Dermatol Ther (Heidelb) (2018) 8:173–194
https://doi.org/10.1007/s13555-018-0230-9

REVIEW

Biosimilar Drugs for Psoriasis: Principles, Present, and Near Future

Jose-Manuel Carrascosa · Ira Jacobs · Danielle Petersel · Robert Strohal

Received: November 15, 2017 / Published online: March 16, 2018

ABSTRACT

Psoriasis is a chronic, inflammatory, lifelong disease with a high prevalence (afflicting approximately 1–5% of the population worldwide) and is associated with significant morbidity. The introduction of biologic therapies has improved the management of this disease. Multiple biologic medicines that block cytokine signaling, including tumor necrosis factor (TNF) antagonists (adalimumab, etanercept, and infliximab) and inhibitors of interleukin (IL)-17 (brodalumab, ixekizumab, and secukinumab), IL-23 (guselkumab), or IL-12/23 (ustekinumab), are approved for the treatment of psoriasis. Despite the clinical benefits associated with use of biologics in psoriasis, many patients are not treated with biologic therapy, and access to treatment may be limited for various reasons, such as high treatment costs. Patents for many biologics have expired or will soon expire, and biosimilar versions of these agents are available or in development. A biosimilar is a biological product that is highly similar to an approved biologic (i.e., originator or reference) product, and has no clinically meaningful differences in safety, purity, or potency when compared with the reference product. Biosimilars may offer less expensive treatment options for patients with psoriasis; they also may increase access to and address problems with underutilization of biologic therapy. Biosimilar development and approval follows a well-regulated process in many countries, with guidelines developed by the European Medicines Agency, US Food and Drug Administration, and World Health Organization. Currently, several anti-TNF biosimilars are available for use in patients with psoriasis, and other monoclonal antibodies are in development. This review provides dermatologists and those who treat and/or manage psoriasis with a working knowledge of the scientific principles of biosimilar development and approval. It also examines real-world experience with biosimilars available for or used in dermatology that will enable physicians to make informed treatment decisions for their patients with psoriasis.

Funding: Pfizer Inc.

Enhanced content To view enhanced content for this article go to https://doi.org/10.6084/m9.figshare.5886511.

J.-M. Carrascosa
Hospital Universitari Germans Trias I Pujol, Universitat Autònoma de Barcelona, Badalona, Barcelona, Spain

I. Jacobs (✉) · D. Petersel
Pfizer Inc, New York, NY, USA
e-mail: ira.jacobs@pfizer.com

R. Strohal
Federal Academic Teaching Hospital of Feldkirch, Feldkirch, Austria

Keywords: Biologics; Biosimilars; Interchangeability; Psoriasis; Safety; Switching

INTRODUCTION

Psoriasis is a chronic, inflammatory disease that affects between 1% and 5% of the population worldwide [1]. Psoriasis is associated with significant morbidity and imparts a negative impact on health-related quality of life similar to the impact of depression, diabetes mellitus, and congestive heart failure [1, 2]. Indeed, patients with psoriasis often experience social stigmatization, pain, discomfort, physical disability, psychological distress, and financial hardship [3]. Psoriasis is also associated with an increased prevalence of comorbid diseases and risk factors, such as obesity, metabolic syndrome, cardiovascular disease, psoriatic arthritis (PsA), and autoimmune disease [4]. Furthermore, severe psoriasis is associated with an increased risk of mortality, most commonly due to cardiovascular death [5].

Psoriasis is a lifelong disease, and long-term treatment is necessary to manage the debilitating and serious consequences of this condition. Biologic therapies have changed the way psoriasis is managed, offering systemic treatments that target key mechanisms of disease pathogenesis. Biologics approved for the treatment of psoriasis include tumor necrosis factor (TNF) antagonists (adalimumab, etanercept, and infliximab), interleukin (IL)-17 antagonists (brodalumab, ixekizumab, and secukinumab), and inhibitors of IL-23 (guselkumab) or IL-12/23 (ustekinumab) [6–19].

Patents for many biologics are expiring [20], thus granting others besides the patentees the ability to make or sell the off-patented products. This has led to the development and approval of biosimilars. A biosimilar is a biologic product that is highly similar to an approved biologic (i.e., originator or reference) product, "notwithstanding minor differences in clinically inactive components," and has no clinically meaningful differences in safety, purity, and potency from the reference product [21]. This review provides dermatologists and those who treat and/or manage psoriasis with a working knowledge of the scientific principles for biosimilar development. It also examines real-world experience with biosimilars that may enable physicians to make informed decisions for treatment of patients with psoriasis.

Compliance with Ethics Guidelines

This article does not involve any new studies of human or animal subjects performed by any of the authors.

CHALLENGES WITH BIOLOGIC THERAPY FOR PSORIASIS: THE ROLE OF BIOSIMILARS

Despite the benefits associated with clinical use of biologics in patients with psoriasis or PsA [18, 22–32], not all patients with these diseases receive biologic therapy [33–37]. In a 2011 National Psoriasis Foundation survey of patients with psoriasis or PsA in the USA, fewer than 30% reported receiving biologic therapies [33]. Similarly, in the 2012 Multinational Assessment of Psoriasis and Psoriatic Arthritis survey of patients, dermatologists, and rheumatologists in North America and Europe, 5–25.9% of patients with moderate-to-severe psoriasis or PsA reported receiving biologic therapies [34–36]. Physician-reported estimates of prescribing biologic therapies were higher (dermatologists, 19.6–46.9%; rheumatologists, 33.4–52.7%), but also indicated underutilization [36, 37].

Concerns regarding safety and/or tolerability and lack or loss of effectiveness were the most common reasons that patients discontinued treatment or why physicians did not initiate or continue patients' treatment with biologic therapies [33–37]. However, patients, dermatologists, and rheumatologists also reported inadequate insurance coverage and/or cost as a contributing factor [33–37]. The extent or absence of insurance coverage impacts treatment costs, and such factors can create financial barriers that limit or contribute to inequalities in access to biologic therapies. This is particularly true in regions such as Latin America where biologics used to treat moderate-to-severe psoriasis are reimbursed in some (e.g.,

Argentina, Colombia, Mexico, Venezuela) but not other (e.g., Brazil, Chile) countries [38, 39].

The percentage of patients with moderate-to-severe psoriasis worldwide who could benefit from biological therapy may increase if financial constraints were improved. Patents for adalimumab, etanercept, and infliximab have expired or will soon expire in Europe and in the USA [20]. As a result, anti-TNF biosimilars are available or in development. The European Medicines Agency (EMA) and the US Food and Drug Administration (FDA) have approved biosimilars of adalimumab [Amgevita/Solymbic and Imraldi (EMA); Amjevita (FDA) and Cyltezo (EMA and FDA)], etanercept [Benepali (EMA) and Erelzi (EMA and FDA)], and infliximab [Remsima/Inflectra and Flixabi (EMA); Inflectra, Ixifi, and Renflexis (FDA)] (Table 1) [40–59]. Additional biosimilars are under review by these regulatory agencies, and more are in research and development (Table 2) [60–63]. As a treatment option for patients with psoriasis, biosimilars may provide savings and efficiencies to healthcare systems and increase patient access to therapy, improving the problem of underutilization of biologic therapy [64–66].

REGULATORY FRAMEWORK FOR BIOSIMILAR DEVELOPMENT AND APPROVAL: A GLOBAL PERSPECTIVE

Biologic medicines include a range of products that are isolated from natural sources or manufactured using living systems. Biologics are typically 100- to 1000-fold larger than chemically synthesized drugs and have molecular structures that are not as easily characterized [67]. Many biologics are proteins developed through recombinant DNA technology. This multistep process is technically challenging, and knowledge about the development of a biologic is proprietary and confidential to the manufacturer [68]. Consequently, a biosimilar developer must use reverse-engineering manufacture to independently establish a new production process capable of delivering a drug that is highly similar to the originator [68, 69].

Variability in or changes to any step of the manufacturing process for a biologic or differences between the manufacturing processes for an originator and biosimilar can substantially impact the physicochemical and functional properties of a biologic product (Fig. 1) [68, 69]. For this reason, and because of the size and complexity of biologics, it is not possible to create an exact copy of an originator drug. Therefore, developers must demonstrate biosimilarity between the proposed biosimilar and the licensed product [21, 70–72], which means "the biological product is highly similar to the reference product notwithstanding minor differences in clinically inactive components" and that "there are no clinically meaningful differences between the biological product and the reference product in terms of safety, purity, and potency of the product" [21]. This is in contrast to regulatory approval of small-molecule generics, which only requires a demonstration of pharmaceutical equivalence and bioequivalence.

The process of biosimilar development and approval is well regulated in many countries, with guidelines developed by the EMA, FDA, Health Canada, and World Health Organization (WHO), among others [21, 70–74]. Regulatory agencies recommend using a stepwise approach to generate data that support a demonstration of biosimilarity [21, 70–72]. As a first step, guidelines recommend extensive analytical (structural and functional) assessments, beginning with a detailed analysis of the primary amino acid sequence and secondary and tertiary structure for the potential biosimilar and the originator [21, 71–74].

Additional relevant characterization studies are usually conducted to confirm similarity between the potential biosimilar and originator and may include higher-order structural analyses of dimers or other complexes, post-translational modifications, and other potential variations (e.g., deamidation and oxidation) that could impact the biologic activity of the protein [21, 72, 74]. For example, immunoglobulin (Ig) class G (IgG) therapeutic proteins are typically glycosylated, and the degree of glycosylation at the Fc (crystallizable fragment) domain affects

Table 1 Anti-TNF biosimilars approved in Europe and the USA for the treatment of patients with moderate-to-severe plaque psoriasis

Reference product, brand name (INN)	Biosimilar	Brand name (INN); year of authorization[a]		Indication(s) tested[b]	PASI (%), biosimilar product	PASI (%), reference product
		Europe	USA			
Humira (adalimumab)	ABP 501	Amgevita/Solymbic (adalimumab); 2017 [52]	Amjevita (adalimumab-atto); 2016 [49]	Moderate-to-severe plaque psoriasis; moderate-to-severe RA [58, 59]	Week 16 PASI 75: 74.4 PASI 90: 47.1	Week 16 82.7 47.4
	BI 695501	Cyltezo (adalimumab); 2017 [52]	Cyltezo (adalimumab-adbm); 2017 [51]	Moderate-to-severe active RA [53]	NA	NA
	SB5	Imraldi (adalimumab); 2017 [52]	–	Moderate-to-severe RA [57]	NA	NA
Enbrel (etanercept)	SB4	Benepali (etanercept); 2016 [52]	–	RA [41]	NA	NA
	GP2015	Erelzi (etanercept); 2017 [52]	Erelzi (etanercept-szzs); 2016 [43]	Moderate-to-severe plaque psoriasis [42]	Week 12 PASI 75: 73.4 PASI 90: NR	Week 12 75.7 NR
Remicade (infliximab)	SB2	Flixabi (infliximab); 2016 [52]	Renflexis (infliximab-abda); 2017 [50]	Moderate-to-severe RA [40]	NA	NA
	CT-P13	Inflectra/Remsima (infliximab); 2013 [52]	Inflectra (infliximab-dyyb); 2016 [46]	AS; RA [44, 45, 47, 48, 54]	NA	NA
	PF-06438179/GP1111	–[c]	Ixifi (infliximab-qbtx); 2017 [56]	RA [55]	NA	NA

