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REVIEW

Bioequivalence of Biosimilar Tumor Necrosis Factor-α Inhibitors Compared With Their Reference Biologics

A Systematic Review

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Background: Biosimilars are of growing clinical, regulatory, and commercial importance.

Purpose: To summarize evidence about the bioequivalence between biosimilar and reference tumor necrosis factor-α (TNF-α) inhibitors.

Data Sources: PubMed, EMBASE, Cochrane Central Register of Controlled Trials, and LILACS from inception through 13 April 2016 and ClinicalTrials.gov, World Health Organization International Clinical Trials Registry Platform, EU Clinical Trials Register, U.S. Food and Drug Administration, and European Medicines Agency from inception through 30 April 2016.

Study Selection: Published English-language studies of any size or design that compared the pharmacokinetics, clinical efficacy, adverse events, or immunogenicity of a biosimilar TNF-α inhibitor with a reference biologic in humans.

Data Extraction: Two reviewers independently screened titles and abstracts, extracted data from selected studies, and assessed study quality.

Data Synthesis: Of 19 eligible studies, 8 were phase 1 randomized trials, 5 were phase 3 randomized trials, and 6 were observational studies. Most phase 1 trials (n = 7) involved healthy volunteers, phase 3 trials involved patients with rheumatoid arthritis, and observational studies involved those with rheumatoid arthritis or inflammatory bowel disease. All phase 1 trials showed that pharmacokinetic parameters of the biosimilar and respective biologic were within the prespecified equivalence margin of 80% to 125%. Phase 3 trials suggested similar clinical responses and adverse events. Adverse events were usually of mild to moderate severity. Two cross-sectional observational studies showed cross-reactivity between products, whereas 4 cohort studies of patients switched from reference to biosimilar products suggested similar efficacy and safety outcomes.

Limitation: Possible publication bias, small sample sizes of many studies, and lack of published studies for several biosimilars.

Conclusion: Preliminary evidence supports the biosimilarity and interchangeability of biosimilar and reference TNF-α inhibitors.

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Biologics, or medical products made by or derived from a living organism, represent the fastest growing pharmaceutical sector. By 2017, sales for these products are expected to make up approximately 20% of the total pharmaceutical market (1). With many top-selling biologics facing patent expiration, the introduction of noninnovator products promises significant savings for health care systems.

The pharmacologic activity of biologics is heavily dependent on the manufacturing process, wherein small changes can alter the structure of the resulting protein (2). Due to the large, complex structures of biologics and the variability inherent in the manufacturing process, it is impossible to create a precise replica, or "generic version," of a biologic (3). Instead, the term *biosimilar* is commonly used to refer to noninnovator biologics. The European Medicines Agency (EMA) defines a biosimilar as "a biological medicinal product that contains a version of the active substance of an already authorised original biological medicinal product (reference medicinal product)" (4). For marketing authorization, manufacturers must show that the product is similar to the reference medical product in terms of physicochemical characteristics, adverse effects, and clinical efficacy (4). The U.S. Food and Drug Administration (FDA) defines a biosimilar as being a product highly similar to an authorized biologic with no clinically meaningful difference from the reference product (5). In many cases, manufacturers are also asked to show that a biosimilar and its reference product are interchangeable. *Interchangeability*, as defined by the FDA, means that the product is expected to produce the same clinical result as the reference product in any given patient (5).

One of the largest contributors to expenditures on biologics is tumor necrosis factor-α (TNF-α) inhibitors (1), which block cytokine TNF-α and reduce chronic inflammation (6). At the time of their introduction, these drugs were an important innovation in the management of inflammatory disorders, such as inflammatory bowel disease (IBD) and rheumatoid arthritis (RA) (1, 7). Currently, 5 innovator TNF-α inhibitors are on the market: adalimumab (Humira), certolizumab pegol (Cimzia), etanercept (Enbrel), golimumab (Simponi), and infliximab (Remicade) (6).

