

# The Efficacy, Safety, and Immunogenicity of Switching Between Reference Biopharmaceuticals and Biosimilars: A Systematic Review

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To date, no consensus exists among stakeholders about switching patients between reference biological products (RPs) and biosimilars, which may have been curbing the implementation of biosimilars in clinical practice. This study synthesizes the available data on switching and assesses whether switching patients from a RP to its biosimilar or vice versa affects efficacy, safety, or immunogenicity outcomes. A total of 178 studies, in which switch outcomes from a RP to a biosimilar were reported, was identified. Data were derived from both randomized controlled trials and real-world evidence. Despite the limitations stemming from a lack of a robust design for most of the studies, the available switching data do not indicate that switching from a RP to a biosimilar is associated with any major efficacy, safety, or immunogenicity issues. Some open-label and observational studies reported increased discontinuation rates after switching, which were mainly attributed to placebo effects. Involvement of the prescriber in any decision to switch should remain and attention should be paid to the mitigation of a potential placebo effect.

Following the expiry of exclusivity rights on original biological medicines (further called the reference products (RPs)), the market opens up for biosimilar versions. Due to the intrinsic variability that is inherent to biological medicines and the complex manufacturing process of these products, a biosimilar cannot be an exact copy to the RP, but needs to demonstrate that it is a highly similar version of the RP. As defined by the European Medicines Agency (EMA), a biosimilar is “a biological medicinal product that contains a version of the active substance of an already authorized original biological medicinal product in the European Economic Area. Similarity to the reference medicinal product in terms of quality characteristics, biological activity, safety, and efficacy based on a comprehensive comparability exercise needs to be established.”<sup>1</sup>

Since the authorization of the first biosimilar in 2006 in Europe (somatropin, Omnitrope by Sandoz GmbH), > 50 biosimilars for a wide range of products and therapeutic areas have been approved in the European Union (EU).<sup>2</sup> The first wave of approved biosimilars included mainly relatively small therapeutic proteins, such as hormones (e.g., somatropin and insulin glargine) and growth factors (e.g., filgrastim and epoetin). Over the last years, more complex biosimilars, such as monoclonal antibodies (mAbs) and fusion proteins used in rheumatology, gastroenterology, and oncology, have been approved and entered the market in Europe.<sup>2</sup> Since the first biosimilar approval in 2015 in the United States (filgrastim, Zarzio by Sandoz), the US Food and Drug Administration (FDA)

approved > 20 biosimilar products.<sup>3</sup> An overview of approved biosimilars in Europe and the United States can be found in **Table 1**.

The market entry of biosimilars can play an important role in containing escalating healthcare expenditures, as they can be offered at lower prices than the RP and lead to price competition. The adoption of biosimilars can also lead to increased patient access to biological treatments and free healthcare budgets for the reimbursement of innovative medicines.<sup>4</sup>

An approved biosimilar is similar in efficacy, safety, and quality to the RP and any observed differences are deemed clinically irrelevant.<sup>1</sup> Therefore, biological treatment of a bio-naïve patient (i.e., a patient without previous treatment with a particular biological medicine) can be initiated with a corresponding biosimilar without any efficacy or safety concerns, other than those proclaimed for the RP. However, the case of switching patients under treatment with the RP to its biosimilar has been questioned and there are still concerns remaining among many healthcare professionals (HCPs) and patients.<sup>5,6</sup> Concerns have been raised that switching between highly similar, but not identical versions of a biological medicine, may lead to an increase in immunogenicity, due to the subsequent exposure to potentially different sets of epitopes (for example, due to differences in glycosylation between the products<sup>7</sup>),<sup>8</sup> although this has never been observed in clinical studies. The formation of anti-drug antibodies (ADAs), although these uncommonly result in a clinically harmful effect, could subsequently lead to safety issues or a loss of efficacy (LOE) to the treatment.<sup>9</sup>

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**Table 1 Overview of approved biosimilars in Europe and the United States**

Product	Europe		United States	
	Reference product	Biosimilar(s) <sup>2</sup>	Reference product	Biosimilar(s) <sup>a,3</sup>
Adalimumab	Humira	Amgevita Halimatoz/Hefiya/Hyrimoz Hulio Idacio/Kromea Imraldi	Humira	Amjevita (adalimumab-atto) Cyltezo (adalimumab-adbm) Hyrimoz (adalimumab-adaz)
Bevacizumab	Avastin	Mvasi Zirabev	Avastin	Mvasi (adalimumab-awwb)
Enoxaparin	Clexane	Inhixa Thorinane	Lovenox	–
Epoetin alfa Epoetin zeta	Eprex	Abseamed Binocrit Epoetin Alfa Hexal Retacrit Silapo	Epogen/Procrit	Retacrit (epoetin alfa-epbx)
Etanercept	Enbrel	Benepali Erelzi	Enbrel	Erelzi (etanercept-szsz) Eticovo (etanercept-ykro)
Filgrastim	Neupogen	Accofil, Grastofil Filgrastim Hexal/Zarzio Nivestim Ratiograstim/Tevagrastim	Neupogen	Zarxio (filgrastim-sndz) Nivestym (filgrastim-aafi)
Follitropin alfa	Gonal-F	Bemfolia Ovaleap	Gonal-F	–
Infliximab	Remicade	Flixabi Inflextra/Remsima Zessly	Remicade	Inflectra (infliximab-dyyb) Renflexis (infliximab-abda) Ixifi (infliximab-qbtix)
Insulin glargine	Lantus	Abasaglar Semglee	Lantus	–
Insulin lispro	Humalog	Insulin lispro Sanofi	Humalog	–
Pegfilgrastim	Neulasta	Fulphila Grasustek Pelgraz Pelmeg Udenyca Ziextenzo	Neulasta	Fulphila (pegfilgrastim-jmdb) Udenyca (pegfilgrastim-cbqv)
Rituximab	Mabthera	Blitzima/Ritemvia/Rituzena/ Truxima Rixathon/Riximyo	Rituxan	Truxima (rituximab-abbs)
Somatropin	Genotropin	Omnitrope	Genotropin	–
Teriparatide	Forsteo	Movymia Terrosa	Forteo	–
Trastuzumab	Herceptin	Herzuma Kanjinti Ogivri Ontruzant Trazimera	Herceptin	Herzuma (trastuzumab-pkrb) Ogivri (trastuzumab-dkst) Ontruzant (trastuzumab-dttb) Trazimera (trastuzumab-qyyp)

Europe: Biosimilar candidates are evaluated by the European Medicines Agency and subsequently authorized by the European Commission in case of a positive opinion. The centralized marketing authorisation for biosimilars is valid in all EU Member States as well as in the European Economic Area countries Iceland, Liechtenstein, and Norway. Over 50 biosimilars have been approved, since the approval of the first biosimilar (biosimilar of somatropin) in 2006.<sup>2</sup>

United States: Biosimilar candidates are evaluated and subsequently approved by the US Food and Drug Administration (FDA). Over 20 biosimilars have been approved by the FDA, since the approval of the first biosimilar (biosimilar of filgrastim) in 2015.<sup>3</sup>

INN, international nonproprietary name.

Products separated with a “/” are duplicates of each other (i.e., these products contain identical active substances, but are licensed under a different tradename).

<sup>a</sup>In the United States, biosimilars of some early biologic drugs, such as somatropin and insulin, have been approved as generics, due to differences between the regulatory pathway of some protein originator products (historically approved under the Food, Drug, and Cosmetic (FD&C) Act) and later originator biological medicines. The FDA will transition these products to be regulated as biologicals under the Public Health Service Act.<sup>85</sup> The FDA assigns four-letter suffixes to approved reference biologics, biosimilars, and (future) interchangeable biosimilars. Recent FDA draft guidance states that suffixes will not be retroactively assigned to previously authorized biologicals without suffix or transition products.<sup>86</sup>

## KEY CONCEPTS AND TERMINOLOGY

Switching is the act by the treating physician “to exchange one medicine for another with the same therapeutic intent.”<sup>10</sup> Switching can refer to a change between two different molecules (with a different international nonproprietary name (INN) e.g., infliximab to adalimumab) or a change between a RP and its biosimilar version (e.g., infliximab to CT-P13) or between biosimilars of the same RP. Switching from a RP to a biosimilar (or *vice versa*) or between biosimilars is also referred to as nonmedical switching (i.e., switching merely for cost-saving reasons). Dörner and colleagues proposed the term transitioning for this type of switching,<sup>11</sup> in an effort to delineate the different types of switches reported in the literature. In this paper, the term switching refers to the switch from a RP to a biosimilar (or *vice versa*). Automatic substitution is “the act of dispensing one medicine instead of another equivalent and interchangeable medicine at the pharmacy level without consulting the prescriber.”<sup>10</sup> The practice of substitution is regulated on a member state level and for biological medicines prohibited or advised against in most European countries.<sup>12</sup> Interchangeability is a characteristic of two medicines and “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,”<sup>10</sup> either prior to the start of a biological treatment or during (stable) treatment.