AS ankylosing spondylitis, *EMA* European Medicines Agency, *FDA* US Food and Drug Administration, *INN* International Nonproprietary Name, *NA* not applicable, *NR* not reported, *PASI* Psoriasis Area and Severity Index, *RA* rheumatoid arthritis, *TNF* tumour necrosis factor

[a] Authorization by EMA or FDA

[b] Refers to comparative efficacy and safety trials of biosimilar to reference product(s)

[c] Marketing authorization application was submitted for review by EMA, May 2017 [62]

their interaction with target cells and subsequent effector functions [67, 75, 76]. IgGs lacking terminal galactose demonstrate reduced binding to complement protein C1q, resulting in reduced complement-dependent cytotoxicity [76]. By contrast, IgGs lacking the core fucose residue demonstrate enhanced binding to the Fc receptor FcγRIIIa and, therefore, show increased antibody-dependent cellular cytotoxicity [76]. The presence of high mannose or sialylated glycans can also affect IgG binding and, as a consequence, increase or decrease antibody-dependent cellular cytotoxicity and complement-dependent cytotoxicity [77]. In addition, high-mannose glycans can influence protein half-life by increasing serum clearance of IgG [75]. Furthermore, deamidation, oxidation, and other chemical modifications that promote degradation could lead to the formation of protein aggregates that exhibit little or no drug activity and increase the potential for immunogenicity [78].

Next, in vitro studies of biologic activity, and any other relevant characteristics, are conducted to confirm that the biosimilar acts on the same target or physiologic process and with similar potency as the originator [21, 71–74]. The potential impact of (even subtle) differences in structure or function between the biosimilar and originator on efficacy and safety may not be clear on the basis of analytical data alone and, therefore, must be further evaluated in nonclinical and clinical studies. Nonclinical

Table 2 Proposed anti-TNF biosimilar products in development

Reference product	Proposed biosimilar (Pharma)	Stage of development
Adalimumab	BCD-057 (Biocad)	Clinical trials (phase III in moderate-to-severe plaque psoriasis)[a]
	CHS-1420 (Coherus BioSciences Inc)	Clinical trials (phase III in moderate-to-severe plaque psoriasis)[a]
	FKB327 (Fujifilm Kyowa Kirin Biologics Co, Ltd)	Clinical trials (phase III in active RA)[a]; submitted for review by EMA, May 2017 [61]
	GP2017 (Sandoz)	Clinical trials (phase III in moderate-to-severe active RA and moderate-to-severe plaque psoriasis)[a]; submitted for review by EMA, May 2017 [62]
	LBAL (LG Life Sciences Ltd/Mochida Pharmaceutical Co, Ltd)	Clinical trials (phase III in active RA)[a]
	M923 (Momenta Pharmaceuticals Inc)	Clinical trials (phase III in moderate-to-severe plaque psoriasis)[a]
	MSB11022 (EMD Serono Research & Development Institute, Inc/Merck KGaA)	Clinical trials (phase III in moderate-to-severe plaque psoriasis, and moderate-to-severe active RA)[a]; submitted for review by EMA, December 2017 [63]
	Myl-1401A (Mylan)	Clinical trials (phase III in moderate-to-severe chronic plaque psoriasis)[a]
	ONS-3010 (Oncobiologics Ltd)	Clinical trials (phase III in moderate-to-severe plaque psoriasis)[a]
	PF-06410293 (Pfizer Inc)	Clinical trials (phase III in moderate-to-severe active RA)[a]
Etanercept	CHS-0214 (Coherus BioSciences Inc/ Daiichi Sankyo Co, Ltd/Shire)	Clinical trials (phase III in active RA and plaque psoriasis)[a]
	LBEC0101 (LG Life Sciences Ltd/ Mochida Pharmaceutical Co, Ltd)	Clinical trials (phase III in active RA)[a]; submitted for review by Japanese Medicines Regulatory Agency, Jan 2017 [60]
Infliximab	ABP 710 (Amgen)	Clinical trials (phase III in moderate-to-severe active RA)[a]
	BCD-055 (Biocad)	Clinical trials (phase III in AS, and active RA)[a]
	NI-071 (Nichi-Iko Pharmaceutical Co, Ltd)	Clinical trials (phase III in active RA)[a]

AS ankylosing spondylitis, *Pharma* pharmaceutical company, *RA* rheumatoid arthritis, *TNF* tumour necrosis factor
[a] Registered on ClinicalsTrials.gov, the International Clinical Trials Registry Platform, or the European Union Clinical Trials Register

in vivo studies include assessment of toxicokinetics and/or toxicity [21, 72, 73]. The need for and extent of in vivo animal studies will depend on "the extent of known similarities or differences" between the proposed biosimilar and originator, as determined through analytical assessments [21]. However, regulatory agencies may be moving away from requiring in vivo nonclinical evaluation because extensive physicochemical and in vitro biological

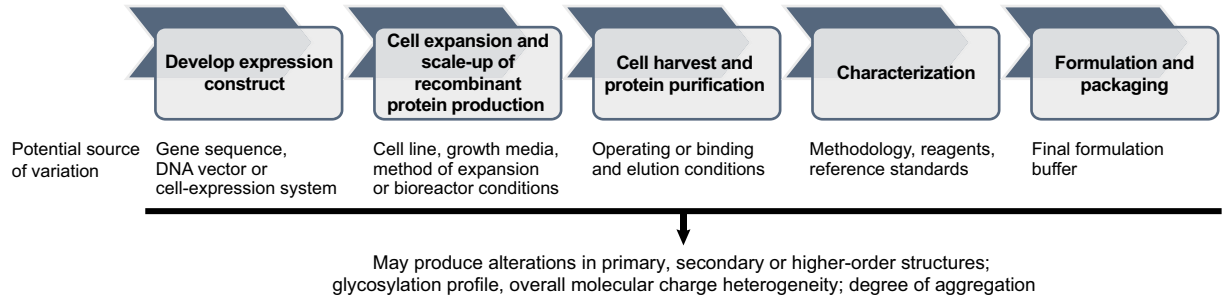

Fig. 1 Overview of biologic manufacturing process [69]. Most biologics are recombinant proteins produced through a multistep process. First, a vector containing complementary DNA for the protein of interest and a selectable marker is transferred into a suitable host cell (e.g., bacterium, mammalian cell). Next, a master cell bank is established through positive selection of transformed cells expressing the selectable marker in the presence of an antibiotic or inducing agent. A starter culture of cells is then transferred from the master cell bank to a bioreactor where, under optimal growth conditions, it can undergo large-scale expansion and recombinant protein production. Cell cultures are recovered through centrifugation, and the recombinant protein is purified from culture media through a series of chromatographic steps. The physicochemical and biological properties of the recombinant protein are extensively characterized, after which it undergoes formulation and packaging. Changes to any steps in the manufacturing process (arrows and text) can alter the safety and effectiveness of the biologic product. For example, changing the cell-expression system in which a recombinant protein is produced could alter its glycosylation patterns and, in turn, the protein's immunogenic potential [69]. Differences in a licensed originator biologic may arise over time as a result of planned changes to its manufacturing process made by the same manufacturer [68]. Accordingly, pre-change and post-change products are compared to demonstrate that any changes to the manufacturing processes have no adverse impact on the quality of the product [68]. This comparability assessment is based on extensive knowledge about the product and existing manufacturing process as well as the nature of the manufacturing change, and is typically addressed with analytical studies [68]. The comparability assessment is distinct from the biosimilarity assessment, which requires a demonstration of no clinically meaningful differences between the potential biosimilar and originator product based on extensive comparative analytical, nonclinical, and clinical assessments [68]

characterization establishes the core of biosimilarity [79].

On the basis of the totality of the evidence from analytical and nonclinical studies, a tailored clinical trial program for the potential biosimilar is designed as a final comparative evaluation to confirm that the product has similar efficacy, safety, and immunogenicity to the originator. Requirements include comparative clinical pharmacokinetics and clinical studies [21, 71–73]. The most suitable design for biosimilarity studies is an equivalence trial because its primary objective is to show that differences between treatment groups are not clinically meaningful [80]. Furthermore, guidelines recommend using a population of patients, treatment setting, and clinical endpoints that are adequately sensitive to identify any potential differences versus the originator [21, 72, 73]. Finally, biosimilarity studies are not required to demonstrate the mechanism of action, dose-finding, or clinical benefit over the current standard treatment because these were established by clinical studies conducted for the originator [72, 81].

BIOSIMILARS IN DERMATOLOGY: KEY ISSUES AND CLINICAL EXPERIENCE

Postapproval Safety Monitoring

As for most biological products, data from preapproval clinical studies of a biosimilar are usually too limited to identify all potential adverse events (AEs) [72]. In addition, preapproval clinical testing is usually insufficient to detect rare but potentially serious safety risks

because of the small or limited study populations in which the biosimilar is evaluated [21, 72, 73]. Therefore, the WHO and regulatory agencies such as the EMA and FDA recommend postapproval monitoring to evaluate the long-term safety of biosimilar products [21, 72, 73].

In general, the WHO and regulatory agencies recommend that pharmacovigilance plans consider any known or potential safety issues associated with use of the reference product and its class, correspond with plans used for the originator, and include ongoing assessment of immunogenicity [21, 72, 73]. However, regulatory agencies vary in their requirements for postapproval monitoring. For example, the EMA requires that pharmacovigilance and risk management plans are included as part of biosimilars regulatory submissions [73]. By contrast, the FDA has not yet defined a requirement for pharmacovigilance plans [21]. Rather, the agency encourages sponsors to discuss their pharmacovigilance plans with appropriate regulatory divisions as some aspects of postapproval safety monitoring are product-specific [21].