In April 2016, the FDA approved the infliximab biosimilar Inflectra, which is only the second biosimilar to

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Table 1. Characteristics of Randomized, Controlled Trials Comparing BSM With REF TNF-α Inhibitors

Study, Year (Reference)	Study Design	Location
Healthy adults		
Gu et al, 2011 (24)	Phase 1 open-label, single-dose, 2-period, crossover trial	Korea
Yi et al, 2012 (25)	Phase 1 double-blind, single-dose, 2-period, 2-sequence, crossover trial	Korea
Park et al, 2015 (26)	Phase 1 double-blind, single-dose, 3-group, parallel-group trial	Germany
Shin et al, 2015 (27)	Phase 1 double-blind, single-dose, 3-group, parallel-group trial	Germany
Lambert et al, 2016 (28)	Phase 1 double-blind, single-dose, parallel-group trial	United Kingdom
Lee et al, 2016 (29)	Phase 1 single-blind, single-dose, 2-period, 2-sequence, crossover trial	Germany
Patients with AS		
Park et al, 2013 (30) Park et al, 2016 (31)	PLANETAS trial: Phase 1 double-blind, multicenter, parallel-group trial	Multinational
Patients with RA		
Takeuchi et al, 2015 (32)	Phase 1 double-blind, multicenter, parallel-group trial	Japan
Yoo et al, 2013 (33) Yoo et al, 2015 (34)	PLANETRA trial: Phase 3 double-blind, multicenter, parallel-group study	Multinational
Choe et al, 2015 (35)	Phase 3 double-blind, multicenter, parallel-group study	Multinational
Emery et al, 2015 (36)	Phase 3 double-blind, parallel-group, multicenter study	Multinational
Jani et al, 2015 (37)	Phase 3 double-blind, multicenter, parallel-group trial	India
Bae et al, 2016 (38)	Phase 3 double-blind, multicenter, parallel-group trial	Korea

AE = adverse effects; AS = ankylosing spondylitis; BSM = biosimilar; CE = clinical efficacy; EU = European Union; IMM = immunogenicity; PK = pharmacokinetic; PLANETAS = Programme Evaluating the Autoimmune Disease Investigational Drug CT-P13 in Ankylosing Spondylitis Patients; PLANETRA = Programme Evaluating the Autoimmune Disease Investigational Drug CT-P13 in Rheumatoid Arthritis Patients; RA = rheumatoid arthritis; REF = reference biologic; TNF-α = tumor necrosis factor-α; US = United States.
* Published results limited to end points at week 24.

receive market approval in the United States (8). Inflectra (marketed as Remsima in some countries) is now available in Canada, Australia, Korea, and all countries under the jurisdiction of the EMA (9). Korea has 2 approved etanercept biosimilars, the first of which was approved in November 2014 (10, 11), and 1 approved infliximab biosimilar (12). India has a handful of biosimilars currently marketed (13–15). Despite the growing availability of these products, questions remain about their comparability with reference biologics (16–18). We conducted a systematic review of evidence about the comparability of the pharmacokinetics, clinical efficacy, adverse events, and immunogenicity of biosimilar TNF-α inhibitors and their respective reference biologics.

METHODS

Protocol

We registered a protocol on 12 August 2015 (PROSPERO: CRD42015025262) (19) and modified it to update and extend searches through April 2016.

Data Sources and Searches

We searched PubMed, EMBASE, Cochrane Central Register of Controlled Trials, and LILACS without language or publication type restrictions from inception through 13 April 2016 to identify eligible articles using relevant keywords and Medical Subject Headings (**Appendix Table 1**, available at www.annals.org). To help assess possible publication bias and identify ongoing trials, we also searched ClinicalTrials.gov, World Health Organization International Clinical Trials Registry Platform, EU Clinical Trials Register, and FDA and EMA Web sites on 30 April 2016 (**Appendix Table 1**).

Study Selection

Two reviewers independently reviewed the titles and abstracts of studies, which had been downloaded from the searches into EndNote X7.3.1 (Thomson Reuters), and came to consensus about eligibility. We required that studies compare the adverse effects, immunogenicity, clinical efficacy, or pharmacokinetic bioequivalence of a biosimilar TNF-α inhibitor and a reference biologic in humans. Only studies of TNF-α biosimilars that had full-text publications of studies comparing them with their reference biologic were included. We excluded biomimics, which are noninnovator biologics that were approved for marketing before the development of biosimilar regulations. Examples of etanercept biomimics include Etanar (approved in Colombia) and Yisaipu (approved in China). We did not apply any restrictions about the study population, sample size, or study design and included studies of healthy volunteers and case series describing patients who were switched from a reference biologic to a corresponding biosimilar. Studies in which no English translation was available were excluded.