Switching and substitution practices and the designation of interchangeability are not regulated on an EU level as prescribing practices fall within the responsibilities of the different EU member states.<sup>10</sup> In the United States, the FDA has created a regulatory designation pathway for the scientific evaluation of interchangeability. An interchangeable product needs to meet additional requirements in addition to being authorized as a biosimilar.<sup>13</sup> For the proposed interchangeable product, it needs to be shown that it “can be expected to produce the same clinical result as the RP in any given patient; and for a product that is administered more than once to an individual, the risk in terms of safety or diminished efficacy of alternating or switching between use of the product and its RP is not greater than the risk of using the RP without such alternation or switch.”<sup>13</sup> According to the Biologics Price Competition and Innovation Act (BPCI Act) section 351(k)(4), the pharmacist would be allowed to substitute a prescribed biological RP with an interchangeable biosimilar without the involvement of the prescriber, if allowed by state laws.<sup>13</sup> Thus far, no biosimilars have yet been deemed interchangeable by the FDA.<sup>3</sup>

In 2012, Ebbers *et al.* investigated the safety of switching between therapeutic proteins, addressing the key question surrounding the use in practice of biosimilars. The study did not find evidence from clinical trial data or postmarketing surveillance (PMS) data that switching to and from different biological medicines led to safety concerns.<sup>14</sup> Since then, many more biosimilars have been approved and entered the market.<sup>2</sup> Increasingly, national competent authorities and HCP organizations formulated guidance about switching.<sup>15</sup> However, switching remains a highly debated topic and the arrival of the more complex mAb biosimilars to the market further sparked the discussion.<sup>8,16</sup> Various biological medicines, especially blockbuster mAbs, are used in a chronic setting, stressing the need

to address these questions in an effort to aid (clinical) decision making. Furthermore, the uncertainty about switching limits the competition potential of biosimilars to curb the increasing burden on healthcare budgets and to increase treatment access for patients.

This systematic literature review aims to synthesize the currently available data on switching and to assess the safety, immunogenicity, and efficacy of switching between RPs and their respective biosimilar version(s). This review broadens the scope of previous studies<sup>14,17</sup> by reviewing switch data for biologicals of every therapeutic class for which a European market authorization has been granted, more specifically: (i) recombinant human growth hormones (rhGHs), (ii) erythropoietins, (iii) granulocyte colony stimulating agents, (iv) insulins, (v) tumor necrosis factor alpha inhibitors (anti-TNFs), (vi) gonadotropins, (vii) low-molecular-weight heparins, and (viii) mAbs used in oncology. Further, we aim to provide a critical insight on the current state-of-the-art related to switching. This overview can be useful for HCPs and other stakeholders in their (clinical practice) decision making.

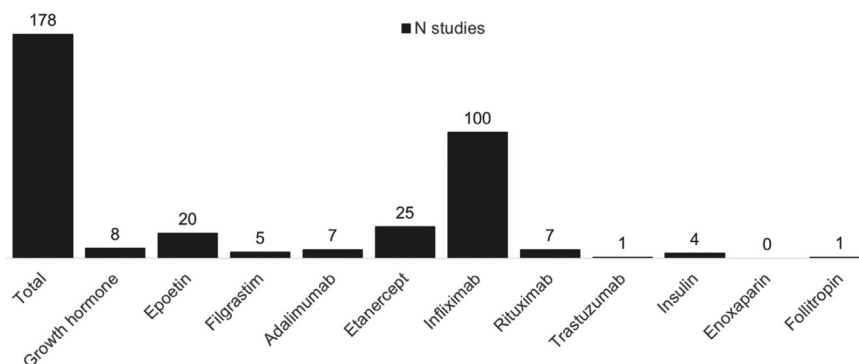
Information on the methodology of this systematic literature review is shown in the online **Supplementary Information (Box S1, Figure S1, Tables S1 and S2)**.

## STUDIES SWITCHING BETWEEN BIOLOGICAL REFERENCE PRODUCTS AND BIOSIMILARS

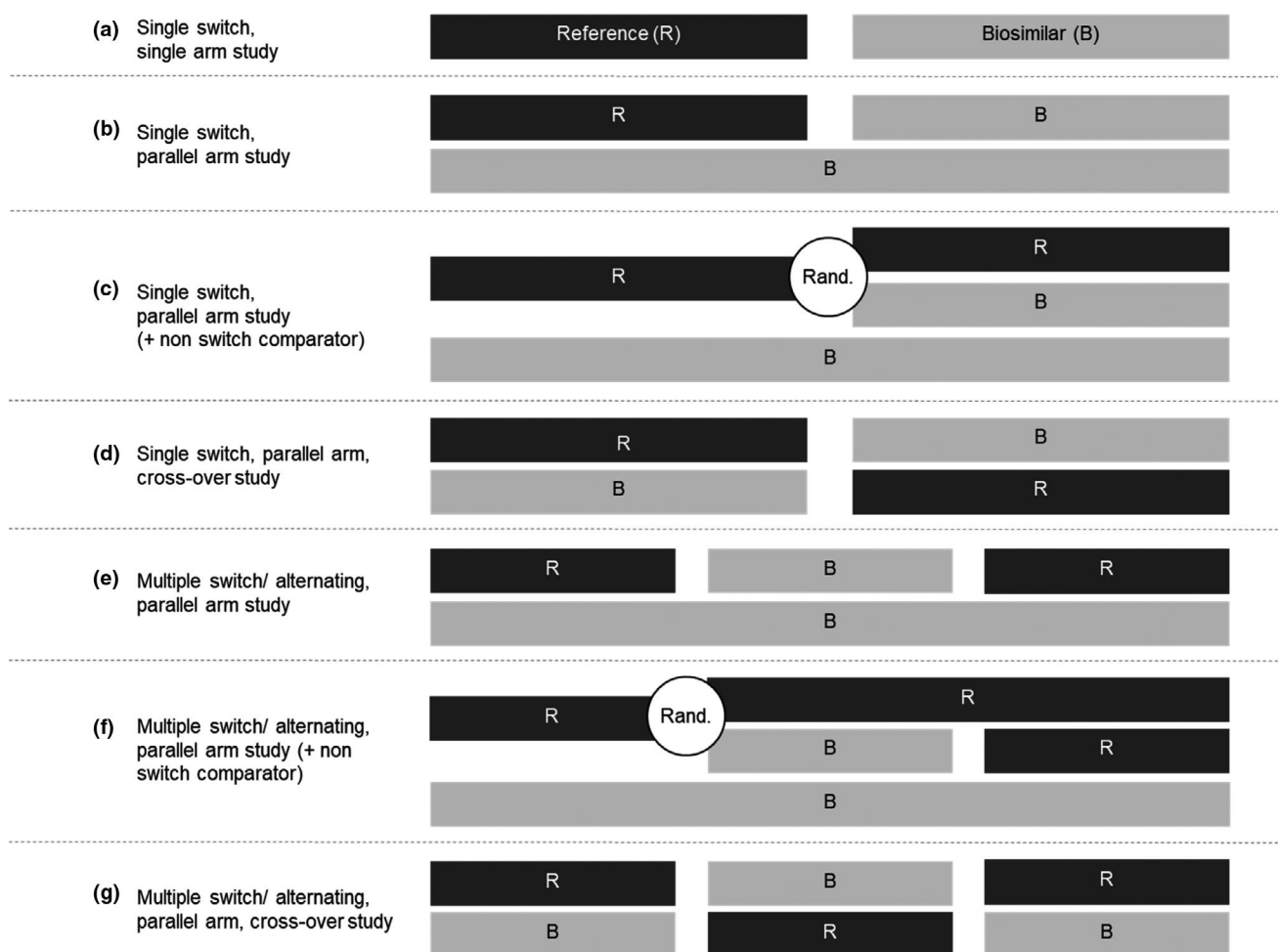
In total, 178 studies (accumulating up to approximately 21,000 switched patients) were identified and included in the systematic literature review. Switch studies were identified for somatropin, epoetin, filgrastim, insulin, anti-TNFs (adalimumab, etanercept, and infliximab), follitropin, and mAbs used in oncology (rituximab and trastuzumab). No switch data were identified for patients treated with enoxaparin. **Figure 1** provides an overview of the number of identified studies across products. The majority of the studies related to switching from an anti-TNF RP to a biosimilar (132/178), and more specifically most studies related to switching from the infliximab RP to CT-P13 (Remsima/Inflectra).

Different types of study design were identified. **Figure 2** illustrates the main different switch designs. Most of the studies consisted of a single switch (i.e., patients changed one time from the RP to a biosimilar). Only six studies with a multiple switch design (i.e., patients changed multiple times between the RP and the biosimilar, alternating back on forth) were identified.<sup>18–23</sup> No studies on switching between biosimilars were identified.

Data are originating from two main classes of studies. First, 38 studies (21%) can be categorized as randomized controlled trials (RCTs) and open-label extension studies (mostly these studies are part of the phase I/III clinical development of the proposed biosimilar, but also include for example the NOR-SWITCH trial).<sup>24</sup> An overview of the study design and switch results of this first class of switch studies, across products and disease areas, can be found in **Table 2**. Second, the bulk of the data ( $N = 140$ ; 79%) is originating from studies conducted in the real-world setting (i.e., real-world evidence (RWE), defined as nonrandomized studies outside the biosimilar candidate's clinical development). The identified RWE consists of parallel arm, nonrandomized, nonblinded studies and predominately studies



**Figure 1** Overview of number of switch studies across products.



**Figure 2** Overview of different switch study designs. B, biosimilar; R, reference product; rand., randomization.

following a single arm design (i.e., the total patient cohort that (systematically, sometimes driven by procurement decisions) switches from the RP to the biosimilar, without a comparator arm). Further, registries, such as the DANBIO registry for the switch from the infliximab RP to CT-P13 and the switch from the etanercept RP to SB4, were identified.

In addition to efficacy and safety outcomes, the measurement of trough levels (TLs) and ADAs upon switching was screened. TLs

and ADAs were reported in 71 of 178 studies. **Figure 3** shows the number of studies reporting on ADA and/or TL across products.

Based on the conclusion of the authors, the majority of the studies did not identify major efficacy, safety, or immunogenicity issues due to switching from a RP to its biosimilar version.

Study-specific results per product are further discussed below and shown in **Tables S3–S11** in the online **Supplementary Information**.

