amgevita	HV	54% vs. 67% vs. 55%	18% vs. 21% vs. 22%	Mod/sev RA (RMP = US)	40.2% vs. 40.1%	9.1% vs. 11.1%
Hulio	HV	69.5% vs. 73.3% vs. 70.0%	59.3% vs. 60.0% vs. 56.7%	Mod/sev RA	At week 24: 62% vs. 59.4%[b]	At week 24: 61.1% vs. 59.1%[b]
Imraldi	HV	98.4% vs. 95.2% vs. 100%	79.0% vs. 80.0% vs. 82.5%	Mod/sev RA	32.1% vs. 31.2%	NP
Amsparity	HV	85.5% vs. 90.0% vs. 94.4%	53.6% vs. 61.4% vs. 66.2%	Mod/sev RA	44.4% vs. 50.5%	13.8% vs. 14.0%
Halimatoz/Hefiya/ Hyrimoz	HV	66.5% vs. 70.6%[a]	59.0% vs. 60.8%[a]	Mod/sev Psoriasis	36.8% vs. 34.1%	80.2% vs. 80.0%[c]
Idacio	HV	82.1% vs. 83.5% vs. 81.3%	~70% in the three groups	Mod/sev Psoriasis	88.1% vs. 88.4%	46.6% vs. 47.9%[c]
Infliximab biosimilars compared with the reference product Remicade						
Flixabi	HV	47.2% vs. 37.7% vs. 37.7%	56.0% vs. 70.0% vs. 35.0%[c]	RA	62.4% vs. 57.5%	92.7% vs. 87.5%[c]
Zessly	HV	12.2% vs. 29.2% vs. 22.4%	83.3% vs. 85.7% vs. 81.8%[c]	RA	48.6% vs. 51.2%	79% vs. 85.6%[c]
Inflectra/Remsima	AS, week 54	34.4% vs. 32.0% (EU)	19.6% vs. 23.0% of total	Mod/sev RA	55.6% vs. 54.3%	NP
Bevacizumab biosimilars compared with the reference product Avastin						
Mvasi	HV	No subjects tested positive	No subjects tested positive	Adv NSCLC	1.3% vs. 3.3%	0%
Zirabev	HV	NP	NP	Adv NSCLC	1.5% vs. 1.4%	0% vs. 0.9%
Rituximab biosimilars compared with the reference product Mabthera						
Ruxience	≥2°L RA	10.9% vs. 10.8% (EU)	NP	1°L adv FL	19.5% vs. 18.8%	NP
Rixathon/Riximyo	≥2°L RA	11% vs. 21.4%	3.7% vs. 1.2%	1°L adv FL	0.4% vs. 0.7%[b]	0.3% vs. 0.7%
Blitzima/Truxima/ Ritemvia	≥2°L RA	14% vs. 28% vs. 23%	NP	RA	19% vs. 20%[b]	NP
Trastuzumab biosimilars compared with the reference product Herceptin						
Zercepac	Male HV	No subjects tested positive	NA	MBC	2/248 and 2/251	2/248 and 2/251
Trazimera	Male HV	0% vs. < 1%	NA	MBC	0.3% vs. 0.3%[b]	NP
Ontruzant	Male HV	No subjects tested positive	NA	Early BC, neoadj	0.7% vs. 0.7%	0.5% vs. 0.5%
Herzuma	Male HV	NP	NP	Early BC, neoadj	4/271 vs. 8/278 in neoadj period	No subjects tested positive
Kanjinti	Male HV	NP	NP	Early BC, neoadj	0.5% vs. 1.4%	No subjects tested positive
Etanercept biosimilars compared with the reference product Enbrel						
Benepali	HV	0% vs. 7/45 EU Enbrel	0% vs. 1/7[b]	Mod/sev RA	1% vs. 7.1%	0% vs. < 1%
Nepexto	HV	None detected	NA	Mod/sev RA	2/264 vs. 21/260	0 vs. 2/260
Erelzi	HV	3/54 after crossover phase II	No subjects tested positive	Psoriasis	0% vs. 1.9%	No subjects tested positive