Data Extraction and Quality Assessment

Two reviewers independently extracted data about the study design, study population, intervention and comparator, pharmacokinetics, clinical efficacy, adverse events, and immunogenicity. Pharmacokinetic outcomes included area under the curve (AUC) and the maximum and minimum serum levels of the drug (C_{max} and C_{trough}) at different time intervals. Clinical efficacy was defined on the basis of primary outcomes of the trials, which typically used such standardized measures of disease activity as the Assessment of SpondyloArthritis international Society (ASAS) response criteria (20) and

Table 1–Continued

Funding Source	BSM vs. REF	Study Length, *wk*	Outcomes
Mycenax Biotech and Biotrion	TuNEX vs. etanercept	3 per period, 1-wk washout	PK, AE
Hanwha Chemical Biologics	HD203 vs. etanercept	3 per period, 4-wk washout	PK, AE
Celltrion	CT-P13 vs. infliximab (REF for EU) vs. infliximab (REF for US)	8	PK, AE
Samsung Bioepis	SB2 vs. infliximab (REF for EU) vs. infliximab (REF for US)	10	PK, AE, IMM
Epirus Biopharmaceuticals	BOW015 vs. infliximab	12	PK, AE, IMM
Samsung Bioepis	SB4 vs. infliximab (REF for EU) vs. infliximab (REF for US)	3 per period, 4-wk washout	PK, AE, IMM
Celltrion	CT-P13 vs. infliximab	54	PK, CE, AE, IMM
Celltrion and Nippon Kayaku	CT-P13 vs. infliximab	54	PK, CE, AE, IMM
Celltrion	CT-P13 vs. infliximab	54	PK, CE, AE, IMM
Samsung Bioepis	SB2 vs. infliximab	54	PK, CE, AE, IMM
Samsung Bioepis	SB4 vs. etanercept	52*	PK, CE, AE, IMM
Cadila Healthcare	ZRC-3197 vs. adalimumab	12	CE, AE, IMM
Hanwha Chemical Biologics	HD203 vs. etanercept	48	CE, AE, IMM

the American College of Rheumatology (ACR) remission criteria (21). We defined adverse events as undesirable medical occurrences that may or may not have been causally related to the exposure in question and extracted them as quantified in the included studies. We also extracted immunogenicity data that reported the proportion of patients exposed to a biosimilar or reference product who developed antibodies to the product.

Two reviewers independently assessed quality at the study level using the Cochrane Risk of Bias Tool (22) for clinical trials and the Newcastle–Ottawa Scale (23) for observational studies. We assessed detection bias based on whether authors explicitly stated that the outcome assessors were masked and attrition bias based on whether data seemed complete for the primary end point and whether methods for addressing missing data were clearly described. Reporting bias was evaluated on the basis of whether the study outcomes were prespecified, and outcome reporting was consistent with what was described in either the published study protocol, if available, or clinical trial registration.

Data Synthesis and Analysis

First, we grouped extracted data on the basis of whether they reported information about pharmacokinetics, clinical efficacy, adverse events, and immunogenicity. Then, we qualitatively summarized outcomes given that the outcome measures differed substantially across studies, precluding quantitative pooling of results. Finally, we examined the influence of study design and population on the outcomes to draw conclusions about the comparability of biosimilars and their reference TNF-α inhibitors.

Role of the Funding Source

This study was supported in part by the Johns Hopkins Center of Excellence in Regulatory Science and Innovation (grant U01 FD004977-01). The funding source had no role in defining questions, developing the protocol, carrying out the review, interpreting data, or deciding to submit the review for publication.