**Table 2 Overview of RCT and open label extension switch studies**

Authors	Product	Population	Study design	No. patients switched	Follow-up <sup>a</sup>	Efficacy, safety, and immunogenicity outcomes	ADA rep.	Reported conclusion/switch advice
Single switch studies								
<i>Adalimumab biosimilars</i>								
Cohen et al. (2017) <sup>50</sup>	Adalimumab – ABP 501	RA	OLE of RCT phase III trial	237	46 weeks	Similar efficacy between switch and BS cont. arms. Rate of TEAEs and ADA similar between switch and BS cont. arms.	Yes	Long-term safety, immunogenicity, and efficacy results similar between switch and cont. arms
Cohen et al. (2018) <sup>54</sup>	Adalimumab – BI695501	RA	Randomized, double-blind, parallel arm, phase III trial (VOLTAIRE-RA)	147	34 weeks	ACR20/50/70 response rates, safety and immunogenicity (ADA, ADA titers, and neutralizing antibodies) were similar across the 3 arms (RP-BS switch, RP cont., BS cont.)	Yes	The switch had no impact on efficacy, safety, and immunogenicity
Hodge et al. (2017) <sup>53</sup>	Adalimumab – CHS-1420	Ps and PA	Double-blind, randomized, parallel arm, phase III trial	124	8 weeks	PASI75 achieved in 84.6%, 81.6%, and 88.3% pts in BS cont., switch, and RP cont. arms. TEAE reported in 20.1%, 19.4%, and 16.3% pts in BS cont., switch, and RP cont. arms. ADA reported in 4.0 %, 0.8%, and 2.3% in BS cont., switch, and RP cont. arms	Yes	Similar safety and efficacy between switched and nonswitched pts
Papp et al. (2017) <sup>51</sup>	Adalimumab – ABP 501	Ps	Randomized, double-blind, parallel arm, phase III trial	77	36 weeks	PASI percentage improvements from baseline similar across arms (RP-BS switch, RP cont., BS cont.). No significant differences across arms in percentages of PASI 50, 75, 90, and 100 responders. No new safety signals detected. AEs balanced between arms. Incidence of overall ADA comparable across arms.	Yes	Similar efficacy, safety, and immunogenicity profiles after single switch between arms
Weinblatt et al. (2018) <sup>52</sup>	Adalimumab – SB5	RA	Extension, double-blind, randomized, controlled phase III trial	125	28 weeks	ACR response rates comparable between switch and cont. arms. Comparable trends in DAS28, SDAI, and CDAI across arms. The safety profile was consistent across arms. Proportion of pts with ADA, neutralizing ADA and sustained ADA was similar between arms.	Yes	Switching had no treatment emergent issues, such as increased AEs, increased immunogenicity, or loss of efficacy

(Continued)

Table 2 (Continued)

Authors	Product	Population	Study design	No. patients switched	Follow-up <sup>a</sup>	Efficacy, safety, and immunogenicity outcomes	ADA rep.	Reported conclusion/switch advice
<i>Etanercept biosimilars</i>								
Emery et al. (2017) <sup>56</sup>	Etanercept – SB4	RA	OLE of randomized, double-blind, phase III trial	119	48 weeks	ACR response rates sustained and comparable between BS cont. and switch arms (ACR20 response rates at week 100 77.9% vs. 79.1%, respectively). TEAE rates 47.6% vs. 48.7%, respectively. One patient in each arm developed non-neutralizing ADA.	Yes	Efficacy, safety, and immunogenicity comparable between the cont. and switch arms. No risk associated with switching pts from RP to SB4.
O'Dell et al. (2017) <sup>56</sup>	Etanercept – CHS-0214	RA	Randomized, double-blind, parallel arm study	220	24 weeks	Response rates maintained in cont. and switch arms (93.8% vs. 92.7% for ACR20, 75.0% vs. 73.6% for ACR50, 49.6% vs. 51.4% for ACR70, respectively). AEs in 74.4% vs. 76.6% pts, SAE in 4.6% vs. 7.5% pts, SAEs related to study drug in 0.9% vs. 1.9% pts. Treatment-emergent binding ADA in 1.4% pts receiving BS cont. and 0.7% of switched pts.	Yes	No clinically meaningful differences in efficacy, safety, or immunogenicity between switch and BS cont. arms
Matucci-Cerinic et al. (2018) <sup>57</sup>	Etanercept – GP2015	RA	Randomized, double-blind, parallel arm, phase III study (EQUIRA)	166	24 weeks	The mean change in DAS28-CRP was comparable between the cont. and switch arms. EULAR and ACR 20/50/70 response rates were comparable between arms. TEAEs in 42.9% vs. 38.0%, SAEs in 2.3% vs. 2.4% pts, injection site reactions in 0% vs. 3.6% pts in the cont. vs. switch arm. 2.4% pts in the cont. arm had single-event, very low titer, non-neutralizing ADA.	Yes	The switch did not affect efficacy and safety of etanercept treatment in pts with moderate-to-severe RA
Song et al. (2018) <sup>58</sup>	Etanercept – LBEC0101	RA	OLE of randomized controlled double-blind phase III trial	78	48 weeks	DAS28-ESR score maintained in cont. and switch arms. Response rates at week 100: 79.7% vs. 83.3% for ACR20, 65.2% vs. 66.7% for ACR50, and 44.9% vs. 42.3% for ACR70 for cont. and switch arms, respectively. AE incidence comparable between arms (70.0% vs. 70.5%). Proportion of pts with newly developed ADA similar between arms (1.4% vs. 1.3%).	Yes	Efficacy and safety comparable in both cont. and switch arms

(Continued)



Table 2 (Continued)

Authors	Product	Population	Study design	No. patients switched	Follow-up <sup>a</sup>	Efficacy, safety, and immunogenicity outcomes	ADA rep.	Reported conclusion/switch advice
<i>Infliximab biosimilars</i>								
Alten et al. (2018) <sup>40</sup>	Infliximab – PF-06438179/GP1111	RA	Randomized, double-blind, parallel arm phase III study	143	24 weeks	ACR20 rates and DAS28-CRP scores comparable between arms. Incidence of TEAE 36.8%, 33.6%, and 37.8%, SAEs (4.6%, 7.7%, and 2.8%) and infusion-related reactions (3.2%, 8.4%, and 4.2%) comparable between the cont. BS, cont. RP and switch arm. Predose and postdose ADA rates were comparable between arms.	Yes	Study showed the absence of clinically meaningful differences in efficacy, safety, and immunogenicity between switch and cont. arms
Jørgensen et al. (2017) <sup>24</sup>	Infliximab – CT-P13	RA, CD, UC, Ps, PA, SpA	Randomized, double-blind, parallel arm, single switch noninferiority phase IV trial (NOR-SWITCH)	241	52 weeks	Disease worsening occurred in 26% and 30% of pts in the cont. and switch arms, respectively. The 95% CI of the adjusted treatment difference (–4.4%) was –12.7 – 3.9, fell within the prespecified noninferiority margin. The frequency of AEs was similar between arms. Trough drug concentrations similar in the two arms. Incidence of ADA detected during the study was 7% vs. 8% for cont. and switch arm, respectively.	Yes	NOR-SWITCH showed that switching to CT-P13 was not inferior to cont. treatment with the RP based on noninferiority margin of 15%. No noninferiority was shown in individual diseases (study not powered for this).
Goll et al. (2017) <sup>38</sup>	Infliximab – CT-P13	RA, CD, UC, Ps, PA, SpA	OLE, parallel arm NOR-SWITCH	183	26 weeks	Disease worsening occurred in 16.8% and 11.6% of pts in the cont. and switch arms, respectively. Three and 5 pts in the cont. and switch arms, respectively, developed ADA. TEs and the frequencies of reported AEs comparable between arms.	Yes	OLE of NOR-SWITCH trial did not show any difference between pts who maintained CT-P13 vs. pts who switched
Kim et al. (2017) <sup>42</sup>	Infliximab – CT-P13 or vice versa	CD	Randomized, controlled, single switch, parallel arm phase III trial	110	24 weeks	Clinical remission and CDAI-70 response rates maintained and similar among arms (BS cont., RP cont., RP-BS switch, and BS-RP switch) after switching. One-year safety similar among arms. At week 30, 1 IRR reported after switching (pt ADA positive at time of switch). No further IRR reported in switch arms after. No clinically meaningful differences in immunogenicity reported.	Yes	The switch arm was comparable to RP and BS cont. arms in terms of efficacy and safety profiles

(Continued)

Table 2 (Continued)

Authors	Product	Population	Study design	No. patients switched	Follow-up <sup>a</sup>	Efficacy, safety, and immunogenicity outcomes	ADA rep.	Reported conclusion/switch advice
Park et al. (2017) <sup>36</sup>	Infliximab – CT-P13	AS	OLE study of double-blind RCT (PLANETAS extension)	86	48 weeks	ASAS20, ASAS40, and ASAS partial remission rates similar between arms. Proportion of pts with at least one TEAE was 48.9% vs. 71.4% in the cont. and switch arms, respectively. Proportion of pts with ADA similar in cont. and switch arms.	Yes	Switching from RP to CT-P13 is possible without negative effects on safety or efficacy
Smolen et al. (2018) <sup>37</sup>	Infliximab – SB2	RA	Extension randomized controlled phase III trial	94	24 weeks	ACR20 was comparable across switch, RP cont., BS cont. arms. TEAEs in 36.2%, 35.6%, and 40.3%, respectively. Newly developed ADAs in 14.6%, 14.9%, and 14.1%, respectively.	Yes	Efficacy, safety, and immunogenicity comparable between switch and cont. arms. No treatment-emergent issues or clinically relevant immunogenicity after switching.
Tanaka et al. (2017) <sup>41</sup>	Infliximab – CT-P13	RA	OLE of phase I/II trial	33	69.0 ± 29.5 weeks	The type and frequency of AEs were similar between arms. Number of ADA-positive pts 48.5% vs. 31.6% in switch and maintenance arm, respectively.	Yes	CT-P13 was well tolerated in pts who switched
Kay et al. (2016) <sup>39</sup>	Infliximab – BOW015	RA	OLE of double-blind RCT	53	32 weeks	No significant difference in proportion of pts achieving ACR20, 50, or 70 responses between arms. Mean improvements in CRP, ESR, and tender and swollen joint counts did not differ significantly between arms.	NR	Durability of response to BOW015 has been demonstrated. No switch advice
Volkers et al. (2017) <sup>87</sup>	Infliximab – infliximab BS	IBD	Randomized, double-blind, single switch, parallel arm, phase IV non-inferiority trial	15	30 weeks	One pt (switch arm) experienced relapse of IBD. Two pts experienced an SAE, not related to the study drug.	NR	Preliminary results show that switching from infliximab RP to infliximab BS is feasible and safe
Yoo et al. (2017) <sup>35</sup>	Infliximab – CT-P13	RA	OLE of double-blind RCT (PLANETRA extension)	144	48 weeks	Similar ACR20, ACR50, and ACR70 rates between the cont. and switch arms. Proportion of pts with at least one TEAE comparable between cont. and switch arm (53.5% and 53.8%, respectively). Proportion of pts developing ADA similar between arms.	Yes	Switching not associated with any detrimental effects on efficacy, safety, or immunogenicity