Extrapolation

Biosimilar guidelines permit extrapolation of data, allowing the approval of a biosimilar for use in an indication that was not directly studied in a comparative clinical trial with the biosimilar, but for which the originator biologic is approved [21, 70–73]. For example, biosimilars of infliximab [CT-P13 (Inflectra/Remsima), PF-06438179/GP1111 (Ixifi) and SB2 (Flixabi; Renflexis)] were studied in patients with rheumatoid arthritis (RA) and/or ankylosing spondylitis (AS) in the initial development programs [40, 44, 45, 47, 48, 54, 55], but through extrapolation have been approved by the EMA or FDA for all licensed indications of the originator, excluding those protected by data exclusivity [56, 82–86]. The comparative clinical study to assess efficacy and safety of the etanercept biosimilar GP2015 (Erelzi) was conducted in patients with chronic plaque psoriasis [42]. With the application of extrapolation, the EMA and FDA approved GP2015 for all licensed indications of the originator [43, 87]. After being evaluated in a comparative clinical study in patients with RA [41], another etanercept biosimilar, SB4 (Benepali), also was granted marketing authorization by the EMA for the full range of indications of the originator [88, 89].

Similarly, two comparative clinical studies were conducted for the adalimumab biosimilar ABP 501 (Amgevita/Solymbic; Amjevita): one in patients with moderate-to-severe psoriasis and one in patients with moderate-to-severe RA [58, 59]. Both were submitted for regulatory review, and through extrapolation, ABP 501 was approved by the EMA for all licensed indications of the originator and by the FDA for the treatment of RA, juvenile idiopathic arthritis, PsA, AS, psoriasis, adult Crohn's disease (CD), and ulcerative colitis (UC) [49, 90, 91]. Finally, the adalimumab biosimilars SB5 (Imraldi) and BI 695501 (Cyltezo) were studied in patients with moderate-to-severe RA [53, 57], but through extrapolation SB5 was approved by the EMA for all and BI 695501 was approved by the EMA and FDA for multiple indications of the originator product [51, 92, 93].

Extrapolation reduces the need for clinical studies with the biosimilar in all licensed indications of the originator product [94]. However, there must be sufficient scientific justification for extrapolation that addresses the molecular mechanism(s) of action (e.g., target receptors, binding, dose–response and pattern of molecular signalling upon target binding, and location and expression of the target/receptors) in each indication for which approval is sought; the pharmacokinetics, biodistribution, and immunogenicity of the product in different patient populations; and differences in expected toxicities in each indication and patient population [21, 71–73]. Furthermore, to be considered for extrapolation, biosimilarity to the originator product must be demonstrated using a clinical model that is sensitive to detect potential differences between the originator and the potential biosimilar [21, 71–73]. Safety and immunogenicity of the biosimilar should be sufficiently characterized, and no unique or additional safety issues should be expected for the non-studied indications [72].

Different indications have been seen as the most sensitive clinical model for

extrapolation [95]. For example, in the case of infliximab, psoriasis may be more sensitive than RA to detecting potential differences between an originator and the potential biosimilar because of its greater discriminatory ability in terms of response [e.g., placebo-adjusted difference in response is 74–82% for Psoriasis Area and Severity Index (PASI) 75 vs. 8–25% for American College of Rheumatology 20] [95]. In addition, use of concomitant methotrexate for treatment of RA could confound conclusions about potential differences in immunogenicity [95]. While these considerations are important, regulatory decisions about extrapolation are based on the totality of the evidence, including structural, physicochemical, functional, nonclinical, and clinical data, all of which must support similarity of the biosimilar to the originator [21, 72, 73].

As described, all infliximab and some adalimumab and etanercept biosimilars were approved for psoriasis on the basis of extrapolation of clinical data from studies conducted in patients with rheumatic disease. The lack of clinical data for psoriasis and other extrapolated indications could impact the use of biosimilars in clinical practice. In a survey of US speciality physicians, including dermatologists, gastroenterologists, hematologist-oncologists, medical oncologists, nephrologists, and rheumatologists, only 12.3% of respondents cited they were comfortable with the concept of extrapolation and would use a biosimilar for all approved indications [96]. However, education of physicians about biosimilars could increase their acceptance of indication extrapolation. A cross-sectional survey of dermatologists worldwide reported that physicians who were "fairly to very familiar" with biosimilars were also more comfortable in prescribing biosimilars for psoriasis if studied in a non-psoriasis indication versus physicians who were "very unfamiliar" with biosimilars [97].

Transitioning or Switching

With the availability of biosimilars, clinicians may need to consider switching between an originator product and a biosimilar. Clinical decisions about switching should take into account the possible effects of changing therapy on drug efficacy and patient safety [98]. Accordingly, physicians may rely on data from biosimilar studies in which patients transition from one treatment to another (e.g., from A to B, but not vice versa), switch once from each treatment to the other (e.g., single-switch from A to B and from B to A), or switch treatments multiple times (e.g., from A to B to A and from B to A to B) [98].

Infliximab

Three randomized controlled trials (RCTs) have compared originator infliximab (Remicade®) and the infliximab biosimilar CT-P13 (Inflectra/Remsima) in patients with rheumatic disease: the PLANETRA trial in patients with RA, the PLANETAS trial in patients with AS, and a phase I/II trial in Japanese patients with RA (Takeuchi et al.) [44, 45, 47, 48, 54]. In each trial, patients who completed the 54-week double-blind treatment phase received CT-P13 in an open-label extension (OLE) study and, therefore, provided data on single transition from originator infliximab to CT-P13 (transition group) versus continued treatment with CT-P13 (maintenance group) [99–101].

All studies demonstrated similar efficacy between transition and maintenance groups after 48 (PLANETRA and PLANETAS) or 72 (Tanaka et al.) weeks [99–101]. Furthermore, in each trial the proportion of patients with anti-drug antibodies (ADAs) was similar between transition and maintenance groups, suggesting that there is no detrimental effect of transitioning on immunogenicity: PLANETRA: 44.8% (64/143) versus 40.3% (64/159); PLANETAS: 27.4% (23/84) versus 23.3% (21/90); Tanaka et al.: 17.4% (4/23) versus 15.6% (5/32) [99–101]. The incidence of treatment-emergent AEs (TEAEs) was comparable between transition and maintenance groups in the PLANETRA [53.8% (77/143) vs. 53.5% (85/159)] and Tanaka et al. [87.9% (29/33) vs. 89.5% (34/38) at week 105] studies, but numerically higher for transition versus maintenance groups in the PLANETAS study [71.4% (60/84) vs. 48.9% (44/90)] [99–101]. However, incidence of TEAEs in both groups of the PLANETAS study was within the

range reported in historical studies of originator infliximab, and the majority of TEAEs were mild to moderate in severity [99].

A limitation of these OLE studies is that they were not designed or powered to evaluate noninferiority or equivalence of transitioning from originator infliximab to CT-P13 versus continued treatment with CT-P13 [99–101]. However, their results are complemented by data from the NOR-SWITCH study that was designed to evaluate noninferiority of transitioning from originator infliximab to CT-P13 versus continued treatment with originator infliximab. In the NOR-SWITCH trial, adult patients with psoriasis, PsA, RA, spondyloarthritis, CD, and UC on stable infliximab treatment for at least 6 months were randomized in a blinded manner to either continued treatment with originator infliximab (maintenance group, $n = 241$) or a transition to CT-P13 (transition group, $n = 241$) [102]. The incidences of TEAEs (70% vs. 68%) and ADAs (7% vs. 8%) were similar between maintenance and transition groups, respectively [102]. Among all patients, 26.2% of those in the maintenance group and 29.6% in the transition group experienced disease worsening after 52 weeks [102]. The 95% confidence interval (CI; − 12.7% to 3.9%) of the adjusted treatment difference (− 4.4%) was within the prespecified non-inferiority margin (15%) and confirmed noninferiority in efficacy between groups [102]. However, sample sizes were small (psoriasis, $n = 35$; PsA, $n = 30$; RA, $n = 77$; spondyloarthritis, $n = 91$; CD, $n = 155$; and UC, $n = 93$) and the study was not powered to demonstrate noninferiority within each indication [102]. In addition, the noninferiority margin of 15% might have been too wide to exclude all clinically important differences between treatments [102].

One RCT evaluated the safety and efficacy of switching (at week 30) from CT-P13 to originator infliximab (CT-P13 switch) and from originator infliximab to CT-P13 (INX switch; $n = 55$/group) versus continued treatment with CT-P13 (CT-P13 maintenance, $n = 56$) or originator infliximab (INX maintenance, $n = 54$) in patients with CD [103]. At week 54, Crohn's Disease Activity Index-70 response rate (CT-P13 maintenance, 78.6%; CT-P13 switch, 70.9%; INX maintenance, 70.4%; and INX switch, 76.4%) and other measures of efficacy were comparable among the treatment groups [103]. Likewise, after week 30, incidence of adverse drug reactions (CT-P13 maintenance, 5.4%; CT-P13 switch, 7.3%; INX maintenance, 11.1%; and INX switch, 9.1%) and other safety outcomes were comparable across groups [103]. The study was not powered to compare groups after switching [103]; however, the data build on other evidence that support switching patients from originator infliximab to CT-P13.

Observational studies of real-world experience with CT-P13 also provide transition data. One of the largest transition cohorts comprised 802 patients in Denmark with RA, PsA, or axial spondyloarthritis treated with originator infliximab for a median of more than 6 years [104]. All patients transitioned to CT-P13 for economic (non-medical) reasons and were monitored prospectively in the nationwide DANBIO registry for 413 (339–442) days. Disease activity and flare rates were similar in the 3 months before and after transition to CT-P13 [104]. Furthermore, preliminary data in a subgroup of patients ($n = 231$) demonstrated comparable rates of ADA-positivity before and after transitioning (56% vs. 51%) [105].

Real-world data on transitioning from originator infliximab to CT-P13 in patients with psoriasis are available from a small, single-center observational study [106]. The authors reported no changes of PASI and visual analog pain scale scores ($p > 0.05$) and no additional AEs in patients ($n = 30$) who transitioned to CT-P13 [106]. However, clinical response data after transition were not reported, and follow-up was limited [median of 23 (range 13–33) weeks] [106]. One additional study of patients in Denmark with moderate-to-severe psoriasis treated with biologics and monitored prospectively in the DERMBIO registry reported no significant difference in risk of discontinuation between patients who transitioned from originator infliximab to CT-P13 (Remsima) and those who continued originator infliximab over a 2-year period (hazard ratio 1.64, 95% CI 0.69–3.89, $p = 0.264$) [107].

Published data from other small ($n = 31$–56) or single-center studies of transition from

originator infliximab to CT-P13 in patients with rheumatic disease are generally consistent, demonstrating no apparent negative impact of transitioning on efficacy or safety [108–112]. However, varying discontinuation rates (3–28.2%) have been reported across observational studies [104, 108–112]. In addition, some studies reported patients who discontinued CT-P13 and switched back to originator infliximab [108, 110, 111]. However, in at least some cases, these patients discontinued for subjective reasons without objective deterioration of disease [108, 110, 111].