RESULTS

Of 4463 reviewed titles and abstracts, 19 studies described in 21 articles met inclusion criteria (**Appendix Figure 1**, available at www.annals.org). Fifteen of the articles were reports of randomized, controlled trials (24–38); 2 of these (31, 34) provided extended, 54-week results of trials that had been described in previous publications (30, 33). Six articles were observational studies, including 2 cross-sectional studies, 2 prospective cohort studies, 1 retrospective cohort study, and 1 retrospective case series (39–44). Articles addressed the following biosimilars: TuNEX (etanercept), HD203 (etanercept), CT-P13 (infliximab), SB2 (infliximab), BOW015 (infliximab), SB4 (infliximab), and ZRC-3197 (adalimumab). No published studies were found for several biosimilars, such as Intacept (etanercept biosimilar developed by Intas Pharmaceuticals and commercially available in India since March 2015) (45), CHS-0214 (etanercept biosimilar by Coherus BioSciences that is still in the pipeline) (46), and ABP 501 (adalimumab biosimilar by Amgen and submitted for regulatory approval to the FDA) (47).

Of the 13 RCTs, 8 were phase 1 trials (24–32), and 5 were phase 3 trials (33–38) (**Table 1** and **Appendix Table 2**, available at www.annals.org). Most trials were assessed as having moderate risk of bias because of concerns about attrition bias, potential conflicts of interest of the authors, or possible reporting bias. Of note, all trials but 1 (28) were registered and the listed primary outcome in the registry matched the designated primary outcome in the published article (**Appendix Figure 2**, available at www.annals.org). Observational studies had moderate to high risk of bias because of inadequate control groups or comparators, inadequate sample size and follow-up, heterogeneity

of switching time among participants, potential conflicts of interest of authors, or inability to establish temporality in cross-sectional studies (Appendix Figure 3, available at www.annals.org).

Pharmacokinetic Outcomes of Trials

Eight phase 1 trials (24–32), with sample sizes ranging from 23 to 250 persons, evaluated pharmacokinetic outcomes (Appendix Table 3, available at www.annals.org). Participants in these trials were healthy volunteers, except for 2 trials that involved patients with ankylosing spondylitis (AS) (30, 31) and RA (32). Phase 1 trials were a mix of crossover studies and parallel-group studies. Of note, 3 phase 1 studies compared the biosimilar with both the U.S. and E.U. versions of the reference biologic (26, 27, 29). (The FDA regulations require a biosimilar to be compared specifically with a reference biologic approved in the United States.)

All phase 1 trials specified an equivalence margin of 80% to 125%, and the ratio of geometric means for each outcome for all trials was within the prespecified margin indicating equivalence. Three phase 3 (33–36) trials designed primarily to assess clinical efficacy also examined pharmacokinetic outcomes. Treatment groups in these trials had similar average C_{max} and C_{trough} values based on an 80% to 125% equivalence margin. However, in the phase 3 SB4 trial (36), the steady-state AUC was relatively higher for SB4 than the reference etanercept.

Clinical Outcomes of Trials

Table 2 highlights the main clinical outcomes and related secondary end points in each trial. For the phase 1 trial featuring the infliximab biosimilar CT-P13 for treatment of AS (30, 31), the main clinical efficacy outcome was the ASAS response criteria, which was recorded at multiple time points. The ASAS20 and ASAS40 refer to a 20% and 40% improvement, respectively, in a set of clinically relevant measures of AS activity (20). Although this study was not powered to assess clinical efficacy, it compared the clinical efficacy of CT-P13 with the reference biologic in the AS population. No statistically significant differences in the ASAS outcomes were found. At week 30, the odds ratio (biosimilar ÷ reference product) for the ASAS20 and ASAS40 were 0.91 (95% CI, 0.51 to 1.62) and 1.19 (CI, 0.70 to 2.00), respectively. Similar findings were observed at other time points.

All phase 3 trials were parallel-group trials enrolling patients with RA (33–38). These trials typically lasted for 48 to 54 weeks, and sample size generally ranged from 250 to 606 patients, with 1 exception (37). One trial compared the biosimilar ZRC-3197 with the reference adalimumab for 12 weeks and included only 120 patients (37).