(Continued)



Table 2 (Continued)

Authors	Product	Population	Study design	No. patients switched	Follow-up <sup>a</sup>	Efficacy, safety, and immunogenicity outcomes	ADA rep.	Reported conclusion/switch advice
<i>mAbs in oncology</i>								
Von Minckwitz et al. (2018) <sup>69</sup>	Trastuzumab – ABP 980	Early breast cancer (adjuvant phase)	Randomized, double-blind, phase III study	171	NR	Percent of pts with disease progression/recurrence/death was 5.3% vs. 2.9% in the RP cont. and RP/BS switch arm, respectively. No increase in frequency or severity of AEs and no unexpected safety signals. No increase in cardiotoxicity. In adjuvant phase, 1 pt in the switch arm developed binding non-neutralizing ADA. In neoadjuvant phase (pre-switch), 2 pts in the RP cont. and in the BS cont. arm developed binding non-neutralizing ADA.	Yes	Switching from trastuzumab to ABP 980 was safe. Switching did not increase the frequency or severity of AEs, no unexpected safety signals were noted, and it did not increase the incidence of developing ADAs. Event-free survival was also similar between treatment groups.
Cohen et al. (2018) <sup>66</sup>	Rituximab – PF-05280586	RA	Randomized extension study (REFLECTIONS)	126	96 weeks	No notable differences in drug concentrations between groups, and no apparent relationship between IRR and ADA with or without switch. Long-term safety and tolerability of PF-05280586 acceptable in all groups. Percentage of subjects with a low disease activity score and disease activity score remission was similar across groups for all time points.	Yes	Tolerability and acceptable safety of a single switch was demonstrated. No increased immunogenicity due to switching based on either ADA or IRR reports.
Park et al. (2017) <sup>63</sup>	Rituximab – CT-P10	RA	OLE phase I study	20	24 weeks	All efficacy end points (DAS28-ESR, DAS28-CRP, and EULAR response) comparable between cont. and switch arms, no statistically significant differences. No significant differences in AEs. ADA incidence similar between cont. and switch arms.	Yes	Switching had no notable impact on the efficacy or safety of treatment
Shim et al. (2017) <sup>64</sup>	Rituximab – CT-P10	RA	OLE phase III study	109	24 weeks	DAS28 and ACR response rate comparable between arms, B-cell depletion comparable after the first infusion and maintained until 24 weeks in all arms. Safety profiles comparable between arms. No remarkable changes in immunogenicity profile followed the switch.	Yes	Switch arms were comparable to BS and RP arms groups in efficacy, safety, and immunogenicity

(Continued)

Table 2 (Continued)

Authors	Product	Population	Study design	No. patients switched	Follow-up <sup>a</sup>	Efficacy, safety, and immunogenicity outcomes	ADA rep.	Reported conclusion/switch advice
Tony et al. (2017) <sup>65</sup>	Rituximab – GP2013	RA	Randomized, double-blind, parallel-group trial (ASSIST-RT)	53	24 weeks	Hypersensitivity reactions, ADA, and the rate of AEs were similar between arms	Yes	The safety of pts between switch and cont. arms was comparable
Nasonov et al. (2017) <sup>62</sup>	Rituximab – BCD-020	RA	Double-blind RCT, parallel crossover switch	80	24 weeks	There were no significant differences in ACR20 after partial crossover at 48 weeks (24-week switch). AEs rates: 44.44% for cont. BS, 38.46% for cont. RP, 57.14% in RP-BS switch arm, 62.50% in BS-RP switch arm. Incidence of ADA was 3.85% in cont. BS arm, no binding ADA in other groups.	Yes	One-year data show that switching between products does not affect treatment outcomes
<i>Smaller biologics</i>								
Romer et al. (2009) <sup>25</sup>	Somatropin – Omnitrope	GHD in children	Randomized, open-label phase III clinical study	45	75 months	6.8% pts developed low ADA titers. At the final visit, no pts had detectable ADA	Yes	Switch between rhGH preparations was well-tolerated and safe
Hadijianni et al. (2016) <sup>88</sup>	Insulin glargine – LY2963016	T1D & T2D	Randomized, controlled clinical study	362	24 weeks	TD1: no significant differences in efficacy parameters, but more weight gain in switch arm compared to cont. No significant differences in TEAEs and SAEs. TD2: no significant differences in efficacy parameters. No significant differences in TEAEs. Significantly, fewer pts in switch arm experienced ≥ 1 SAE. Proportion of detectable ADA in switch arm statistically significantly higher compared to cont. arm (potentially due to baseline imbalances).	Yes	Pts who switched from RP to insulin BS have similar efficacy and safety outcomes compared to pts under con. RP treatment
Goh et al. (2007) <sup>26</sup>	Originator – GerEPO	Hemodialysis pts	Randomized, open-label, parallel arm, single switch study	87	12 weeks	Both arms showed a similar decline in Hb. More pts in switch arm reported AEs due to subjective symptoms, more pts in switch arm were withdrawn due to AE or decrease in Hb (similar Hb decline in both arms).	NR	Results are convincing with respect to efficacy measured in terms of Hb response, the duration of trial was only 3 months, which is insufficient for safety evaluation

(Continued)

**Table 2 (Continued)**

Authors	Product	Population	Study design	No. patients switched	Follow-up <sup>a</sup>	Efficacy, safety, and immunogenicity outcomes	ADA rep.	Reported conclusion/switch advice
Haag-Weber et al. (2009) <sup>27</sup>	Epoetin – HX575	CKD	Randomized, controlled, open-label clinical trial	314	54 weeks	Mean changes in Hb levels were 0.15 ± 0.09 g/dl and 0.06 ± 0.12 g/dl in switch and cont. arm respectively. Difference between arms: 0.08 g/dl (95% CI: –0.17 to 0.34). No antibody formation detected.	Yes	No differences in safety, immunogenicity, or efficacy profiles following the switch. The long-term safety profile of the BS was comparable to the RP.
Harzallah et al. (2015) <sup>28</sup>	Epoetin Hemax – BS epoetin Epomax	Hemodialysis pts	Phase III trial	53	43 days	No significant difference in mean Hb levels between arms. Five pts discontinued after switch (2 due to unrelated abdominal pain, unclear for other 3).	NR	Epomax was effective at maintaining the Hb levels at target concentrations and was well-tolerated
Krivoshiev et al. (2010) <sup>29</sup>	Epoetin zeta – RP	CKD	Randomized, observer-blind, controlled phase III trial	230	28 weeks	Percentage of pts with infections and infestations was similar. No pts developed ADA.	Yes	Epoetin zeta is equivalent to epoetin alfa in respect of its clinical efficacy. The safety profile of both products is similar: no unexpected AEs were observed, no pts developed anti-erythropoietin antibodies. No switch advice.
Gatzemeier et al. (2009) <sup>31</sup>	Filgrastim – XM02	NP in pts under chemotherapy	Randomized, controlled phase III study	80	Max 6 chemotherapy cycles	The AE profile was similar between cont. and switch arms	NR	XM02 is safe and well-tolerated. No switch advice.
Engert et al. (2009) <sup>32</sup>	Filgrastim – XM02	NP in pts under chemotherapy	Randomized, controlled, phase III trial	29	Max 6 chemotherapy cycles (3-week/cycle)	Incidence of observed/protocol defined FN was 31.7% and 41.4% in the cont. and switch arms, respectively. The AE profile was similar between switch and cont. arms.	Serum concentrations	XM02 has a similar efficacy profile and does not seem to have different safety profiles as compared with the RP. XM02 is safe and well-tolerated. No switch advice.
Strowitzki et al. (2016) <sup>61</sup>	Follitropin – Ovaleap	Assisted fertility	OLE phase III trial	67	Cycle 2 & 3 (treatment up to 20-day/cycle)	Safety and efficacy findings were comparable to the outcomes in the main phase III study, comparing Ovaleap and Gonaf-f	Yes	Results in support of the safety and efficacy of a switch to Ovaleap

(Continued)

Table 2 (Continued)