The first number mentioned is always the biosimilar, vs. the RP

Phase I PK study: ADA- and nAb-positivity was defined as at least one postdose positive sample

Phase III (efficacy/safety/immunogenicity) study: ADA- and nAb-positivity was defined at any time up to/or before the switch

ADA antidrug antibody, *Adv* advanced, *AS* ankylosing spondylitis, *BC* breast cancer, *BS* biosimilar, *FL* follicular lymphoma, *HV* healthy volunteer, *MBC* metastatic breast cancer, *mod* moderate, *NA* not applicable or not done, *nAb* neutralizing antibodies, *neoadj* neoadjuvant, *NP* data not presented in the EPAR, *NSCLC* non-small cell lung carcinoma, *pts* patients, *RA* rheumatoid arthritis, *RMP* reference medicinal product, *sev* severe, *vs*. versus reference, *EPAR* European Public Assessment Report, *HV* health volunteers, *PK* pharmacokinetic, *EU* European Union, *US* United States, *RP* reference product, *PK* pharmacokinetic

[a]RMP EU and US pooled results

Table 2 (continued)

[b]Last time point of the study

[c]Proportion of patients positive for ADA

For each product studied, the immunogenicity ranges were highly comparable between the originator and the biosimilar.

3.3.2.6 Etanercept Etanercept biosimilars and the reference product Enbrel share a low intrinsic immunogenicity, with no ADAs measured in HVs and < 10% positivity for ADA in patient studies (Table 2). The neutralizing capacity was very low. Surprisingly, 7 of 45 patients in the originator Enbrel arm were ADA-positive, compared with none in the biosimilar Benepali arm; however, this finding was regarded as an artefact due to drug interference in the ADA assay.

For each product studied, the immunogenicity ranges were highly comparable between the originator and the biosimilar.

3.3.3 Classification of Immunogenicity According to ADA Rates

The immunogenicity profile that was observed in the biosimilar comparability trials confirms previous observations regarding immunogenicity, i.e. there are active substances with comparatively high intrinsic immunogenicity (≥ 10%, e.g. adalimumab, infliximab), there are products with comparatively low intrinsic immunogenicity (< 10%, e.g. bevacizumab, trastuzumab, etanercept), and those with high or low immunogenicity, depending on the therapeutic indications in which they are used (e.g. rituximab).

For products that are known to exhibit comparatively high immunogenicity (≥ 10%), there was a noticeable trend of a higher percentage of ADA-positive samples compared with historical published data. This was most notable for adalimumab; for example, in the phase III trial of Halimatoz in psoriasis patients, ADA incidences were significantly higher in both the Halimatoz and Humira arms (> 34%) than those reported in the psoriasis studies for the initial MAA of Humira (< 10%; Summary of Product Characteristics [SmPC] of Humira [25]). Similarly, in the phase III trial of Imraldi or Amsparity in patients with moderate/severe rheumatoid arthritis, ADA incidences were significantly higher (> 80%) than those reported in the RA studies for the initial MAA of Humira (12.4% if not administered concomitant methotrexate, compared with 0.6% when adalimumab was used as add-on to methotrexate; SmPC Humira [25]). This is to be expected as currently used assays are generally more sensitive for the detection of antidrug antibodies than those in use when the reference products were developed.

Interestingly, there was no increase in ADA occurrence in low-immunogenic products, even when more sensitive assays were used.

3.3.4 ADAs in Clinical Comparability Studies

The immunogenicity profile was compared between biosimilar mAbs and fusion proteins and their reference products based on data provided from phase I/PK and pivotal phase III comparability studies. All reviewed products included immunogenicity data from comparisons involving the biosimilar versus EU reference products versus US reference products in the phase I/PK trial and a two-way comparison in the phase III trial.