Finally, one RCT evaluated the safety and efficacy of transitioning from originator infliximab to the infliximab biosimilar SB2 (Flixabi; Renflexis) [113]. In this study, patients with moderate-to-severe RA were randomized to receive originator infliximab or SB2 during a 46-week, double-blind treatment phase. Then, patients who received originator infliximab were re-randomized at week 54 to receive either SB2 (transition group, $n = 94$) or originator infliximab (maintenance group, $n = 101$) up to week 70. Disease activity was comparable between transition and maintenance groups, as was the incidence of TEAEs (36.2% vs. 35.6%) and ADA-positivity rates (45.7% vs. 50.5%).

Etanercept

One RCT has compared originator etanercept (Enbrel®) and the etanercept biosimilar SB4 (Benepali) in patients with RA [41]. In this trial, patients who completed a 52-week, double-blind treatment period were enrolled into an OLE study, during which they received SB4 for an additional 48 weeks and, therefore, provided data on single transition from etanercept to SB4 (transition group, $n = 119$) versus continued treatment with SB4 (maintenance group, $n = 126$) [114]. Efficacy was comparable between transition and maintenance groups, as was the incidence of TEAEs (48.7% vs. 47.6%) and ADA-positivity rates (0.9% vs. 0.8%) [114]. Real-world data on transitioning from etanercept to SB4 are available from one observational study of patients in Denmark with moderate-to-severe psoriasis treated with biologics and monitored prospectively in the DERMBIO registry [107]. The authors reported no significant difference in risk of discontinuation between patients who transitioned from originator etanercept to SB4 and those who continued originator etanercept over a 6-month period (hazard ratio 0.46, 95% CI 0.11–1.98, $p = 0.297$) [107].

Another RCT (EGALITY) comparing originator etanercept to the etanercept biosimilar GP2015 (Erelzi) in patients with psoriasis incorporated a multiple-switch design to evaluate the safety and efficacy of alternating between treatments [42, 115]. In this study, patients were randomized to receive originator etanercept or GP2015 during a 12-week, double-blind treatment period [treatment period 1 (TP1)], after which patients were re-randomized either to continue the same treatment (continued etanercept and continued GP2015) or to undergo a sequence of three treatment switches (switch etanercept and switch GP2015) every 6 weeks until week 30 (TP2). Thereafter, patients were maintained on the last treatment received, up until week 52. An analysis of pooled continued and pooled switch groups demonstrated that repeated switching between the two treatments did not have any negative effect on drug efficacy [42, 115]. The incidence of TEAEs during TP2 was similar between pooled continued (34.9%) and pooled switch (36.7%) treatment groups [115]. Furthermore, no patients from either the pooled continued or pooled switch groups tested positive for ADAs during TP2 [115].

Adalimumab

Two RCTs have evaluated single transition from originator adalimumab (Humira®) to the adalimumab biosimilar ABP 501 (Amgevita/Solymbic; Amjevita), one each in patients with RA or psoriasis [116, 117]. In the RA study, patients who completed a 26-week, double-blind treatment period were enrolled into an OLE study, during which patients transitioned from originator adalimumab to ABP 501 (transition group) or continued treatment with ABP 501 (maintenance group) for an additional 68 weeks [116]. The authors reported similar safety and efficacy profiles between the transition and maintenance groups; however, clinical outcomes for individual groups were not presented [116].

In the psoriasis study, patients were randomized to receive originator adalimumab or ABP 501 during a 16-week, double-blind treatment phase, after which patients on originator adalimumab were re-randomized to either continued treatment with originator adalimumab (maintenance group) or a transition to ABP 501 (transition group) [117]. Safety and efficacy were not reported. However, incidence of ADAs in the transition group (72.7%) was noninferior to that in the maintenance group (74.7%); the upper bound of the 95% CI (− 13.3% to 13.0%) for the treatment difference was within the noninferiority margin of 21.7% [117].

Transition data for the adalimumab biosimilars BI 695501 (Cyltezo) and SB5 (Imraldi) are available from RCTs conducted in patients with RA [118, 119]. In the study of BI 695501, patients receiving originator adalimumab during the initial 24-week treatment period were re-randomized to transition to BI 695501 (full analysis set, $n = 147$; safety analysis set, $n = 146$) or continue on originator adalimumab ($n = 148$) until week 48 [118]. Response rates and changes from baseline in disease activity were similar between transition and continuation groups up to week 48, as was the incidence of TEAEs from weeks 24 to 58 (42.5% vs. 34.5%) [118]. Likewise, immunogenicity was similar between groups up to week 48; ADA-positivity rates at weeks 24 and 48, respectively, were 44.5% and 36.2% for patients who transitioned to BI 695501 and 50.3% and 49.6% for patients who continued originator adalimumab [118]. In the study of SB5, patients on originator adalimumab during the initial 24-week treatment period were re-randomized to transition to SB5 ($n = 125$) or continue on originator adalimumab ($n = 129$) up to week 50 [119]. Efficacy was comparable between transition and continuation groups up to week 52, as was the incidence of TEAEs (37.6% vs. 33.1%) and ADA-positivity rates (16.8% vs. 18.3%) [119].

Summary and Considerations Regarding Transitioning or Switching

Currently available studies of infliximab, etanercept, and adalimumab biosimilars are encouraging, and suggest that transitioning from an originator biologic to its biosimilar has no adverse effects on efficacy, safety, or immunogenicity. However, the level of evidence varies across products, with most published data for infliximab and most transition studies conducted in patients with rheumatic disease. No published studies of infliximab or adalimumab biosimilars and only one published study (EGALITY) of etanercept biosimilars investigated the safety and efficacy of alternating between an originator biologic and its biosimilar. Few studies were conducted in patients with psoriasis; however, switch data from EGALITY as well as transition data from one RCT of ABP 501 and one observational study of CT-P13 (Remsima) and SB4 are encouraging.

When considering a change in therapy, results obtained with one biosimilar should not be generalized to other biosimilars of the same biologic or to biosimilars of other biologic drugs [98]. For example, the effect of repeated switching between etanercept and GP2015 on immunogenicity should not be generalized to other etanercept biosimilars or to biosimilars of other anti-TNF biologics with higher immunogenic potential. Finally, not all studies were formally designed to evaluate non-inferiority or equivalence of transitioning, or switching between originator and biosimilar products. Accordingly, further studies with adequate power to evaluate statistical significance of differences between transition or switch and maintenance groups will be welcome and contribute clinically meaningful information about the safety and efficacy of transitioning, switching, or alternating between an originator biologic and its biosimilar drug.

Interchangeability

In the USA, an approved biosimilar may also be granted interchangeability status by the FDA [120]. To receive this regulatory designation, draft guidance issued by the FDA requires that an application for an interchangeable biosimilar product include sufficient evidence to show that the biosimilar product "can be expected to produce the same clinical result as the reference product in any given patient" [120].

Furthermore, for interchangeability designation, information in the application must be sufficient to show that "for a biological product [biosimilar] 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 biological product [biosimilar] and the reference product is not greater than the risk of using the reference product without such alternation or switch" [120].

To support a demonstration of interchangeability, draft guidance requires data from a switching study(ies) that incorporates two or more alternating exposures (switch intervals) to the potential interchangeable product and the originator product [120]. VOLTAIRE-X is the first study in the USA to investigate interchangeability designation for an adalimumab biosimilar [121]. This study is recruiting patients with moderate-to-severe chronic plaque psoriasis and will compare the pharmacokinetics, efficacy, safety, and immunogenicity of repeated switching between originator adalimumab and the adalimumab biosimilar BI 695501 versus continued treatment with adalimumab [121]. The aforementioned EGALITY study also incorporated a multiple-switch design that is in agreement with draft interchangeability guidance; however, as noted above, the study was not powered to demonstrate equivalence of repeated switching between originator etanercept and the etanercept biosimilar GP2015 versus continued treatment with either drug [42].

Interchangeable designation may allow for automatic substitution [120]; however, substitution policies are determined by individual state laws, not by the FDA. By contrast, European regulations do not define interchangeability, and such regulatory designation is not granted by the EMA [70, 122]. Rather, decisions about interchangeability and substitution are made by individual member states. Several national organizations and societies have issued papers or statements on interchangeability, substitution, and other considerations for the use of biosimilars in psoriasis with recommendations that support improving access to biologic therapies and ensuring patient safety (Table 3) [123–127].

NON-COMPARABLE BIOTHERAPEUTIC PRODUCTS

Clinicians should also be aware of "non-comparable biotherapeutic products", also known as "intended copies" [128]. Intended copies have not been approved following a regulatory pathway that is in alignment with requirements for establishing biosimilarity, as defined by leading regulatory authorities (e.g., EMA, FDA, and Health Canada) or the WHO [21, 70–72, 128]. As such, these products cannot be considered biosimilars [128]. Intended copies have not been identified in the USA or European Union [129], but were introduced in some countries without stringent regulatory frameworks or before the implementation of pathways for biosimilar approval [128]. Intended copies are marketed in several Latin American countries; however, some countries have issued regulation mandating re-evaluation of these products in accordance with current regulation for biosimilars [129, 130].