Authors	Product	Population	Study design	No. patients switched	Follow-up <sup>a</sup>	Efficacy, safety, and immunogenicity outcomes	ADA rep.	Reported conclusion/switch advice
Multiple switch studies								
Blauvelt et al. (2017) <sup>19</sup>	Adalimumab – GP2017 or vice versa	Ps	Parallel arm, randomized, double-blind phase III trial (ADACCESS) <b>4 x switch:</b> at week 17, week 23, week 29, and week 35. Follow-up until week 51.	126	34 weeks	No clinically relevant differences in efficacy and safety between the cont. and switch arms (RP cont., BS cont., RP-BS switch, and BS-RP switch) across the study duration. Overall, differences in the frequency of ADA detection were < 11% among the arms.	Yes	There were no clinically meaningful differences in long-term efficacy between the cont. and multiple RP-GP2017 switch groups. Switching was well-tolerated.
Genovese et al. (2017) <sup>20</sup>	Adalimumab – FKB327	RA	Randomized OLE of RCT phase III trial (ARABESC-OLE) <b>2 x switch:</b> at week 0 (start OLE) and week 28. Follow-up until week 76.	216	48–76 weeks	Interim analysis: ACR20 response rate at week 30 comparable between cont. (BS-BS 82.5%; RP-RP 84.3%) and switch (BS-RP 86.5%; RP-BS 89.1%) arms. Safety profiles comparable for all treatment sequences (group sizes reduced after switching). No consistent differences in ADA profiles between cont. and switch arms.	Yes	Interim OLE results indicate that long-term safety, efficacy, and immunogenicity were comparable between cont. and switch arms
Gerdes et al. (2017) <sup>21</sup>	Etanercept – GP2015	Ps	Randomized, double-blind, parallel arm, multiple switch phase III study (EQUALITY). <b>3 x switch:</b> at week 12, week 18, and week 24. Follow-up until week 52.	196	40 weeks (6-week interval)	PASI 50, PASI 75, and PASI 90 response rates, percent change from baseline in PASI scores and all other efficacy parameters similar between switch and cont. arms. Incidence of TEAEs, including injection site reactions comparable between arms. No pts positive for binding ADA.	Yes	Similar efficacy between cont. and switch arm. No clinically relevant differences in safety or immunogenicity between arms, indicating no impact of repeated switches between GP2015 and RP.
Wizemann et al. (2008) <sup>18</sup>	Epoetin alfa – epoetin zeta or vice versa	CKD, anemia	Double-blind, crossover phase III trial <b>2 x switch:</b> at week 0, at week 12	239	12 weeks	Hb levels were equivalent. Pts underwent minor dose adjustments during treatment crossover. AE profile was similar. No pts developed neutralizing ADA.	Yes	Epoetin zeta is therapeutically equivalent to epoetin alfa in the maintenance of target Hb levels in pts with renal anaemia. No unexpected AEs were seen.

(Continued)

Table 2 (Continued)

Authors	Product	Population	Study design	No. patients switched	Follow-up <sup>a</sup>	Efficacy, safety, and immunogenicity outcomes	ADA rep.	Reported conclusion/switch advice
Blackwell et al. (2015) <sup>23</sup>	Filgrastim – EP2006	NP in pts under chemotherapy	Randomized, phase III trial <b>5 x switch:</b> at each chemo cycle every 3 weeks	109	4 treatment cycles	Alternating between biosimilar and RP or vice versa showed no clinically meaningful differences regarding efficacy and safety. No increased risk of developing ADA under repeated alternating.	Yes	Alternating between BS and the RP or vice versa showed no clinically meaningful differences regarding efficacy and safety. The immunogenic response to filgrastim assessed under conditions of repeated alternating and nonalternating also showed no increased risk of developing anti-G-CSF antibodies.

ACR, American College of Rheumatology; ADA, antidrug antibody; ADA rep., ADA measurements reported; AE, adverse event; BS, biosimilar; CI, confidence interval; CD, Crohn's disease; CKD, chronic kidney disease; cont., continuous; CRP, C reactive protein; DAS, Disease Activity Score; ESR, Erythrocyte Sedimentation Rate; FN, febrile neutropenia; G-CSF, granulocyte colony-stimulating factor; GHD, growth hormone deficiency; Hb, hemoglobin; IBD, inflammatory bowel disease; IRR, infusion-related reaction; mAbs, monoclonal antibodies; NP, neutropenia; NR, not reported; OLE, open label extension; PA, psoriatic arthritis; PASI, Psoriasis Area and Severity Index; Ps, chronic plaque psoriasis; pts, patients; RA, rheumatoid arthritis; RCT, randomized controlled trial; rhGH, recombinant human growth hormone; RP, reference product; SAE, serious adverse event; SpA, Spondyloarthritis; T1D, type 1 diabetes; T2D, type 2 diabetes; TEAE, treatment-emergent adverse event; TL, trough level; UC, ulcerative colitis.

<sup>a</sup>Follow-up after switch.

### SWITCH STUDIES FOR SOMATROPIN

One biosimilar (Omnitrope) of somatropin (RP Genotropin), a rhGH, has been authorized in the EU.<sup>2</sup> Eight switch studies from the RP of somatropin to Omnitrope have been identified (Table S3 in the online **Supplementary Information**). Seven studies consisted of a single arm study design and one was a randomized open-label phase III trial.<sup>25</sup> All studies consisted of a single switch from the RP to the biosimilar. Overall, none of these studies indicated safety or efficacy issues related to switching.

### SWITCH STUDIES FOR EPOETIN ALFA/ZETA

Five biosimilars (representing two unique products) of epoetin alfa (RP Eprex) are EU approved (Epoetin Alfa Hexal/Abseamed/Binocrit, and Silapo/Retacrit).<sup>2</sup> The marketing authorization holder of Silapo/Retacrit requested another INN for their active substance (i.e., epoetin zeta).<sup>2</sup> A total of 20 switch studies were identified for epoetin alfa and epoetin zeta (Table S4 in the online **Supplementary Information**). Five switch RCTs were identified, of which one trial can be considered as a multiple switch study.<sup>18,26–29</sup> In this study, patients were treated with an originator prior to enrollment. Upon the start of the trial, a part of these patients were switched to a biosimilar, followed by a second switch to the originator during the study duration.<sup>18</sup> Further, 14 single arm studies were identified. One of the studies, a retrospective matched control study in hemodialysis patients, demonstrated a dosing penalty (i.e., requiring higher doses to maintain Hb level) after switching.<sup>30</sup> In this study, 163 patients were switched and followed up during 24 weeks. Higher doses of 40% were reported to be required to maintain anemia control.<sup>30</sup>

### SWITCH STUDIES FOR FILGRASTIM

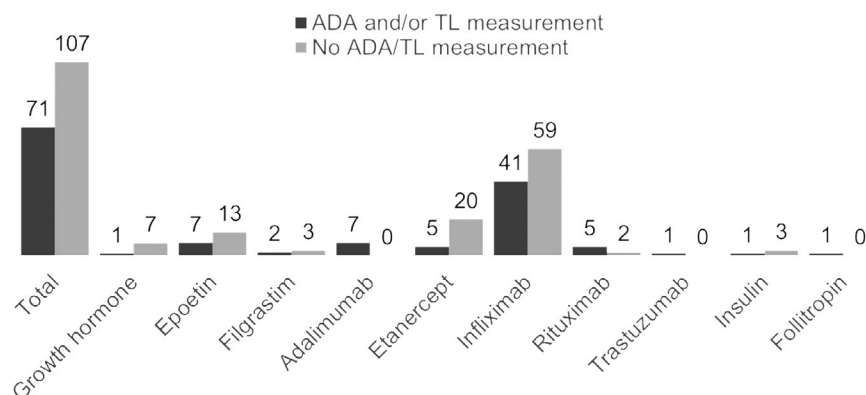
Seven biosimilars (representing four unique products) of filgrastim (RP Neupogen) have been approved in the EU (i.e., Zarzio/Filgrastim Hexal, Tevagrastim/Ratiograstim, Nivestim, and Grastofil/Accofil).<sup>2</sup>

Five studies included a switch from the filgrastim RP to a filgrastim biosimilar (Table S5 in the online **Supplementary Information**). Three of these consisted of a randomized phase III trial design, of which one study included a multiple switch.<sup>31,32,23</sup> The other two studies consisted of a retrospective chart/database review. Overall, none of these studies indicated safety or efficacy issues related to switching. In all these studies, patients were treated with chemotherapy.

### SWITCH STUDIES FOR INSULIN GLARGINE/LISPRO

Two unique biosimilars of insulin glargine (RP Lantus) are approved in the EU (i.e., Abasaglar and Semglee).<sup>2</sup> Insulin lispro Sanofi is an EU-approved biosimilar of the insulin lispro RP (Humalog).<sup>2</sup>

Four studies incorporating a switch between the insulin glargine RP and a biosimilar were identified (Table S6 in the online **Supplementary Information**). One of these studies, based on a retrospective chart review, indicated an increase in insulin dosage by 2.4 units after switching 24 patients to the



**Figure 3** Number of studies with ADA and/or trough level measurements. ADA, antidrug antibody; TL, trough level.

biosimilar.<sup>33</sup> The results of another retrospective chart review, of 73 patients switched from Basalin to Lantus showed further reductions in blood glucose, although the insulin glargine dose did not increase.<sup>34</sup> The hypoglycemia incidence was low during both Basalin and Lantus treatment (2.4% vs. 1.2%, respectively), with no cases of severe hypoglycemia. Authors concluded that further studies are needed to verify these findings.<sup>34</sup> Basalin is not approved in the EU or in the United States, thus, not to be considered a true biosimilar evaluated by a stringent regulatory framework. A lack of true biosimilarity could, thus, potentially explain the observed pre- and post switch differences. The retrospective design poses further a limitation to the interpretation of the results. No insulin lispro switch studies were identified.

### SWITCH STUDIES FOR ANTI-TNFS

The study parameters and results of the RCT and open-label switch studies for infliximab, adalimumab, and etanercept are shown in **Table 2**. A complete overview of all the anti-TNF switch studies can be found in **Tables S7–S9** in the online **Supplementary Information**.