Most phase I/PK trials had a three-arm comparison and used EU and non-EU reference products as a comparator (16/23); one product had a pooled analysis of US and EU reference (Halimatoz), six products had only EU reference products (Remsima, Ruxience, Rixathon, Truxima, Erelzi, Nepexto = 6/23) as a comparator, and one had used only US reference products as a comparator throughout the development program ($n = 1$; Herzuma).

For all comparisons, only small differences in ADA levels were found between the biosimilars and reference products. There were only two cases (Flixabi and Amgevita) where immunogenicity was numerically higher for the biosimilar than for the EU reference products in the phase I/PK trial and also in the corresponding phase III trial (about a 10% difference). In both instances, a marketing authorization was granted based on the totality of evidence, which included highly similar quality and preclinical data, and also considering that such ADA differences did not translate into any clinically relevant effects, including potential immune-mediated adverse effects. These results demonstrate that the intrinsic immunogenicity observed for each reference product was also observed for the respective biosimilars. In no instances did reference products with high immunogenicity have a biosimilar with low immunogenicity, or vice versa. As a general remark, observations regarding comparability of immunogenicity made in the phase I/PK trial were, in all instances, confirmed in the phase III trial, i.e. in no instances were there discordant results for immunogenicity on the phase I/PK trial and comparable results in the phase III trial or vice versa.

From the analysis of all immunogenicity data available for the 23 development programs, there were only minor differences in frequency of ADA-positive subjects, with

a variability of <10% in products known to have higher immunogenicity.

Our analysis suggests that as long as there is no (1) unexpected or 'out-of-range' immunogenicity (e.g. a very high ADA result for a biosimilar or an otherwise low immunogenic RMP), or (2) clinically harmful immunogenicity, then minor differences such as those presented above may be viewed as being within normal variability and thus irrelevant.

3.4 Interchangeability

3.4.1 Characteristics of Switch Studies

In this report, *interchangeability* refers to the possibility of exchanging one medicine for another medicine that is expected to have the same clinical effect. This could mean replacing a reference product with a biosimilar (or vice versa) or replacing one biosimilar with another: *switching,* which is when the prescriber decides to exchange one medicine for another medicine with the same therapeutic intent or by *substitution* (automatic), which is the practice of dispensing one medicine instead of another equivalent and interchangeable medicine at pharmacy level without consulting the prescriber [2].

EPARs are focused on quality, efficacy, and safety, but not on interchangeability. Thus, the switch studies were only analyzed from the safety point of view. Safety analyses, including the switch studies, were not powered to detect statistical differences in any particular safety parameter. The switch studies had variable designs (Fig. 1). The largest studies were conducted with infliximab and adalimumab biosimilars (Table 3). Most studies involved a single switch in the original reference group that was randomized to either continue with the reference or be switched to the biosimilar. In the efficacy and safety analysis, the switched patients were compared with non-switched patients treated with the biosimilar and/or the reference product (Fig. 1a). All included studies were extensions of the pivotal efficacy and safety studies that were submitted to the EMA during the marketing authorization process, or post marketing.

Studies on the biosimilar adalimumabs Amsparity and Hulio had two consecutive switches (reference to biosimilar to reference) (Fig. 1b, c), whereas the study of the biosimilar adalimumabs Hyrimoz/Hefiya/Halimatoz had thee switches (Fig. 1d). Switch data were not available from the biosimilar