Baseline characteristics of patients with RA were similar across trials, although the mean tender joint count was lower in Takeuchi and colleagues' phase 1 trial (32) relative to the other trials (Appendix Table 4, available at www.annals.org). The primary clinical end point for the phase 3 trials was the ACR20 outcome, which is defined as a 20% or greater improvement in the core set of measures for RA activity (21). These outcomes were consistent with those of the primary end points that were used in the reference biologic trials (48, 49). The time point for the primary analysis of ACR20 differed across trials, with end points ranging from weeks 12 to 54. Most phase 3 trials concluded equivalence if the 95% CI for treatment difference was within a ±15% margin at the specified time point. The exceptions were Jani and coworkers' trial (37), which specified a margin of 28.5%, and Bae and colleagues' trial (38) (comparing HD203 with reference etanercept), which specified a margin of 20%. All phase 3 trials showed equivalence between biosimilars and reference biologics based on their prespecified margins (Table 2). In contrast, the small phase 1 trial on CT-P13 (32), which included patients with RA but was not designed to establish equal clinical efficacy, reported a modestly higher clinical response in the biosimilar group than the reference group at week 54 (the ACR70 response rate at week 54 was 42.0% and 13.7% in biosimilar and reference groups, respectively) (32).

Adverse Events Reported in Trials

Adverse events were examined in all trials, with the analytic population including all patients who received at least 1 dose of either a reference drug or biosimilar (Table 3). These events included both treatment-emergent adverse events, or undesired changes in health that were not present before initiation of treatment, and serious adverse events, reflecting those associated with serious injury or death (50).

For most studies, the proportion of patients with treatment-emergent adverse events and the proportion of those with serious adverse events were similar between biosimilar and reference groups. Differences in serious adverse events and adverse events that led to discontinuation were typically not considered to be related to the study treatment. However, in Bae and colleagues' trial (38), which compared the biosimilar HD203 with the reference etanercept, the authors reported that 1 of the deaths in the reference group was due to renal failure that may have been related to etanercept treatment. Further, no deaths were considered to be related to the treatment in any of the other studies examined.

No consistent differences in the type of adverse events between treatment groups were noted. Most treatment-emergent adverse events were of mild to moderate severity. Commonly reported adverse events across trials were similar and included upper respiratory tract infections, latent tuberculosis, increased alanine aminotransferase levels, headache, cough, nasopharyngitis, dizziness, upper abdominal pain, injection site reactions, allergic reactions, oropharyngeal pain, and rash.

Immunogenicity Data Reported in Trials

Ten of the 13 trials assessed immunogenicity (27–38). In 7 of these trials, immunogenicity was determined using an electrochemiluminescent immunoassay, whereas the remaining 3 (28, 37, 38) either used

Table 2. Clinical Efficacy in Randomized, Controlled Trials Comparing BSM With REF TNF-α Inhibitors