ECONOMIC IMPACT OF BIOSIMILARS ON THE BURDEN OF PSORIASIS

Costs associated with psoriasis can place considerable economic burden on patients and healthcare systems. Recent estimates of the annual total and direct healthcare costs of moderate-to-severe psoriasis were $22,713 per patient and $13,731 (mean), respectively, in the USA (adjusted to 2012 US dollars) and €1617–13,343 and €1314–8966 per patient-year, respectively, across France, Germany, Italy, and Spain (adjusted to 2015 euros) [131, 132]. Furthermore, healthcare expenditure is substantially greater with biologic drugs versus conventional systemic therapies [39, 133]. In a 2014 meeting on economic crisis and healthcare, the Council of the European Union concluded "the prices of many new innovative medicines are very high in relation to the public health expenditure capacities of most Member

Table 3 National organization or society positioning on the use of biosimilars in psoriasis

Society	General considerations	Switching	Interchangeability	Substitution	Pharmacovigilance plan
AAD [123]	–	–	–	Yes, if biosimilar has unique INN; interchangeable designation; physician provides explicit permission for and patient is informed of substitution; pharmacist notifies prescriber and pharmacy and prescriber retain permanent record of substitution and document any AEs	–
CAPP [124]	Distinct INN eliminates confusion and accidental substitution, and facilitates accurate attribution of AEs Encourage developers to provide patient and physician support programs; payers to consider full costs to healthcare system vs. cost of medication	Yes, but not required	No	No automatic substitution	Yes
NPF [126]	–	–	–	Yes, if biosimilar has unique INN; interchangeable designation; follows same route of administration and dosage form as reference product; pharmacist notifies prescriber; prescriber has not blocked substitution; patient is informed of substitution and pharmacy and prescriber retain permanent record of substitution	–
PCD & SPDV [127]	Biosimilar development must be critically evaluated; evidence for bioequivalence, quality, efficacy, and safety should take priority over potential economic or financial benefit Choose biosimilars studied in patients with psoriasis as treatment instead of biosimilars studied in other indications Careful biosimilar identification and recording is critical for safety and traceability Physicians must retain full authority over selection of therapeutic agent	No	–	Yes, if recommended by prescribing physician and patient is informed of and consents to substitution; no automatic substitution	Yes
AEDV [125]	Biosimilar use should not imply reduction in therapeutic efficacy, patient safety, or prescriber's choice of treatment Physician takes responsibility for prescribing biosimilar. Decision should be based on scientific evidence, not economic factors alone; assessed on a case-by-case basis and requires patient consent Include patients with psoriasis and PsA in biosimilar trials to obtain direct information about efficacy and safety vs. extrapolation of findings from other indications Patient and prescriber information about biosimilar product should be clear and precise to support treatment decisions	Yes, if decided by physician with patient consent	–	–	Yes

AAD American Academy of Dermatology, *AE* adverse event, *AEDV* Spanish Academy of Dermatology and Venereology, *CAPP* Canadian Association of Psoriasis Patients, *INN* International Nonproprietary Name, *NPF* National Psoriasis Foundation, *PCD* Portuguese College of Dermatology, *PsA* psoriatic arthritis, *SPDV* Portuguese Society of Dermatology and Venerology, – not addressed

States, and that this pricing situation could destabilize health systems in Member States already weakened by the financial crisis" [134].

Biosimilars may provide a lower-cost alternative to biologic therapies. For example, an analysis of commercial databases providing data on biosimilar market share and price discounts (vs. originator biologics) in Europe estimated the average biosimilar price discount around 15% (range 0–32%) across Belgium, France, Germany, Greece, Hungary, Italy, Poland, Spain, Sweden, and the UK [135]. Likewise, a survey of biosimilar pricing and reimbursement in Central and Eastern European countries reported biosimilar price discounts ranging from 5% to 30% over the originator biologic across Bulgaria, Croatia, Czech Republic, Estonia, Hungary, Latvia, Lithuania, Poland, Romania, and Slovakia [136].

As a lower-cost alternative to originator biologics, biosimilars have the potential to reduce economic burden among patients with psoriasis. For example, a budget impact analysis estimated that switching patients with RA in France, Germany, Italy, and the UK from originator infliximab to biosimilar infliximab (30% price discount) could generate a potential cost saving of €433,520,000 over a 5-year period [66]. Furthermore, cost savings from the use of a biosimilar could be reinvested to treat additional patients with the same agent or may allow for expanded access to other biologic therapies [64, 65], potentially improving overall health outcomes. For example, the potential annual cost savings generated from Remsima (30% price discount) could support Remsima treatment for an additional 7561 patients in Belgium, Germany, Italy, the Netherlands, and the UK [65].

CONCLUSIONS

Although biologic therapies have greatly improved treatment of psoriasis, patient access to these therapies is often limited. Biosimilars have the potential to impact patient care by improving access to biologics and by reducing the economic burden on healthcare. As a lower-cost alternative to originator biologic products, biosimilars also may generate cost savings that can be reinvested into the development of innovative treatment options for patients with psoriasis.

In recent years, adalimumab, etanercept, and infliximab biosimilars have become available to patients with psoriasis (Table 1). Some anti-TNF biosimilars were studied in patients with psoriasis in the initial development programs and, consistent with the biosimilar concept, more were approved for treatment of psoriasis on the basis of extrapolation of clinical data from studies in patients with rheumatic disease. The currently available data for anti-TNF biosimilars are reassuring in terms of safety and efficacy and provide evidence to support transitioning patients from an originator product to a biosimilar. Further studies incorporating multiple-switch designs, such as VOLTAIRE-X [121], will contribute additional clinical data about the safety and efficacy of alternating between originator and biosimilar therapies.

An approved biosimilar is expected to have the same clinical efficacy and safety as the originator. Therefore, all patients who are eligible for treatment with anti-TNF agents are potential candidates for using a biosimilar. Differences exist between countries in biosimilar prescribing policies, and some regulations may favor the selection of biosimilars as first-line treatment or require the use of biosimilars over originator products unless a medical reason is specified [137]. Education of physicians about the scientific principles underlying biosimilar development and approval as well as key issues (e.g., interchangeability, switching, substitution, and intended copies) and clinical experience with biosimilar use may help them to make informed treatment decisions in clinical practice. With the availability of biosimilars, we can expect to see wider use of biologics in clinical practice, which may lead to better health outcomes for patients with psoriasis as well as potentially improved adherence to treatment.

ACKNOWLEDGEMENTS

Funding. This review and article processing charges were funded by Pfizer Inc.

Authorship. All named authors meet the International Committee of Medical Journal Editors (ICMJE) criteria for authorship for this manuscript, take responsibility for the integrity of the work as a whole, and have given final approval for the version to be published.

Medical Writing and/or Editorial Assistance. Medical writing support was provided by Merry Saba, PharmD, and Elyse Smith, PhD, of Engage Scientific Solutions and was funded by Pfizer Inc.

Disclosures. Ira Jacobs is a full-time employee of and declares stock holdings and/or stock options from Pfizer Inc. Danielle Petersel is a full-time employee of and declares stock holdings and/or stock options from Pfizer Inc. Jose-Manuel Carrascosa and Robert Strohal have nothing to disclose.

Compliance with Ethics Guidelines. This article does not contain any new studies with human or animal subjects performed by any of the authors.

REFERENCES

1. World Health Organization. Global report on psoriasis. Geneva: World Health Organization; 2016.
2. Rapp SR, Feldman SR, Exum ML, Fleischer AB Jr, Reboussin DM. Psoriasis causes as much disability as other major medical diseases. J Am Acad Dermatol. 1999;41:401–7.
3. Strohal R, Kirby B, Puig L, et al. Psoriasis beyond the skin: an expert group consensus on the management of psoriatic arthritis and common co-morbidities in patients with moderate-to-severe psoriasis. J Eur Acad Dermatol Venereol. 2014;28:1661–9.
4. Oliveira Mde F, Rocha Bde O, Duarte GV. Psoriasis: classical and emerging comorbidities. An Bras Dermatol. 2015;90:9–20.
5. Abuabara K, Azfar RS, Shin DB, Neimann AL, Troxel AB, Gelfand JM. Cause-specific mortality in patients with severe psoriasis: a population-based cohort study in the U.K. Br J Dermatol. 2010;163:586–92.
6. AbbVie Inc. Humira (Adalimumab) US prescribing information. http://www.rxabbvie.com/pdf/humira.pdf (2017). Accessed 6 Feb 2017.
7. Amgen Inc. Enbrel (Etanercept) US prescribing information. http://pi.amgen.com/~/media/amgen/repositorysites/pi-amgen-com/enbrel/enbrel_pi.ashx (2017). Accessed 6 Feb 2017.
8. Committee for Medicinal Products for Human Use (CHMP). Summary of product characteristics: Remicade (infliximab). http://www.ema.europa.eu/docs/en_GB/document_library/EPAR_-_Product_Information/human/000240/WC500050888.pdf (2017). Accessed 8 Mar 2017.
9. Committee for Medicinal Products for Human Use (CHMP). Summary of product characteristics: Taltz (ixekizumab). http://www.ema.europa.eu/docs/en_GB/document_library/EPAR_-_Product_Information/human/003943/WC500205804.pdf (2018). Accessed 28 Feb 2018.
10. Committee for Medicinal Products for Human Use (CHMP). Summary of product characteristics: Cosentyx (secukinumab). http://www.ema.europa.eu/docs/en_GB/document_library/EPAR_-_Product_Information/human/003729/WC500183129.pdf (2017). Accessed 8 Mar 2017.
11. Committee for Medicinal Products for Human Use (CHMP). Summary of product characteristics: Stelara (ustekinumab). http://www.ema.europa.eu/docs/en_GB/document_library/EPAR_-_Product_Information/human/000958/WC500058513.pdf (2017). Accessed 8 Mar 2017.
12. Committee for Medicinal Products for Human Use (CHMP). Summary of product characteristics: Humira (adalimumab). http://www.ema.europa.eu/docs/en_GB/document_library/EPAR_-_Product_Information/human/000481/WC500050870.pdf (2017). Accessed 8 Mar 2017.
13. Committee for Medicinal Products for Human Use (CHMP). Summary of product characteristics: Enbrel (etanercept). http://www.ema.europa.eu/docs/en_GB/document_library/EPAR_-_Product_Information/human/000262/WC500027361.pdf (2018). Accessed 28 Feb 2018.

14. Eli Lilly and Company. Taltz (ixekizumab) US prescribing information. https://pi.lilly.com/us/taltz-uspi.pdf (2017). Accessed 28 Feb 2018.

15. Janssen Biotech Inc. Remicade (infliximab) US prescribing information. https://www.remicade.com/shared/product/remicade/prescribing-information.pdf (2017). Accessed 6 Feb 2017.

16. Janssen Biotech Inc. Stelara (ustekinumab) US prescribing information. https://www.stelarainfo.com/pdf/prescribinginformation.pdf (2018). Accessed 28 Feb 2018.

17. Novartis Pharmaceuticals Corporation. Cosentyx (secukinumab) US prescribing information. https://www.pharma.us.novartis.com/sites/www.pharma.us.novartis.com/files/cosentyx.pdf (2018). Accessed 28 Feb 2018.

18. Valeant Pharmaceuticals North America LLC. Siliq (brodalumab) US prescribing information. https://www.accessdata.fda.gov/drugsatfda_docs/label/2017/761032lbl.pdf (2017). Accessed 24 Apr 2017.

19. Janssen Biotech Inc. Tremfya (guselkumab) US prescribing information. http://www.janssenlabels.com/package-insert/product-monograph/prescribing-information/TREMFYA-pi.pdf (2017). Accessed 26 Jan 2018.

20. Philippidis A. Biosimilars: 11 drugs to watch [news report]. https://www.genengnews.com/the-lists/biosimilars-11-drugs-to-watch/77900135 (2014). Accessed 28 Feb 2018.

21. US Food and Drug Administration. Scientific considerations in demonstrating biosimilarity to a reference product: guidance for industry. http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM291128.pdf (2015). Accessed 9 Feb 2017.

22. Chaudhari U, Romano P, Mulcahy LD, Dooley LT, Baker DG, Gottlieb AB. Efficacy and safety of infliximab monotherapy for plaque-type psoriasis: a randomised trial. Lancet. 2001;357:1842–7.