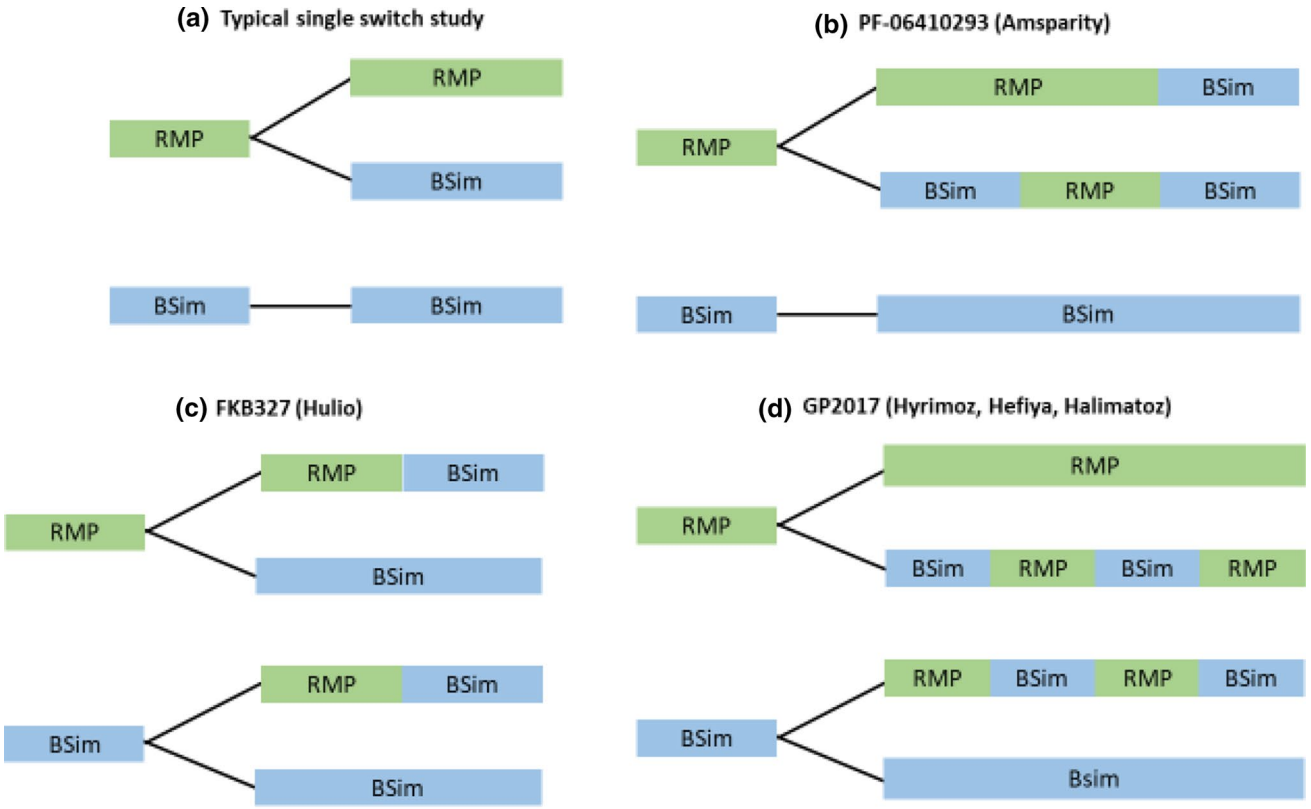

Fig. 1 Designs of switch studies of biosimilar monoclonal antibodies

Table 3 Characteristics of switch studies

Product[a]	Active substance	No. of patients/*switch groups*[b]	Design	No. of switches	Comment
Zessly	Infliximab	RA 280/*143/143*	Extension Randomized	One Ref to BSim	Concomitant methotrexate
Flixabi	Infliximab	RA 291/*101/94*	Extension Randomized	One Ref to BSim	Concomitant methotrexate
Remsima/Inflectra[c]	Infliximab	RA *158/144* AS *88/86*	Extension Non-randomized	One Ref to BSim	Concomitant methotrexate
Idacio	Adalimumab	Psoriasis 214/*101/101*	Extension Randomized	One Ref to BSim	
Amgevita	Adalimumab	Psoriasis 152/*79/77*	Extension Randomized	One Ref to BSim	
Hyrimoz/Hefiya/ Halimatoz	Adalimumab	Psoriasis *126/127/63/63*	Randomized Extension	Three (see text)	
Amsparity	Adalimumab	RA *267/123/127*	Randomized Extension	Two (see text)	Concomitant methotrexate
Imraldi	Adalimumab	RA 201/*111/106*	Randomized Extension	One Ref to BSim	Concomitant methotrexate
Hulio	Adalimumab	RA *216/108/108/213*	Randomized Extension	Two (see text)	Concomitant methotrexate
Erelzi	Etanercept	Psoriasis 151/151/*196*	Randomized Extension	One Ref to BSim BSim to Ref	
Benepali	Etanercept	RA *126/119*	Randomized Extension	One Ref to BSim	Concomitant methotrexate
Nepexto	Etanercept	RA *10/8*	Non-randomized	One Ref to BSim BSim to Ref	Concomitant methotrexate
Kanjinti	Trastuzumab	HER2+ EBC 364/*190/171*	Adjuvant phase Randomized	One Ref to BSim	
Truxima/Ritemvia/Blitzima	Rituximab	RA 38/*20*	Extension Non-randomized	One Ref to BSim	Concomitant methotrexate
Riximyo/Rixathon	Rituximab	RA *53/54*	Randomized	One Ref to BSim	Concomitant methotrexate

EMA European Medicines Agency, *EPARs* European Public Assessment Reports, *RA* rheumatoid arthritis, *AS* ankylosing spondylitis, *HER2+ EBC* human epidermal growth factor receptor 2-positive early breast cancer, *Ref* reference product, *BSim* biosimilar product

[a]Source (EMA find medicine: EPARs [20])

[b]Numbers in italics indicate the number of patients in the switch groups