#### Infliximab

Four biosimilars (representing three unique products) of infliximab (RP Remicade) have been EU-approved (i.e., Remsima/Inflectra, Flixabi, and Zessly).<sup>2</sup> One hundred studies incorporating a switch between the RP and one of its biosimilars have been identified. The study parameters and results of the switch studies for infliximab can be consulted in **Table S7** in the online **Supplementary Information**.

#### Results of RCTs and extension trials investigating the switch from the infliximab RP to a biosimilar

Most RCTs investigating switching from the infliximab RP to one of its biosimilars incorporated a switch after the assessment of the primary trial end point in the main clinical trial (i.e., in an extension trial). Extension studies of the pivotal PLANETAS and PLANETRA trials, investigating the switch from the infliximab RP to CT-P13 (Remsima/Inflectra) in patients with rheumatoid arthritis (RA) and ankylosing spondylitis respectively, showed no reduced efficacy nor an increase in adverse events (AEs) between the maintenance and the switch groups.<sup>35,36</sup> However, during the

second year of the PLANETAS extension study, the incidence of more than one treatment-emergent adverse events (TEAEs) was 48.9% vs. 71.4% patients in the maintenance CT-P13 and the RP-CT-P13 switch group, respectively.<sup>36</sup> ADA incidence and hypersensitivity reactions observed in both extension trials (PLANETRA and PLANETAS) did not significantly differ between maintenance and switch group.<sup>35,36</sup> Further, a phase III double-blind RCT investigating the single switch from infliximab RP to SB2 (Flixabi) has been conducted in patients with RA (94 patients switched).<sup>37</sup> The efficacy, safety, and immunogenicity profiles were reported to remain comparable between groups up to the end of 24 weeks of follow-up, indicating that there were no TEAEs or clinically relevant differences after switching from the RP to SB2.<sup>37</sup> The landmark NOR-SWITCH trial, supported by the Norwegian government, is an independent randomized, double-blind, noninferiority (NI) study with 52 weeks of follow-up.<sup>24</sup> The NOR-SWITCH trial aimed to evaluate maintenance of efficacy and the monitoring of AEs in patients after the switch from the infliximab RP to CT-P13 in comparison with the efficacy and AEs in patients under continued treatment with the RP. Patients across the six therapeutic indications of infliximab were included (i.e., patients with RA, spondyloarthritis, psoriatic arthritis, chronic plaque psoriasis, Crohn's disease (CD), and ulcerative colitis (UC)). The primary end point of the study was disease worsening (determined by worsening in disease-specific composite measures or a consensus about disease worsening between the investigator and the patient, which lead to a major change in the treatment). The NI margin was set at 15% at 52 weeks, assuming 30% disease worsening in each group. Almost 500 adult patients on stable treatment with the RP for at least 6 months were 1:1 randomized to switch to CT-P13 or to continue treatment with the RP. Disease worsening occurred in 26% of patients in the RP group and in 30% of patients in the CT-P13 group. The lower limit of the 95% confidence interval of the adjusted risk difference fell within the predefined NI margin of 15% (−4.4%; 95% CI −12.7 to 3.9), showing that switching from the RP to CT-P13 was not inferior to continued treatment with the RP. Further, the frequency of serious AEs, overall AEs, and AEs leading to discontinuation was similar between groups. Serum trough concentrations and the incidence of ADAs were also similar between groups. A drawback of this study is the fact that it was not powered to show NI in



the individual therapeutic indications.<sup>24</sup> Patients who completed the 12-month treatment were asked to enter in an open-label follow-up study in which all patients received CT-P13 for 26 weeks. The extension study did not show any difference between patients who maintained CT-P13 compared with patients who switched from the RP to CT-P13.<sup>38</sup> Further, the single switch from the infliximab RP to BOW015 was investigated in an open-label extension phase III trial in patients with RA.<sup>39</sup> The impact of a single switch from the RP to PF-06438179/GP1111 (Zessly) was investigated in an RCT phase III trial<sup>40</sup> and the single switch from RP to CT-P13 was investigated in an open-label extension phase I/II trial<sup>41</sup> and in a RCT phase III trial.<sup>42</sup> Overall, the switch did not negatively affect efficacy, safety, or immunogenicity outcomes in these studies.

### Real-world clinical studies investigating the switch from the infliximab RP to a biosimilar

Several studies (91/100) aimed to collect real-world data about the switch from the infliximab RP to one of its biosimilars, mostly for CT-P13 (first approved infliximab biosimilar). An overview of the study design and results of these studies is available in **Table S7** in the online **Supplementary Information**. A study based on the data from the DANBIO registry reported outcomes of a systematic, nationwide switch from the infliximab RP to CT-P13 of Danish patients with RA, spondyloarthritis, and psoriatic arthritis under infliximab treatment.<sup>43</sup> Investigators reported that the disease activities were similar 3 months pre- and post switch. After 1 year of follow-up, ~84% of patients were still under CT-P13 treatment, which was lower than in the NOR-SWITCH trial (96%). Authors indicated that this difference could be explained by the real-world setting of the study. The 1-year retention rate was slightly lower (3.4%) compared with patients treated with the RP in a historic cohort.<sup>43</sup>

Some infliximab switch studies reported a difference in efficacy, safety, immunogenicity, retention rate, or product dosage before and after switching or between the switch and maintenance group in their final conclusion.<sup>44–48</sup> Multiple studies reported a higher number of discontinued treatment, mainly driven by worsening in patient-reported outcomes, without changes in objective parameters (e.g., in TL, ADAs, and C reactive protein). Mostly, authors concluded that this was probably driven by nocebo effects (i.e., patients' negative expectations leading to experienced AEs or a perceived decrease in response<sup>49</sup>).<sup>44–47</sup>

### Adalimumab

Eight biosimilars (representing five unique products) of adalimumab (RP Humira), have been approved in the EU (i.e., Imraldi, Solymbic/Amgevita, Halimatoz/Hefiya/Hyrimoz, Cyltezo, and Hulio).<sup>2</sup> Seven switch studies from the RP to one of its biosimilars were identified (**Table S8** in the online **Supplementary Information**). These are all double-blind or open-label extension studies of phase III trials as part of the biosimilar development program. Two studies investigated switching from the RP to ABP 501 (Amgevita/Solymbic) in two different patient settings (RA and plaque psoriasis).<sup>50,51</sup> The trial in RA was a phase III open-label extension trial,

incorporating a single switch from the RP to ABP 501 in 237 patients with a follow-up of 46 weeks.<sup>50</sup> The trial by Papp and colleagues investigated a single switch from the RP to ABP 501 in 77 patients with moderate to severe plaque psoriasis, during a phase III RCT.<sup>51</sup> Data from both trials indicated that safety, including immunogenicity, was similar among groups after a single switch.<sup>50,51</sup> One phase III RCT trial investigated the single switch from the RP to SB5 (Imraldi) in 125 patients with RA. Efficacy, safety, and immunogenicity profiles were reported to be comparable between groups. It was stated that no TEAEs or clinically relevant immunogenicity arose by switching.<sup>52</sup> The trial by Blauvelt and colleagues consisted of a sequence of four switches (multiple switch design; switch at week 17, 23, 29, and 35) between the RP and GP2017 (126 patients switched, 34 weeks follow-up after initial switch at week 17). Efficacy, safety, and immunogenicity were reported to be similar among the switch and nonswitch groups.<sup>19</sup> A randomized open-label extension study investigated the impact of a second switch at week 48, after the first switch at week 24 during the double-blinded part of the study, between the RP and FKB327 in patients with RA. The interim results suggest that safety, efficacy, and immunogenicity were comparable between the maintenance and switch groups.<sup>20</sup> Further, for both CHS-1420 and BI695501, a randomized double-blind RCT investigated a single switch from the RP. Overall, no efficacy, safety, or immunogenicity issues were reported.<sup>53,54</sup>

### Etanercept

Benepali and Erelzi are two unique EU-approved biosimilar versions of etanercept (RP Enbrel).<sup>2</sup> In total, 25 etanercept biosimilar switch studies have been identified. Five of these consist of a double-blind or open-label RCT of which four were conducted in rheumatology indications.<sup>55–58</sup> The other study consisted of a multiple switch double-blind RCT (EGALITY) investigating repeated switching between the etanercept RP and GP2015 in patients with plaque psoriasis.<sup>21</sup> Patients were switched at week 12, 18, 24, and 30 and followed up to 52 weeks. It was concluded that the repeated switches between the RP and GP2015 had no negative impact on safety or immunogenicity outcomes.<sup>21</sup> Of 20 RWE studies, 18 were conducted in rheumatology and 2 in dermatology. A multiple switch was performed between the RP and SB4 with patients with rheumatic disease in clinical practice, switching from RP to SB4 and back again after approximately a year and one half.<sup>22</sup> It was reported that the multiple switch did not negatively impact the disease activity. However, a high proportion of patients discontinued SB4 after the first switch. The authors attributed this to nocebo effects, as no worsening in disease activity measures was observed.<sup>22</sup> In a single switch study from etanercept RP to SB4 in patients with rheumatic disease, 39% of patients experienced side effects.<sup>59</sup> The authors underlined the need to improve the patients' experience of switching as a way to decrease side effects.<sup>59</sup> This need was echoed in a single switch from etanercept RP to SB4 in patients with rheumatic disease in a single center in France.<sup>60</sup> Approximately 17% of patients discontinued the biosimilar, whereas no objective parameter concluded a lower efficacy or a

decreased safety profile. The authors suggested that this could be explained by the open study design (i.e., patients were aware of the switch).<sup>60</sup> The study parameters and results of the switch studies for etanercept can be consulted in **Table S9** in the online **Supplementary Information**.