23. Gordon KB, Blauvelt A, Papp KA, et al. Phase 3 trials of ixekizumab in moderate-to-severe plaque psoriasis. N Engl J Med. 2016;375:345–56.

24. Gottlieb AB, Evans R, Li S, et al. Infliximab induction therapy for patients with severe plaque-type psoriasis: a randomized, double-blind, placebo-controlled trial. J Am Acad Dermatol. 2004;51:534–42.

25. Griffiths CE, Reich K, Lebwohl M, et al. Comparison of ixekizumab with etanercept or placebo in moderate-to-severe psoriasis (UNCOVER-2 and UNCOVER-3): results from two phase 3 randomised trials. Lancet. 2015;386:541–51.

26. Langley RG, Elewski BE, Lebwohl M, et al. Secukinumab in plaque psoriasis—results of two phase 3 trials. N Engl J Med. 2014;371:326–38.

27. Leonardi CL, Kimball AB, Papp KA, et al. Efficacy and safety of ustekinumab, a human interleukin-12/23 monoclonal antibody, in patients with psoriasis: 76-week results from a randomised, double-blind, placebo-controlled trial (PHOENIX 1). Lancet. 2008;371:1665–74.

28. Papp KA, Langley RG, Lebwohl M, et al. Efficacy and safety of ustekinumab, a human interleukin-12/23 monoclonal antibody, in patients with psoriasis: 52-week results from a randomised, double-blind, placebo-controlled trial (PHOENIX 2). Lancet. 2008;371:1675–84.

29. Papp KA, Tyring S, Lahfa M, et al. A global phase III randomized controlled trial of etanercept in psoriasis: safety, efficacy, and effect of dose reduction. Br J Dermatol. 2005;152:1304–12.

30. Reich K, Nestle FO, Papp K, et al. Infliximab induction and maintenance therapy for moderate-to-severe psoriasis: a phase III, multicentre, double-blind trial. Lancet. 2005;366:1367–74.

31. Saurat JH, Stingl G, Dubertret L, et al. Efficacy and safety results from the randomized controlled comparative study of adalimumab vs. methotrexate vs. placebo in patients with psoriasis (CHAMPION). Br J Dermatol. 2008;158:558–66.

32. Blauvelt A, Papp KA, Griffiths CE, et al. Efficacy and safety of guselkumab, an anti-interleukin-23 monoclonal antibody, compared with adalimumab for the continuous treatment of patients with moderate to severe psoriasis: results from the phase III, double-blinded, placebo- and active comparator-controlled VOYAGE 1 trial. J Am Acad Dermatol. 2017;76:405–17.

33. Armstrong AW, Robertson AD, Wu J, Schupp C, Lebwohl MG. Undertreatment, treatment trends, and treatment dissatisfaction among patients with psoriasis and psoriatic arthritis in the United States: findings from the National Psoriasis Foundation surveys, 2003–2011. JAMA Dermatol. 2013;149:1180–5.

34. Kavanaugh A, Helliwell P, Ritchlin CT. Psoriatic arthritis and burden of disease: patient perspectives from the population-based multinational assessment of psoriasis and psoriatic arthritis (MAPP) survey. Rheumatol Ther. 2016;3:91–102.

35. Lebwohl MG, Bachelez H, Barker J, et al. Patient perspectives in the management of psoriasis: results

from the population-based multinational assessment of psoriasis and psoriatic arthritis survey. J Am Acad Dermatol. 2014;70(871–81):e1–30.

36. Lebwohl MG, Kavanaugh A, Armstrong AW, Van Voorhees AS. US perspectives in the management of psoriasis and psoriatic arthritis: patient and physician results from the population-based multinational assessment of psoriasis and psoriatic arthritis (MAPP) survey. Am J Clin Dermatol. 2016;17:87–97.

37. van de Kerkhof PC, Reich K, Kavanaugh A, et al. Physician perspectives in the management of psoriasis and psoriatic arthritis: results from the population-based multinational assessment of psoriasis and psoriatic arthritis survey. J Eur Acad Dermatol Venereol. 2015;29:2002–10.

38. Chouela E, Amaya M, Londono A, et al. Psoriasis in Latin America. Dermatol Online J. 2016;22:2.

39. Duarte GV, Porto-Silva L, de Fatima Paim de Oliveria M. Epidemiology and treatment of psoriasis: a Brazilian perspective. Psoriasis Targets Ther. 2015;5:55–64.

40. Choe JY, Prodanovic N, Niebrzydowski J, et al. A randomised, double-blind, phase III study comparing SB2, an infliximab biosimilar, to the infliximab reference product Remicade in patients with moderate to severe rheumatoid arthritis despite methotrexate therapy. Ann Rheum Dis. 2017;76:58–64.

41. Emery P, Vencovsky J, Sylwestrzak A, et al. A phase III randomised, double-blind, parallel-group study comparing SB4 with etanercept reference product in patients with active rheumatoid arthritis despite methotrexate therapy. Ann Rheum Dis. 2017;76:51–7.

42. Griffiths CEM, Thaci D, Gerdes S, et al. The EGALITY study: a confirmatory, randomized, double-blind study comparing the efficacy, safety and immunogenicity of GP2015, a proposed etanercept biosimilar, vs. the originator product in patients with moderate-to-severe chronic plaque-type psoriasis. Br J Dermatol. 2017;176:928–38.

43. Novartis Pharmaceuticals Corporation. FDA approves Sandoz Erelzi to treat multiple inflammatory diseases [news release]. https://www.novartis.com/news/media-releases/fda-approves-sandoz-erelzitm-treat-multiple-inflammatory-diseases (2016). Accessed 24 Feb 2017.

44. Park W, Hrycaj P, Jeka S, et al. A randomised, double-blind, multicentre, parallel-group, prospective study comparing the pharmacokinetics, safety, and efficacy of CT-P13 and innovator infliximab in patients with ankylosing spondylitis: the PLANETAS study. Ann Rheum Dis. 2013;72:1605–12.

45. Park W, Yoo DH, Jaworski J, et al. Comparable long-term efficacy, as assessed by patient-reported outcomes, safety and pharmacokinetics, of CT-P13 and reference infliximab in patients with ankylosing spondylitis: 54-week results from the randomized, parallel-group PLANETAS study. Arthritis Res Ther. 2016;18:25.

46. US Food and Drug Administration. FDA approves Inflectra, a biosimilar to Remicade [news release]. http://www.fda.gov/NewsEvents/Newsroom/PressAnnouncements/ucm494227.htm (2016). Accessed 24 Feb 2017.

47. Yoo DH, Hrycaj P, Miranda P, et al. A randomised, double-blind, parallel-group study to demonstrate equivalence in efficacy and safety of CT-P13 compared with innovator infliximab when coadministered with methotrexate in patients with active rheumatoid arthritis: the PLANETRA study. Ann Rheum Dis. 2013;72:1613–20.

48. Yoo DH, Racewicz A, Brzezicki J, et al. A phase III randomized study to evaluate the efficacy and safety of CT-P13 compared with reference infliximab in patients with active rheumatoid arthritis: 54-week results from the PLANETRA study. Arthritis Res Ther. 2016;18:82.

49. Amgen Inc. FDA approves Amgen's Amjevita (adalimumab-atto) for treatment of seven inflammatory diseases [news release]. https://www.amgen.com/media/news-releases/2016/09/fda-approves-amgens-amjevita-adalimumabatto-for-treatment-of-seven-inflammatory-diseases/ (2016). Accessed 24 Feb 2017.

50. Merck & Co., Inc., Merck announces US launch of Renflexis (infliximab-abda), a biosimilar of Remicade, for all eligible indications [news release]. http://investors.merck.com/news/press-release-details/2017/Merck-Announces-US-Launch-of-RENFLEXIS-infliximab-abda-a-Biosimilar-of-Remicade-for-All-Eligible-Indications/default.aspx (2017). Accessed 26 Feb 2018.

51. Boehringer Ingelheim Pharmaceuticals Inc. Boehringer Ingelheim Pharmaceuticals, Inc. receives FDA approval for Cyltezo™ (adalimumab-adbm), a biosimilar to Humira®, for the treatment of multiple chronic inflammatory diseases [news release]. https://www.boehringer-ingelheim.com/press-release/adalimumab-biosimilar-cyltezo-receives-fda-approval (2017). Accessed 18 Sep 2017.

52. European Medicines Agency. European Public Assessment Reports (biosimilars). http://www.ema.europa.eu/ema/index.jsp?curl=pages%2Fmedicines%2Flanding%2Fepar_search.jsp&mid=WC0b01ac058001d124&searchTab=searchByAuthType&alreadyLoaded=true&isNewQuery=true&status=Authorised&status=Withdrawn&status=Suspended&status=

Refused&keyword=Enter+keywords&searchType=name&taxonomyPath=&treeNumber=&searchGenericType=biosimilars (2016). Accessed 28 Feb 2018.

53. Cohen S, Alonso-Ruiz A, Klimiuk P, et al. FRI0189 similar efficacy and safety of biosimilar candidate BI 695501 and adalimumab originator reference product in patients with moderate to severe active rheumatoid arthritis: 24 week results from a phase III clinical study (Voltaire®-ra). Ann Rheum Dis. 2017;76:553.

54. Takeuchi T, Yamanaka H, Tanaka Y, et al. Evaluation of the pharmacokinetic equivalence and 54-week efficacy and safety of CT-P13 and innovator infliximab in Japanese patients with rheumatoid arthritis. Mod Rheumatol. 2015;25:817–24.

55. Cohen SB, Alten R, Kameda H, et al. A randomized, double-blind study comparing PF-06438179/GP1111, a potential infliximab biosimilar, and infliximab, both in combination with MTX, as treatment for patients with moderate to severe active RA who have had an inadequate response to MTX therapy [abstract]. Arthritis Rheumatol. 2017;69(-suppl 10):4043-44. http://acrabstracts.org/abstract/a-randomized-double-blind-study-comparing-pf-06438179gp1111-a-potential-infliximab-biosimilar-and-infliximab-both-in-combination-with-mtx-as-treatment-for-patients-with-moderate-to-severe-active/. Accessed 2 Jan 2018.

56. FirstWord Pharma. FDA approves new Pfizer biosimilar [news release]. https://www.firstwordpharma.com/node/1529996 (2017). Accessed 2 Jan 2018.

57. Weinblatt ME, Baranauskaite A, Niebrzydowski J, et al. Phase III randomized study of SB5, an adalimumab biosimilar, versus reference adalimumab in patients with moderate-to-severe rheumatoid arthritis. Arthritis Rheumatol. 2018;70:40–8.