[c]The assessment report was incomplete and was complemented by data from the studies by Yoo et al. [26] and Park et al. [27]

bevacizumab products Zirabev and Mvasi, or from the trastuzumab products Ontruzant, Herzuma, Trazimera, Ogivri, and Zercepac.

3.4.2 Single Switch Studies

Table 4 shows the impact of a single switch on efficacy, TEAEs, SAEs, discontinuations of the therapy and immunogenicity. In general, the results demonstrate that efficacy, safety, and immunogenicity were not affected by switching. None of the switch studies were powered to find a certain difference. In a few studies, some individual parameters showed small numerical differences between the switched group and the non-switched group(s). Considering the multitude of different comparisons, the clinical significance of these differences was judged on the basis of the totality of evidence. For example, if there is a small numerical difference in SAEs, the EMA assessors will look at the relatedness and type of SAEs, and discontinuations due to adverse effects (is there a specific pattern or potential immunological AE). Most adverse effects of biologicals are due to exaggerated pharmacological effects and sometimes to immunogenicity. Therefore, efficacy and PK data will be used to support the analysis of the clinical significance of a small difference. Thus, in the context of switch studies,

Table 4 Comparisons of safety parameters of biosimilar mAbs and their reference products in single switch studies

Product	INN	Efficacy	TEAEs	SAEs	Discontinuations	Immunogenicity
Zessly	Infliximab	Comp	BSim < Ref[a]	BSim < Ref[a]	Comp	Comp
Flixabi	Infliximab	Comp	Comp	Comp		Comp
Remsima/inflectra[c]	Infliximab	Comp	BSim > Ref[b]	Comp	Comp	Comp
Idacio	Adalimumab	Comp	Comp	Comp	Comp	Comp
Amgevita	Adalimumab	BSim < Ref[a]	BSim < Ref[d]	Comp	Comp	Comp
Imraldi	Adalimumab	Comp	Comp	Comp	Comp	Comp
Erelzi	Etanercept	Comp	NA	BSim > Ref[e]	NA	Comp
Benepali	Etanercept	Comp	Comp	NA	NA	Comp
Nexpecto	Etanercept	NA	Comp	Comp	NA	NA
Kanjinti	Trastuzumab	NA	BSim > Ref	Comp	Comp	NA
Truxima/Ritemvia/Blitzima	Rituximab	Comp	None	Comp	None for BSim	NA
Riximyo/Rixathon	Rituximab	NA	BS > Ref[f]	BS<Ref[g]	None for BSim	NA