### SWITCH STUDIES FOR FOLLITROPIN ALFA

Two biosimilars (representing two unique products) of follitropin alfa (RP GONAL-f) have been authorized in the EU (i.e., Ovaleap and Bemfola).<sup>2</sup> One open-label extension phase III single switch study from follitropin alfa RP (GONAL-f) to Ovaleap has been reported, which can be consulted in **Table 2** or **Table S10** in the online **Supplementary Information**. The study results were overall in support of the safety and efficacy of the switch.<sup>61</sup>

### SWITCH STUDIES FOR LOW-MOLECULAR-WEIGHT HEPARINS

Two biosimilars (representing one unique product) of enoxaparin (RP Clexane) have been authorized in the EU (i.e., Inhixa and Thorinane).<sup>2</sup> No switch studies between the RP of enoxaparin and an enoxaparin biosimilar have been identified.

### SWITCH STUDIES FOR MONOCLONAL ANTIBODIES IN ONCOLOGY

The study parameters and results of the RCTs and open label switch studies for rituximab and trastuzumab are shown in **Table 2**. A complete overview of all rituximab and trastuzumab biosimilar switch studies is shown in **Table S11** in the online **Supplementary Information**.

#### Rituximab

Six biosimilars (representing two unique products) of rituximab (RP Mabthera) have been approved in the EU (i.e., Truxima/Ritemvia/Blitzima/Rituzena (CT-P10), and Riximyo/Rixathon (GP2013)).<sup>2</sup> Seven switch studies have been identified. Five studies were conducted in the scope of the clinical biosimilar development (i.e., the single partial crossover switch to BCD-020<sup>62</sup>; a Russian product, not approved in the EU or the United States, thus not to be considered a true biosimilar evaluated by a stringent regulatory framework), an open-label extension phase I study for CT-P10,<sup>63</sup> an open-label extension phase III study for CT-P10,<sup>64</sup> a double-blind RCT for GP2013,<sup>65</sup> and a randomized extension phase I study for PF-05280586.<sup>66</sup> All studies were performed in patients with RA. None of these studies detected safety, efficacy, or immunogenicity issues related to switching. In addition, results of two RWE rituximab switch studies were reported, of which one was conducted in non-Hodgkin's B cell lymphoma and one in RA.<sup>67,68</sup> The study of Nisar *et al.* switched 29 patients with RA to CT-P10.<sup>68</sup> It was reported in abstract that 20% of these patients had severe serum sickness with LOE and loss of confidence in the treatment. Authors concluded that they support routine switching to the rituximab biosimilar, however, close monitoring needs to be applied.<sup>68</sup>

#### Trastuzumab

Five unique biosimilars of trastuzumab (RP Herceptin) have been approved in the EU: Herzuma, Kanjinti, Ogivri, Ontruzant, and

Trazimera.<sup>2</sup> For one biosimilar (Kanjinti), a single switch was incorporated during the phase III trial in early breast cancer patients.<sup>69</sup> Efficacy, safety, and immunogenicity was reported to be comparable between the maintenance and switch group.<sup>69</sup> No RWE studies were identified.

### CURRENT SWITCH EVIDENCE – LEARNINGS AND CONSIDERATIONS

This paper provides a systematic overview and a critical insight in the currently available evidence about switching from a biological RP to its biosimilar(s).

Several reviews of switching studies from biological RPs to biosimilars have been published. The first review, in 2012 by Ebbers and colleagues, investigated switching for erythropoietins, rhGHs, and granulocyte colony stimulating agents,<sup>14</sup> products for which, at that time, a biosimilar was approved. Since then, many other biosimilars, for different RPs across several therapeutic classes, have been approved, including the more complex mAb biosimilars.<sup>2</sup> Further, other reviews have been conducted but these mostly focussed on one specific product class or therapeutic area.<sup>17,70,71</sup> Two other systematic literature reviews (McKinnon and Cohen<sup>72,73</sup>) have been published that included switch studies derived from multiple product classes and disease areas. Switch studies were included until June of 2017 in these reviews. Although both reviews, with the exemption of some data points (e.g., the paper of McKinnon excluded studies in which < 20 patients were switched), include similar data, the conclusion of the authors on the safety of switching was divergent.<sup>72,73</sup> Unsurprisingly, as the topic of switching is heavily debated, and the heterogeneity of study designs leaves some room for interpretation. Cohen and colleagues concluded that the body of evidence provides reassurance that switching is not associated with immunogenicity-related safety concerns or decreased efficacy.<sup>73</sup> The review by McKinnon and colleagues concluded that evidence gaps remain around the safety of switching, underlining the need for more robust studies.<sup>72</sup>

This paper aims to provide a systematic and exhaustive review of all switch studies between biological RPs and their respective biosimilars, and this across therapeutic classes and products for which the European Commission (EC) has approved a biosimilar, updating and adding to the existing literature studies. This review provides an exhaustive overview of existing switch studies from biological RPs to biosimilars up to June 2018.

This systematic literature review applied a holistic approach, meaning every study describing a switch from a RP to a biosimilar was included. This was done in an effort to give a complete and unselected/unbiased overview of the existing studies. This can be seen as a strength but also as a limitation of the review, as regardless of the sometimes very limited sample size or incomplete methodology and its associated low(er) level of evidence, studies were included. Further, studies that only reported data in abstract and/or in poster were included as well. This to capture the most recent and most complete data about switching as many data are recent and still emerging. Data from abstracts and posters should be considered as preliminary until published in full-text in a peer-reviewed journal. A major limitation of this study was the heterogeneous

character of the individual studies, limiting the comparability between studies and making a formal meta-analysis impossible. Most of the studies and data were descriptive in nature. Only a few studies, mostly (extension) clinical studies in the development program of a biosimilar, were powered or designed to detect differences in efficacy. Other limitations include potential publication bias of individual switch studies.

### THE DESIGN OF SWITCH STUDIES AND THEIR QUALITY

Based on the currently available data, there are no robust data that indicate that switching from an RP to its biosimilar leads to major safety issues. However, the design of many studies is not sufficiently sensitive or not methodologically robust enough to identify and, thus, exclude differences in the occurrence of rare safety events or differences in efficacy.

LOE during maintenance treatment is quite common for certain therapeutic products and disease fields. For example, between 23% and 46% of patients treated with an anti-TNF in inflammatory bowel disease (IBD) loses response to treatment over time.<sup>74</sup> Juillerat and colleagues identified a dropout rate of 18% during the first year of treatment, followed by 8% and 10% during years 2 and 3 for patients with IBD treated with infliximab.<sup>75</sup> In the case of an experienced or observed decrease or loss in response during a single arm switch study, it is difficult to determine if this is due to (i) the mere “normal” decrease in treatment response over time, (ii) due to nocebo effects of the patient (experienced inefficacy or decreased efficacy), or (iii) due to an hypothesized increased immunogenicity. The evidence derived from single arm studies is thus limited. The use of objective end points, such as the measurement of ADAs or TLs, can partially address the interpretative limitation of single arm studies in case of identified efficacy or safety signals. The same argument can be made for registries. Registries, although informative of nature, can be difficult to interpret as they lack such a comparator arm and may not be able to adjust for all confounding variables.

Not only studies without a parallel arm have limitations for the interpretation of data, well-designed clinical trials can also be insufficiently sensitive to detect small differences in efficacy.<sup>76</sup> Louis and colleagues investigated the risk of relapse of patients with CD in prolonged remission after the discontinuation of infliximab treatment.<sup>76</sup> After a follow-up period of 28 months, more than half of the patients were still in remission. The 1-year relapse rate was  $43.9\% \pm 5.0\%$ .<sup>76</sup> A potential decrease in response after switching could, thus, potentially go undetected in some cases due to sustained remission of treatment on the RP in some patients. Further, most switch trials have a relatively short follow-up period, mostly too short to identify rare immunological events. Further, the sample size of the identified switch studies and RCTs was mostly too small to identify rare AEs.

The bulk of the switch data in the real-world setting consists of monitored switches from the infliximab RP to CT-P13, explained by the fact that CT-P13 was the first infliximab biosimilar, and mAb biosimilar in general, to be introduced on the market. Most of these studies were conducted in IBD. This could be interpreted as an effort of individual hospitals and pharmaceutical companies to gather clinical evidence about the use of infliximab biosimilars

in gastroenterology, given that the product received approval for CD and UC based on the principle of extrapolation of indications.

The body of identified switch studies is heterogeneous in its design, and, by consequence, in the quality of the generated evidence, and cannot exclude every potential risk. On the one hand, the gathered data may provide a general indication that switching seems not to be associated with major efficacy, safety, or immunogenicity issues. On the other hand, findings with respect to switching should be product-specifically and disease-specifically interpreted and cannot be generalized to other products or other diseases, given different immunological complexities of the different products, different disease states, and different concomitant treatments.

### IMMUNOGENICITY REPORTING

The increase in immunogenicity is one of the main voiced concerns surrounding switching from a biological RP to a biosimilar (or *vice versa*). Immunogenicity is evaluated in the development of every biosimilar, as per regulatory requirements.<sup>77</sup> Further, the safety of biosimilars is monitored postmarketing by regulatory authorities, as is the case for biological medicines in general.<sup>10</sup>

ADA determination, however, is not common in clinical practice for many biologics (as also shown by the relatively low level of ADA reporting in the real-world switch studies in this review). Taken into account that, depending on the product or the disease state, the occurrence of ADAs (for example, due to their transient nature) not always translates in a negative clinical outcome, such as the incidence of AEs or LOE, the measurement of TLs may be useful to assess the impact of immunogenicity on clinical outcomes. The measurement of ADAs and/or TLs could provide an objective measurement to help clarify the cause of unexpected AEs or a decreased treatment response in the real-world setting (without any comparator arm).