58. Cohen S, Genovese MC, Choy E, et al. Efficacy and safety of the biosimilar ABP 501 compared with adalimumab in patients with moderate to severe rheumatoid arthritis: a randomised, double-blind, phase III equivalence study. Ann Rheum Dis. 2017;76:1679–87.

59. Papp K, Bachelez H, Costanzo A, et al. Clinical similarity of biosimilar ABP 501 to adalimumab in the treatment of patients with moderate to severe plaque psoriasis: a randomized, double-blind, multicenter, phase III study. J Am Acad Dermatol. 2017;76:1093–102.

60. Generics and Biosimilars Initiative (GaBi). Etanercept biosimilar submitted for approval in Japan [online posting]. http://www.gabionline.net/Biosimilars/News/Etanercept-biosimilar-submitted-for-approval-in-Japan (2017). Accessed 24 Feb 2017.

61. Generics and Biosimilars Initiative (GaBi). Biosimilars of adalimumab [online posting]. http://www.gabionline.net/Biosimilars/General/Biosimilars-of-adalimumab (2017). Accessed 2 Jan 2018.

62. Generics and Biosimilars Initiative (GaBi). Adalimumab and infliximab biosimilars from Sandoz accepted for review by EMA [online posting]. http://www.gabionline.net/Biosimilars/News/Adalimumab-and-infliximab-biosimilars-from-Sandoz-accepted-for-review-by-EMA (2017). Accessed 2 Jan 2018.

63. Fresenius Kabi. Fresenius Kabi submits its first biosimilar marketing authorization application to European Medicines Agency for MSB11022, a biosimilar of adalimumab [news release]. https://www.fresenius-kabi.com/documents/adalimumab_181217-e.pdf (2017). Accessed 2 Jan 2018.

64. Abraham I, Han L, Sun D, MacDonald K, Aapro M. Cost savings from anemia management with biosimilar epoetin alfa and increased access to targeted antineoplastic treatment: a simulation for the EU G5 countries. Future Oncol. 2014;10:1599–609.

65. Jha A, Upton A, Dunlop WC, Akehurst R. The budget impact of biosimilar infliximab (Remsima®) for the treatment of autoimmune diseases in five European countries. Adv Ther. 2015;32:742–56.

66. Kim J, Hong J, Kudrin A. 5 year budget impact analysis of biosimilar Infliximab for the treatment of rheumatoid arthritis in UK, Italy, France and Germany (abstr 1166). In: Paper presented at: American College of Rheumatology; 14–19 November 2014, 2014; Boston, MA.

67. Kuhlmann M, Covic A. The protein science of biosimilars. Nephrol Dial Transplant. 2006;21(Suppl 5):v4–8.

68. Azevedo V, Hassett B, Fonseca JE, et al. Differentiating biosimilarity and comparability in biotherapeutics. Clin Rheumatol. 2016;35:2877–86.

69. Ahmed I, Kaspar B, Sharma U. Biosimilars: impact of biologic product life cycle and European experience on the regulatory trajectory in the United States. Clin Ther. 2012;34:400–19.

70. Committee for Medicinal Products for Human Use (CHMP). Guideline on similar biological medicinal products. http://www.ema.europa.eu/docs/en_GB/document_library/Scientific_guideline/2014/10/WC500176768.pdf (2014). Accessed 24 Feb 2017.

71. Minister of Health. Information and submission requirements for biosimilar biologic drugs. http://www.hc-sc.gc.ca/dhp-mps/alt_formats/pdf/brgtherap/applic-demande/guides/seb-pbu/seb-pbu-2016-eng.pdf (2016). Accessed 24 Feb 2017.

72. Expert Committee on Biological Standardization. Guidelines on evaluation of similar biotherapeutic products (SBPs). http://www.who.int/biologicals/areas/biological_therapeutics/BIOTHERAPEUTICS_FOR_WEB_22APRIL2010.pdf (2009). Accessed 24 Feb 2017.

73. Committee for Medicinal Products for Human Use (CHMP). Guideline on similar biological medicinal products containing biotechnology-derived proteins as active substance: non-clinical and clinical issues. http://www.ema.europa.eu/docs/en_GB/document_library/Scientific_guideline/2015/01/WC500180219.pdf (2014). Accessed 25 Feb 2017.

74. Committee for Medicinal Products for Human Use (CHMP). Guideline on similar biological medicinal products containing biotechnology-derived proteins as active substance: quality issues (revision 1). http://www.ema.europa.eu/docs/en_GB/document_library/Scientific_guideline/2014/06/WC500167838.pdf (2014). Accessed 25 Feb 2017.

75. Goetze AM, Liu YD, Zhang Z, et al. High-mannose glycans on the Fc region of therapeutic IgG antibodies increase serum clearance in humans. Glycobiology. 2011;21:949–59.

76. Jiang XR, Song A, Bergelson S, et al. Advances in the assessment and control of the effector functions of therapeutic antibodies. Nat Rev Drug Discov. 2011;10:101–11.

77. Zhou Q, Shankara S, Roy A, et al. Development of a simple and rapid method for producing non-fucosylated oligomannose containing antibodies with increased effector function. Biotechnol Bioeng. 2008;99:652–65.

78. Cleland JL, Powell MF, Shire SJ. The development of stable protein formulations: a close look at protein aggregation, deamidation, and oxidation. Crit Rev Ther Drug Carrier Syst. 1993;10:307–77.

79. van Aerts LA, De Smet K, Reichmann G, van der Laan JW, Schneider CK. Biosimilars entering the clinic without animal studies. A paradigm shift in the European Union. MAbs. 2014;6:1155–62.

80. Isakov L, Jin B, Jacobs IA. Statistical primer on biosimilar clinical development. Am J Ther. 2016;23:e1903–10.

81. Socinski MA, Curigliano G, Jacobs I, Gumbiner B, MacDonald J, Thomas D. Clinical considerations for the development of biosimilars in oncology. MAbs. 2015;7:286–93.

82. Committee for Medicinal Products for Human Use (CHMP). Assessment report: Inflectra (infliximab). http://www.ema.europa.eu/docs/en_GB/document_library/EPAR_-_Public_assessment_report/human/002778/WC500151490.pdf (2013). Accessed 24 Feb 2017.

83. Committee for Medicinal Products for Human Use (CHMP). Assessment report: Remsima (infliximab). http://www.ema.europa.eu/docs/en_GB/document_library/EPAR_-_Public_assessment_report/human/002576/WC500151486.pdf (2013). Accessed 24 Feb 2017.

84. Committee for Medicinal Products for Human Use (CHMP). Assessment report: Flixabi (infliximab). http://www.ema.europa.eu/docs/en_GB/document_library/EPAR_-_Public_assessment_report/human/004020/WC500208358.pdf (2016). Accessed 24 Feb 2017.

85. Center for Drug Evaluation and Research (CDER). Inflectra (infliximab-dyyb) for injection: summary review. https://www.accessdata.fda.gov/drugsatfda_docs/nda/2016/125544Orig1s000SumR.pdf (2016). Accessed 19 Sep 2017.

86. Center for Drug Evaluation and Research (CDER). Renflexis (infliximab-abda): clinical review. https://www.fda.gov/downloads/Drugs/DevelopmentApprovalProcess/DevelopmentResources/UCM557884.pdf (2017). Accessed 19 Sep 2017.

87. Committee for Medicinal Products for Human Use (CHMP). Assessment report: Erelzi (etanercept). http://www.ema.europa.eu/docs/en_GB/document_library/EPAR_-_Public_assessment_report/human/004192/WC500230144.pdf (2017). Accessed 19 Sep 2017.

88. Committee for Medicinal Products for Human Use (CHMP). Assessment report: Benepali (etanercept). http://www.ema.europa.eu/docs/en_GB/document_library/EPAR_-_Public_assessment_report/human/004007/WC500200380.pdf (2015). Accessed 24 Feb 2017.

89. Committee for Medicinal Products for Human Use (CHMP). Variation assessment report: Benepali (etanercept). http://www.ema.europa.eu/docs/en_GB/document_library/EPAR_-_Assessment_Report_-_Variation/human/004007/WC500222305.pdf (2016). Accessed 19 Sep 2017.

90. Committee for Medicinal Products for Human Use (CHMP). Assessment report: Amgevita (adalimumab). http://www.ema.europa.eu/docs/en_GB/document_library/EPAR_-_Public_assessment_report/human/004212/WC500225277.pdf (2017). Accessed 24 Apr 2017.

91. Committee for Medicinal Products for Human Use (CHMP). Assessment report: Solymbic (adalimumab). http://www.ema.europa.eu/docs/en_GB/document_library/EPAR_-_Public_assessment_report/

human/004373/WC500225367.pdf (2017). Accessed 24 Apr 2017.

92. Committee for Medicinal Products for Human Use (CHMP). Assessment report: Imraldi (adalimumab). http://www.ema.europa.eu/docs/en_GB/document_library/EPAR_-_Public_assessment_report/human/004279/WC500233922.pdf (2017). Accessed 19 Sep 2017.

93. Committee for Medicinal Products for Human Use (CHMP). Assessment report: Cyltezo (adalimumab). http://www.ema.europa.eu/docs/en_GB/document_library/EPAR_-_Public_assessment_report/human/004319/WC500238609.pdf (2017). Accessed 4 Jan 2018.

94. Human Medicines Development and Evaluation. Concept paper on extrapolation of efficacy and safety in medicine development. http://www.ema.europa.eu/docs/en_GB/document_library/Scientific_guideline/2013/04/WC500142358.pdf (2013). Accessed 25 Feb 2017.

95. Lee H. Is extrapolation of the safety and efficacy data in one indication to another appropriate for biosimilars? AAPS J. 2014;16:22–6.

96. Cohen H, Beydoun D, Chien D, et al. Awareness, knowledge, and perceptions of biosimilars among specialty physicians. Adv Ther. 2017;33:2160–72.

97. Manalo IF, Gilbert KE, Wu JJ. The current state of dermatologists' familiarity and perspectives of biosimilars for the treatment of psoriasis: a global cross-sectional survey. J Drugs Dermatol. 2017;16:336–43.

98. Moots R, Azevedo V, Coindreau JL, et al. Switching between reference biologics and biosimilars for the treatment of rheumatology, gastroenterology, and dermatology inflammatory conditions: considerations for the clinician. Curr Rheumatol Rep. 2017;19:37.

99. Park W, Yoo DH, Miranda P, et al. Efficacy and safety of switching from reference infliximab to CT-P13 compared with maintenance of CT-P13 in ankylosing spondylitis: 102-week data from the PLANETAS extension study. Ann Rheum Dis. 2017;76:346–54.

100. Tanaka Y, Yamanaka H, Takeuchi T, et al. Safety and efficacy of CT-P13 in Japanese patients with rheumatoid arthritis in an extension phase or after switching from infliximab. Mod Rheumatol. 2017;27:237–45.