TEAE treatment-emergent adverse event, *SAE* serious adverse event, *Comp* comparable according to the EMA assessors' analysis of the magnitude of difference and other safety or efficacy parameters, *Ref* reference product, *BSim* biosimilar product, *INN* international nonproprietary name, *NA* not available in the public domain, *AEs* adverse events

[a]Small numerical difference without clinical significance

[b]Hypersensitivity reactions, latent tuberculosis, abnormal liver function, upper and lower respiratory infections, and infusion-related reactions were reported in similar proportions of patients

[c]Reference means non-switched BSim in this case

[d]Difference mainly due to musculoskeletal adverse events

[e]3.1% vs. 1.3%

[f]60.8% vs. 51.9%, whereas the frequency of treatment-related AEs was 11.3% vs. 20.4%

[g]3 vs. 9

'comparable' means that a numerical difference can be regarded as clinically insignificant or a chance finding.

3.4.3 Multiple Switch Studies

3.4.3.1 GP2017 (Hyrimoz, Hefiya, Halimatoz) The P17-301 study was the pivotal safety and efficacy study in 465 patients with plaque-type psoriasis. The total follow-up was 49 weeks and the core period lasted for 16 weeks. Thereafter, both treatment arms were re-randomized to either continue the original treatment or switch to the other treatment at week 17 until week 23. At week 23, the switch groups were switched back, and at week 35, the groups were switched again, i.e. returned to their original treatment (Fig. 1d). The final period lasted until week 51.

After the switch at week 17, there were 126 patients in the continued GP2017 group, 127 patients in the continued Humira group, 63 patients in the Humira/GP2017 group, and 63 patients in the GP2017/Humira group. In the period 17 weeks to week 51, there were no clinically meaningful differences between the four groups in reported TEAEs with regard to frequency or system organ classes of preferred terms. Infections were the most common SAEs, but no more than one patient in each group reported a particular AE. During the switching period, there was a difference in ADA prevalence of the continuous GP2017 (35.8%) and Humira (45.1%) groups, whereas in the GP2017-Humira and Humira/GP2017 groups, the ADA prevalences were 46.7% and 39.3%, respectively. The differences were regarded as clinically irrelevant.

3.4.3.2 Amsparity The pivotal randomized, double-blind, efficacy and safety study (B5381002) involved 597 patients with rheumatoid arthritis with baseline methotrexate treatment. In the first period that lasted 26 weeks, patients were randomized into two treatment arms—adalimumab-Pfizer (Amsparity) and Humira sourced from the EU. In the second treatment period that lasted until week 52, Humira patients were re-randomized to remain on Humira or switched to Amsparity. In the third period that lasted until week 78, the remaining Humira patients were switched to Amsparity for an open-label extension (Fig. 1b).

The safety profiles were comparable in the three arms in Period 2 at week 52 (Table 5).

The TEAES were analyzed at the end of the period 3 (Table 6) and showed no clear safety signals.

After the initial study period, 44.4% of ADA-positive subjects were included in the Amsparity arm and 50.5% in the Humira arm. After the first switch period, comparable prevalences and titers of ADAs were recorded in the groups

Table 5 Safety after the second period of study B5381002 of amsparity (first switch)

	Amsparity/amsparity	Humira/humira	Humira Amsparity
Any TEAE[1]	43.5	44.4	38.3
Serious AEs	1.4	4.4	2.3
Discontinuation because of an AE	2.1	5.9	1.5
Infections	17.3	17.0	21.1
Musculoskeletal TEAEs	7.4	9.6	7.5