Biological medicines, such as infliximab and rituximab, are often concomitantly used with methotrexate, which can limit a potential immunogenic response. This should be taken into account when extrapolating switch findings to other disease indications in the absence of such a concomitant treatment.

### CROSS-REACTIVITY OF ANTIDRUG ANTIBODIES BETWEEN RPS AND BIOSIMILARS

Several studies have investigated the immunogenic profile of the infliximab RP and one of its biosimilars CT-P13 (Remsima/Inflectra) and the cross-reactivity of ADAs between both products.<sup>77,78–80</sup> These studies provided similar results in support of the immunogenic similarity between the infliximab RP and CT-P13 in IBD<sup>80,78</sup> or rheumatic diseases.<sup>77,79</sup> It was shown that ADAs against the RP recognized and reacted to the biosimilar in a similar way, indicating that these products share similar immunodominant epitopes. Additional epitopes (e.g., due to differences in the glycosylation pattern, impurities, or aggregations) may not be excluded, but data suggest that the epitopes that are involved in the immune response to the RP are also present for CT-P13.<sup>7</sup> Further, the regulatory quality standards applied for biosimilars preclude meaningful impurities or aggregations. It is obvious that patients showing an immunogenic response under treatment with



the RP (or biosimilar) should not be switched to the biosimilar (or RP), as the existing ADAs will cross-react with both versions. Likewise, ADA-negative patients under treatment with the RP are not expected to assert an immune response to the biosimilar when switched.<sup>80</sup>

### ADDRESSING THE QUESTION OF SWITCHING IN EUROPE

Different from the FDA in the United States, there is no regulatory pathway considering a designation of interchangeability in Europe. Further, there is no official position of the EMA about switching, interchangeability, or substitution, as this falls within the responsibilities of the individual member states. The information guide for HCPs, prepared jointly by the EMA and the EC, indicates that “there is no reason to believe that harmful immunogenicity should be expected after switching between highly similar biological medicines,”<sup>10</sup> referring to an article by a group of European regulators and members of the Biosimilar Medicinal Products Working Party.<sup>81</sup> This group of regulators argues that switching patients from an RP to a biosimilar or *vice versa* can be considered safe, as there is, in their opinion, no reason to believe that the immune system would react differently to the biosimilar compared with the RP, given the fact that they are highly similar.<sup>81</sup> It is concluded that the demonstration of biosimilarity, together with adequate PMS, sufficiently and realistically ensures interchangeability of biosimilars in the EU.<sup>81</sup> Increasingly, guidance about the use of biosimilars in practice and switching is provided by national competent authorities and professional HCP organizations.<sup>15</sup> Several national regulators indicate that switching from a RP to a biosimilar is deemed appropriate, provided that it is done under the supervision of the prescriber, the patient is properly informed, the patient is clinically followed up, and traceability of the products is ensured.<sup>15</sup> Despite an increase in guidelines among certain authorities and organizations, the confidence among many stakeholders remains low and continues to lead to questions. Harmonisation of (national) regulatory guidance and/or scientific recommendations on the use of biosimilars and switching may aid the decision making of HCPs and other decision makers.

### DISCONTINUATION RATES AND THE NOCEBO EFFECT

In several studies,<sup>44–48</sup> authors concluded that patients experienced subjective AEs or LOE, potentially explaining the high discontinuation rate and the need to switch back to the RP. The experienced AEs or LOE were not linked to objective safety signals and investigators ascribed this to attribution or nocebo effects (i.e., patients’ negative expectations leading to experienced AEs or a perceived decrease in response).<sup>49</sup>

Several studies investigating the perspectives of stakeholders identified uncertainty among patients and HCPs about biosimilars and the act of switching from an RP to a biosimilar.<sup>5,6</sup> The potential nocebo effect upon switching highlights the importance of a good knowledge and understanding among physicians and patients about biosimilars. The information provided to patients may play a role in the perceived outcome of the treatment. Well-informed HCPs should inform patients about the product they receive in an evidence-based manner. The nocebo effects further

highlight the importance of shared, evidence-based decision making between the physician and the patient. Strategies mitigating the nocebo effect may improve patient outcomes and discontinuation rates.<sup>49</sup>

### FURTHER CONSIDERATIONS: MULTIPLE SWITCHING, SWITCHING BETWEEN BIOSIMILARS OF THE SAME REFERENCE PRODUCT, AND PRODUCT TRACEABILITY

Until now, a limited number of studies report about multiple switching.<sup>18–23</sup> Overall, no clinically meaningful differences in efficacy, safety, or immunogenicity were reported in the available multiple switch studies. The question about multiple switching among HCPs is increasingly raised, indicating the need for information in this field. Following the FDA interchangeability guidance,<sup>13</sup> multiple switch studies evaluating two or more alternating exposures may emerge in the future. Because multiple, independently developed biosimilars of the same RP have been approved and are on the market, switching between biosimilars of the same RP is a possibility as well. However, not every biosimilar of the same RP is a distinct product. Indeed, some biosimilars are licensed under different brand names but contain exactly the same product (e.g., Remsima and Inflectra contain both the active substance CT-P13, and Blitzima, Ritemvia, Rituzena, and Truxima contain CT-P10). So far, no clinical data about switching between biosimilars of the same RP were identified.

To ensure adequate product traceability, it is of importance to document the specific biological product that is prescribed, including brand name, INN, and batch number when prescribing biologicals or when reporting any AEs. Postmarketing pharmacovigilance remains key for both RPs and biosimilars to track ongoing safety and immunogenicity and detect potential safety signals. PMS is particularly important to identify rare immunological events that can only be detected after a long follow-up period in large patient numbers. To ensure an optimal use and value of registries, brand names and batch numbers need to be included to correctly identify the medicine if any product-specific efficacy, safety, or immunogenicity concerns should arise.<sup>10</sup>

### RESIDUAL UNCERTAINTY

It has been argued that switching could lead to increased immunogenicity, due to potential differences in epitopes between the biosimilar and the RP. Relevant differences in this regard, such as quality differences in terms of high-molecular-weight aggregates or impurities, would, however, be excluded by the robust regulatory evaluation of biosimilars (i.e., such differences would preclude biosimilar approval).

The scientific principles underpinning the biosimilarity exercise are, in fact, based on the comparability concept, a well-established scientific principle, which is used to evaluate the differences of a biological product before and after a manufacturing change (biologicals frequently undergo manufacturing changes after approval<sup>82</sup>).<sup>81,83,84</sup> Demonstrating comparability ensures that the products pre- and post manufacturing change are highly similar and allows regulators to conclude that any observed differences have no adverse impact on efficacy or safety of the product. Demonstrating biosimilarity generally requires a more comprehensive comparison than manufacturing changes. The latter rarely require clinical data,

but for major changes, such as a change of cell-line, large scale clinical studies may be required.<sup>81</sup> Overall, the extensive experience gathered in regulating manufacturing changes of reference products has provided assurance to regulators about the risks associated with switching from one highly similar version of a biological to another.<sup>81</sup>

Although the switch studies presented in this review cannot exclude every potential risk associated with switching from a RP to a biosimilar, as clinical studies are variable and insensitive to assess the impact of minute differences, they do not corroborate the voiced concerns of increased immunogenicity due to switching. Therefore, discouraging a single switch from a RP to a biosimilar is deemed disproportional compared with the residual uncertainty associated with such a switch. Further, residual uncertainty, to a certain extent inherently associated with the use of any biological medicine or any medicine in general, can never be fully excluded. The current body of switch data, together with the robust biosimilar approval pathway, however, helps to limit the residual uncertainty to an acceptable level.

## CONCLUSION

Based on the currently available switch data of over 170 studies, there are no robust data that indicate that switching from a reference biological to a biosimilar is related to any major efficacy, safety, or immunogenicity issues. The switch studies cover different molecules across different therapeutic classes. Most of the currently available data refer to switching for anti-TNFs and, more specifically, from the infliximab RP to CT-P13 (Remsima/Inflectra). Due to a small sample size and generally short follow-up period, most of the identified studies are, however, insufficiently sensitive to detect and, thus, exclude rare AEs. Data on multiple switching and switching between biosimilars for the same RP is so far scarce or not present. Although the decision to switch must be made on an individual and product-specific level, this review on switching between biological RPs and biosimilars supports that, for the products studied, a single switch is not intrinsically linked to an increase in immunogenicity, safety, or efficacy issues. Any decision to switch should involve the prescriber and attention must be paid to the mitigation of a potential nocebo effect.

## SUPPORTING INFORMATION

Supplementary information accompanies this paper on the *Clinical Pharmacology & Therapeutics* website ([www.cpt-journal.com](http://www.cpt-journal.com)).

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biosimilar research sponsored by Hospira (now Pfizer). S.S. was involved in a stakeholder roundtable on biosimilars sponsored by Amgen, Pfizer, and MSD, and has participated in an advisory board meeting for Pfizer. S.S. works with Pfizer to carry out biosimilar research. A.G.V. is involved in consulting, advisory work, and speaking engagements for a number of companies (i.e., AbbVie, Amgen, Biogen, EGA, Pfizer/Hospira, Mundipharma, Roche, and Sandoz). He has no personal benefit from these activities; any compensation is paid to his employer. P.D. participated at advisory board meetings for AbbVie, Amgen Hospira, and Samsung-Bioepis, and is on the Speakers' Bureau of AbbVie, Celltrion, Hospira, Merck Serono, and Roche. At the time of study initiation and during the major part of the study, H.C.E. was employed at the Dutch Medicines Evaluation Board (MEB). The views expressed in this paper are the personal views of the authors and may not be understood or quoted as being made on behalf of or reflecting the position of the MEB. H.E. is currently employed by Biogen, the Netherlands B.V. L.B. declared no competing interests for this work. All authors declare that the research was conducted in the absence of any commercial or financial relationship that could be perceived as a potential conflict of interest.

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