101. Yoo DH, Prodanovic N, Jaworski J, et al. Efficacy and safety of CT-P13 (biosimilar infliximab) in patients with rheumatoid arthritis: comparison between switching from reference infliximab to CT-P13 and continuing CT-P13 in the PLANETRA extension study. Ann Rheum Dis. 2017;76:355–63.

102. Jørgensen KK, Olsen IC, Goll GL, et al. Switching from originator infliximab to biosimilar CT-P13 compared with maintained treatment with originator infliximab (NOR-SWITCH): a 52-week, randomised, double-blind, non-inferiority trial. Lancet. 2017;389:2304–16.

103. Kim Y, Ye BD, Pesegova M, et al. Phase III randomized controlled trial to compare biosimilar infliximab (CT-P13) with innovator infliximab in patients with active Crohn's disease: 1-year maintenance and switching results [abstr LB04]. United Eur Gastroenterol J. 2017;5:1139–40.

104. Glintborg B, Sorensen IJ, Loft AG, et al. A nationwide non-medical switch from originator infliximab to biosimilar CT-P13 in 802 patients with inflammatory arthritis: 1-year clinical outcomes from the DANBIO registry. Ann Rheum Dis. 2017;76:1426–31.

105. Glintborg B, Kringelbach TM, Høgdall E, et al. Non-medical switch from originator to biosimilar Infliximab in patients with inflammatory arthritis—impact on s-Infliximab and antidrug-antibodies. Results from the Danish Rheumatologic Biobank and the Danbio Registry. Arthritis Rheumatol. 2016;68(suppl 10):2547-50. http://acrabstracts.org/abstract/non-medical-switch-from-originator-to-biosimilar-infliximab-in-patients-with-inflammatory-arthritis-impact-on-s-infliximab-and-antidrug-antibodies-results-from-the-danish-rheumatologic-biobank-and. Accessed 16 Oct 2017.

106. Dapavo P, Vujic I, Fierro MT, Quaglino P, Sanlorenzo M. The infliximab biosimilar in the treatment of moderate to severe plaque psoriasis. J Am Acad Dermatol. 2016;75:736–9.

107. Egeberg A, Ottosen MB, Gniadecki R, et al. Safety, efficacy, and drug survival of biologics and biosimilars for moderate-to-severe plaque psoriasis. Br J Dermatol. 2018;178:509–19.

108. Abdalla A, Byrne N, Conway R, et al. Long-term safety and efficacy of biosimilar infliximab among patients with inflammatory arthritis switched from reference product. Open Access Rheumatol. 2017;9:29–35.

109. Benucci M, Gobbi FL, Bandinelli F, et al. Safety, efficacy and immunogenicity of switching from innovator to biosimilar infliximab in patients with spondyloarthritis: a 6-month real-life observational study. Immunol Res. 2017;65:419–22.

110. Holroyd C, Parker L, Bennett S, et al. O52 Switching to biosimilar infliximab: real-world data from the

southampton biologic therapies review service. Rheumatology. 2016;55:i60–1.

111. Malaiya R, McKee Z, Kiely P. 158 Infliximab biosimilars—switching Remicade to Remsima in routine care: patient acceptability and early outcome data. Rheumatology. 2016;55:i125–6.

112. Nikiphorou E, Kautiainen H, Hannonen P, et al. Clinical effectiveness of CT-P13 (infliximab biosimilar) used as a switch from Remicade (infliximab) in patients with established rheumatic disease. Report of clinical experience based on prospective observational data. Expert Opin Biol Ther. 2015;15:1677–83.

113. Smolen JS, Choe JY, Prodanovic N, et al. Safety, immunogenicity and efficacy after switching from reference infliximab to biosimilar SB2 compared with continuing reference infliximab and SB2 in patients with rheumatoid arthritis: results of a randomised, double-blind, phase III transition study. Ann Rheum Dis. 2017;76:1426–31.

114. Emery P, Vencovsky J, Sylwestrzak A, et al. Long-term efficacy and safety in patients with rheumatoid arthritis continuing on SB4 or switching from reference etanercept to SB4. Ann Rheum Dis. 2017. https://doi.org/10.1136/annrheumdis-2017-211591.

115. Gerdes S, Thaci D, Griffiths C, et al. Multiple switches between GP2015, an etanercept biosimilar, with originator product do not impact efficacy, safety and immunogenicity in patients with chronic plaque-type psoriasis: 30-week results from the phase 3, confirmatory EGALITY study. J Eur Acad Dermatol Venereol. 2017. https://doi.org/10.1111/jdv.14605.

116. Cohen S, Pablos JL, Zhang N, et al. ABP 501 Long-term safety/efficacy: interim results from an open-label extension study. Arthritis Rheumatol. 2016;68(suppl 10). http://acrabstracts.org/abstract/abp-501-long-term-safetyefficacy-interim-results-from-an-open-label-extension-study/. Accessed 16 Oct 2017.

117. Gooderham M, Spelman L, Kaliaperumal A, et al. Single transition from adalimumab to ABP 501: evaluation of immunogenicity in a phase 3 study in subjects with moderate to severe plaque psoriasis. J Am Acad Dermatol. 2016;74:AB275.

118. Cohen SB, Alonso-Ruiz A, Klimiuk PA, et al. Biosimilar candidate BI 695501 and adalimumab reference product have similar efficacy and safety in patients with moderately-to-severely active rheumatoid arthritis (RA): 1-year results from a phase III study [abstract]. Arthritis Rheumatol. 2017;69(suppl 10):3495-97. http://acrabstracts.org/abstract/biosimilar-candidate-bi-695501-and-adalimumab-reference-product-have-similar-efficacy-and-safety-in-patients-with-moderately-to-severely-active-rheumatoid-arthritis-ra-1-year-results-from-a-phase-i/. Accessed 3 Jan 2018.

119. Weinblatt M, Baranauskaite A, Niebrzydowski J, et al. Sustained efficacy and comparable safety and immunogenicity after transition to SB5 (an adalimumab biosimilar) vs. continuation of SB5 or reference adalimumab (Humira®) in patients with rheumatoid arthritis: results of phase III study [abstract]. Arthritis Rheumatol. 2016;68(suppl 10):790-92. http://acrabstracts.org/abstract/sustained-efficacy-and-comparable-safety-and-immunogenicity-after-transition-to-sb5-an-adalimumab-biosimilar-vs-continuation-of-sb5-or-reference-adalimumab-humira-in-patients-with-rheumatoi/. Accessed 16 Oct 2017.

120. US Food and Drug Administration. Considerations in demonstrating interchangeability with a reference product: guidance for industry. https://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM537135.pdf (2017). Accessed 25 Feb 2017.

121. Boehringer Ingelheim Pharmaceuticals Inc. Boehringer Ingelheim starts clinical study on interchangeability between its adalimumab biosimilar candidate and HUMIRA® [news release]. https://www.boehringer-ingelheim.com/press-release/interchangeability-study-bi-695501-vs-humira (2017). Accessed 18 Sep 2017.

122. European Medicines Agency. Questions and answers on biosimilar medicines(similar biological medicinal products). http://www.medicinesforeurope.com/wp-content/uploads/2016/03/WC500020062.pdf (2012). Accessed 26 Feb 2018.

123. American Academy of Dermatology. Position statement on generic therapeutic & biosimilar substitution. https://www.aad.org/Forms/Policies/Uploads/PS/PS-Generic%20Therapeutic%20and%20%20Biosimilar%20Substitution.pdf (2013). Accessed 12 Apr 2017.

124. Canadian Association of Psoriasis Patients. Our position on biosimilars: additional considerations. http://www.canadianpsoriasis.ca/index.php/en/biosimilars/our-position (2014). Accessed 12 Apr 2017.

125. Carretero Hernandez G. Puig L, Del Grupo de Psoriasis de la AEDV. The use of biosimilar drugs in psoriasis: a position paper. Actas Dermosifiliogr. 2015;106:249–51.

126. National Psoriasis Foundation. Biosimilar substitution. https://www.psoriasis.org/about-psoriasis/treatments/statement-on-biosimilars (2015). Accessed 12 Apr 2017.

127. Torres T, Ferreira A, Ferreira P, et al. Portuguese position paper on the use of biosimilars in psoriasis. Acta Med Port. 2016;29:574–7.

128. International Federation of Pharmaceutical Manufacturers & Associations (IFMPA). Policy statement. Non-comparable biotherapeutic products. http://www.ifpma.org/wp-content/uploads/2016/02/Non-comparable_Biotherapeutic_Products__English__02.pdf (2014). Accessed 24 Mar 2016.

129. Castaneda-Hernandez G, Szekanecz Z, Mysler E, et al. Biopharmaceuticals for rheumatic diseases in Latin America, Europe, Russia, and India: innovators, biosimilars, and intended copies. Jt Bone Spine. 2014;81:471–7.

130. Generics and Biosimilars Initiative (GaBi). Mexico issues rules on biolimbos [online posting]. http://www.gabionline.net/Guidelines/Mexico-issues-rules-on-biolimbos (2015). Accessed 2 Feb 2018.

131. Feldman SR, Zhao Y, Shi L, Tran MH. Economic and comorbidity burden among patients with moderate-to-severe psoriasis. J Manag Care Spec Pharm. 2015;21:874–88.

132. Burgos-Pol R, Martinez-Sesmero JM, Ventura-Cerda JM, Elias I, Caloto MT, Casado MA. The cost of psoriasis and psoriatic arthritis in 5 European countries: a systematic review. Actas Dermosifiliogr. 2016;107:577–90.

133. Le Moigne M, Sommet A, Lapeyre-Mestre M, et al. Healthcare cost impact of biological drugs compared with traditional systemic treatments in psoriasis: a cohort analysis in the French insurance database. J Eur Acad Dermatol Venereol. 2014;28:1235–44.

134. Council of the European Union. IV. Council conclusions on the economic crisis and healthcare (C 217/02). http://eur-lex.europa.eu/legal-content/EN/TXT/?uri=celex:52014XG0710(01) (2014). Accessed 28 Feb 2018.

135. Remuzat C, Dorey J, Cristeau O, Ionescu D, Radiere G, Toumi M. Key drivers for market penetration of biosimilars in Europe. J Mark Access Health Policy. 2017;5:1272308.

136. Kawalec P, Stawowczyk E, Tesar T, et al. Pricing and reimbursement of biosimilars in Central and Eastern European countries. Front Pharmacol. 2017;8:288.

137. Cohen AD, Wu JJ, Puig L, et al. Biosimilars for psoriasis: worldwide overview of regulatory guidelines, uptake and implications for dermatology clinical practice. Br J Dermatol. 2017;177:1495–502.