Data are expressed as percentages

AE adverse event, *TEAE* treatment-emergent adverse event

Table 6 Safety after the third period of study B5381002 of amsparity (after the second switch)

	Amsparity Amsparity Amsparity	Humira Humira Amsparity	Humira Amsparity Amsparity
Any TEAE	42.6	50.8	37.0
Infections	20.2	19.2	20.5
Musculoskeletal and connective tissue disorders	10.9	17.5	10.2
Skin disorders	2.3	2.5	1.6
Discontinuations due to TEAEs	2.3	2.5	1.6

Data are expressed as percentages

TEAE treatment-emergent adverse event

continuing original treatment—52.3% (Amsparity) and 59.3% (Humira), and 49.6% in the switch group (Humira/Amsparity). The increase in ADA prevalence over the first switch period was 0.8% in the Humira/Amsparity group, compared with 6.7% in the Humira group that did not switch.

3.4.3.3 Hulio (FKB327) The pivotal safety and efficacy study (FKB327-002) in rheumatoid arthritis patients with concomitant methotrexate had an open-label extension study (-003). In the first period of the extension study, eligible patients (324 and 321 patients in the FKB327 [F] and Humira [H] arms, respectively) were re-randomized for an additional 28 weeks of treatment to either continue the original treatment or switch to the opposite treatment (groups F/F, F/H, H/F, H/H). Overall, 88% of patients entered the first period of the extension study. In the second period, all patients were switched to FKB327 for an additional 48 weeks of treatment. The two switches generated four groups: F/F/F (216 patients), F/H/F (108 patients), H/F/F (108 patients), and H/H/F (213 patients). In these groups, 86–93% of patients completed the second period (Fig. 1c).

In the first period of extension, TEAEs were reported in 47.7%, 54.6%, 54.6%, and 54.9% of the F/F, F/H, H/F, and H/H groups, respectively, and treatment-emergent SAEs were reported in 2.3%, 6.5%, 4.6%, and 3.3%, respectively. No individual preferred AE term in the other groups deviated from the H/H group in a clinically relevant way.

In period II, discontinuations due to TEAEs were similar in the treatment groups. On the one hand, the proportion of patients with TEAEs and severe TEAEs was slightly higher in the F/H/F group compared with the other groups (F/F/F, H/F/F, and H/H/F; 61% vs. 55–60% and 8% vs. 1–4%, respectively). On the other hand, the proportion of patients experiencing the most common individual TEAE, i.e. infections, was lowest in the F/H/F group. Interestingly, injection site reactions were rare; reactions greater than grade 2 were only seen in one patient in each switch group. Most patients (96.5%) using an autoinjector had no injection site reactions. When pain was measured by visual analog scale (VAS), Humira-treated patients had the highest scores for injection site pain.

The subgroups at the end of the first and second period of FKB327-003 showed similar levels of ADAs. There was a trend for a slight decrease in the incidence over time, from approximately 60% to 50% in all subgroups. The mean titers of ADAs also decreased. There were no meaningful differences between the groups.

4 Discussion

All approved biosimilar products fulfilled the requirements of high similarity of the safety profile, including immunogenicity. Switching between biosimilars and their reference products did not cause adverse effects, including loss of efficacy. Postmarketing surveillance of biosimilar mAbs up to 7 years post-approval did not reveal any biosimilar-specific safety or immunogenicity concerns despite considerable exposure of more than 1 million patient-treatment years. Self-administration of biosimilar products with different administration devices is feasible and did not lead to an increase in adverse effects. Thus, biosimilar mAbs may be safely administered *de novo* or after switching from the originator product.

This is the first study covering both prelicensing and postmarketing safety data, administration devices, as well as interchangeability data of all marketed biosimilar mAbs and fusion proteins used in autoimmune and oncology indications (cut-off 31 July 2020). The products were administered by health care professionals (pre- and postlicensing) and also by patients/caregivers (postlicensing). The availability of different presentations and administration options allows for increased patient choice but does not prevent switching between the reference product and its biosimilar product.

The main focus of the marketing authorization applications of biosimilars is the comparability of quality, safety, and efficacy (summarized in the EPARs). Switching data were presented for most biosimilar mAbs and assessed from a safety point of view, since interchangeability is not formally declared by the EMA. The switch studies were extensions of pivotal efficacy and safety studies, had variable designs, and were not powered for efficacy. PSURs cover all significant postmarketing safety issues, including immunogenicity. Thus, the present study deals mainly with safety and immunogenicity, with special emphasis on interchangeability.

Considering the analysis of biosimilar mAbs and the overall long-term exposure to biosimilars worldwide (over 2 billion treatment days), the validity of the biosimilarity concept is *de facto* firmly established [28]. Reviews of up to 178 reference/biosimilar switch studies conducted up to 2018 have not revealed any safety problems [29–32]. Our study confirms that the safety and immunogenicity profiles of biosimilar mAbs and etanercepts, and their reference products, for the treatment of autoimmune and malignant diseases are similar and do not change upon switching.

The current clinical data support theoretical considerations suggesting that switching comparable versions of therapeutic proteins does not induce or increase immunogenicity [33–37]. Knowledge of the reference medicine is the best source of data on the expected immunogenicity of a biosimilar. However, immunogenicity is often presented as the main and unpredictable risk of biosimilars in spite of the questionable theoretical basis and lack of any supporting clinical evidence for this hypothesis [13, 38, 41]. Furthermore, much of the discussion on interchangeability has been focused on the requirement for extensive studies with multiple switches, as well as switches between biosimilars of the same reference product [39–51]. Such studies would require hundreds of patients per study, which will discourage the development of biosimilars [32, 41]. Not surprisingly, most publications advocating for systematic switch studies were sponsored by innovator pharmaceutical companies.

In our opinion, based on theoretical considerations, controlled switching studies, and the significant evidence from real-word switching, systematic switch studies may be scientifically and ethically questionable because of enormous wasting of clinical research resources. The continuous discussion of systematic switch studies creates uncertainty among prescribers regarding the safety and interchangeability of biosimilars [17, 18, 52, 53]. Another concern is misinformation on biosimilars [54–57]. It should be noted that the US FDA considers prescriber-initiated switching as medical praxis. Switching studies are only required for automatic substitution in the US [58].

The most experienced National Regulatory Authorities in the EU, as well as the UK, Norway, Iceland, and Liechtenstein, have issued position papers that endorse interchangeability of biosimilars in agreement with, or under the supervision of, the prescriber [59]. Unfortunately, the positions are somewhat heterogeneous, which is confusing and reduces their impact. Learned societies, regulators, and policymakers should act swiftly to create a common European position on interchangeability to promote rational use of biologicals [34, 44, 60]. The European Commission intends to continue working on the uptake of biosimilars, including review of legislation and specifically mentioning interchangeability to stimulate competition [61].

5 Conclusion

Interchangeability of EU-licensed biosimilars has been demonstrated. Thus, automatic substitution at the pharmacy level is, in principle, possible. From the European perspective, substitution should be tailored to the local circumstances, such as methods for traceability, the need for training of patients and pharmacy personnel, and the switch protocol, including the timing of/interval between switches and price differences triggering a substitution [62].

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Declarations

Author contributions PK and EW-H planned the study. IB analyzed the prelicensing safety data; PT analyzed the postmarketing safety data; SB analyzed the administration devices; EW-H analyzed the immunogenicity data; and PK analyzed the interchangeability data. All authors participated in the drafting of the manuscript.

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Consent to participate Not Applicable.

Availability of data and material (data transparency) All data generated or analyzed during this study are included in this published article (and its supplementary information files).

Code availability (software application or custom code) Not applicable.

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