Study, Year (Reference)	Phase	BSM vs. REF	Analytical Population and Primary End Point	Time Point, *wk*	Outcome	Patients With Outcome, %		Effect Estimate
						BSM	REF	Odds Ratio for BSM/REF (95% CI)
Patients with AS								
Park et al, 2013 (30)	1	CT-P13 vs. infliximab	ITT. No primary efficacy end point noted. This trial was not powered to assess efficacy.	14	ASAS20 (ITT)	62.6	64.8	0.91 (0.53 to 1.54)
					ASAS40 (ITT)	41.7	45.9	0.85 (0.51 to 1.42)
				30	ASAS20 (ITT)	70.5	72.4	0.91 (0.51 to 1.62)
					ASAS40 (ITT)	51.8	47.4	1.19 (0.70 to 2.00)
				54	ASAS20 (ITT)	67.0	69.4	0.89 (0.50 to 1.59)
					ASAS40 (ITT)	54.7	49.1	1.26 (0.73 to 2.15)
								Difference Between BSM and REF (95% CI), %
Patients with RA								
Takeuchi et al, 2015 (32)	1	CT-P13 vs. infliximab	FAS. No primary efficacy end point noted. This trial was not powered to assess efficacy.	14	ACR20 (FAS)	74.0	70.6	–
					ACR70 (FAS)	28.0	23.5	–
				30	ACR20 (FAS)	78.0	64.7	–
					ACR70 (FAS)	32.0	27.5	–
				54	ACR20 (FAS)	64.0	49.0	–
					ACR70 (FAS)	42.0	13.7	–
Yoo et al, 2015 (34)	3	CT-P13 vs. infliximab	ITT and PP. Primary end point: PP of ACR20 at week 30.	14	ACR20 (PP)	72.6	65.3	7 (–1 to 15)
					ACR70 (PP)	16.5	13.5	3 (–3 to 9)
				30	ACR20 (ITT)	60.9	58.9	2 (–5 to 10)
					ACR20 (PP)	73.4	70.1	3 (–5 to 11)
					ACR70 (PP)	20.2	17.9	2 (–5 to 9)
				54	ACR20 (PP)	74.7	71.3	3 (–5 to 12)
					ACR70 (PP)	21.3	19.9	1 (–6 to 9)
Choe et al, 2015 (35)	3	SB2 vs. infliximab	PP and FAS. Primary end point: PP and FAS analysis of ACR20 at week 30.	30	ACR20 (PP)	64.1	66.0	–1.88 (–10.26 to 6.51)
					ACR20 (FAS)	55.5	59.0	–2.95 (–10.88 to 4.97)
					ACR70 (PP)	18.2	19.0	–0.25 (–7.26 to 6.75)
					ACR70 (FAS)	15.5	17.1	–1.08 (–7.06 to 4.91)
Emery et al, 2015 (36)	3	SB4 vs. etanercept	PP and FAS. Primary end point: PP of ACR20 at week 24.	24	ACR20 (PP)	78.1	80.3	–2.20 (–9.41 to 4.98)
					ACR20 (FAS)	73.8	71.7	1.92 (–5.24 to 9.07)
					ACR70 (PP)	25.5	22.6	3.02 (–4.47 to 10.51)
					ACR70 (FAS)	23.2	19.9	3.35 (–3.10 to 9.81)
Jani et al, 2015 (37)	3	ZRC-3197 vs. adalimumab	ITT and PP. Primary end point: ITT and PP analysis of ACR20 at week 12.	12	ACR20 (ITT)	78.3	79.7	–1.33 (–15.29 to 12.63)
					ACR20 (PP)	82.0	79.6	2.75 (–11.99 to 17.50)
					ACR70 (ITT)	13.3	15.6	–1.92 (–14.16 to 10.31)
					ACR70 (PP)	14.0	15.1	–1.09 (14.46 to 12.38)
Bae et al, 2016 (38)	3	HD203 vs. etanercept	FAS and PP. Primary end point: PP of ACR20 at week 24.	24	ACR20 (PP)	83.5	81.4	2.12 (–7.65 to 11.89)
					ACR20 (FAS)	79.1	75.6	3.55 (–6.45 to 13.55)
					ACR70 (PP)	31.3	31.4	–0.05 (–11.96 to 11.86)
				48	ACR20 (PP)	87.3	86.5	0.79 (–8.12 to 9.69)
					ACR20 (FAS)	82.1	80.0	2.09 (–7.27 to 11.45)
					ACR70 (PP)	38.2	33.9	4.25 (–8.37 to 16.88)

ACR20 = ≥20% improvement in American College of Rheumatology response criteria; ACR70 = ≥70% improvement in American College of Rheumatology response criteria; ASAS20 = ≥20% improvement in Assessment of SpondyloArthritis international Society response criteria; ASAS40 = ≥40% improvement in Assessment of SpondyloArthritis international Society response criteria; BSM = biosimilar; FAS = full-analysis set; ITT = intention-to-treat analysis; PP = per-protocol analysis; RA = rheumatoid arthritis; REF = reference biologic; TNF-α = tumor necrosis factor-α.

alternative means or did not specify their methods. Both electrochemiluminescent immunoassays and enzyme-linked immunosorbent assays are commonly used. Although the former theoretically has increased sensitivity relative to the latter, this is not always the case and comparisons must be made empirically (51, 52).

Immunogenicity, examined in all patients who received at least 1 dose of either the reference drug or a biosimilar, seemed comparable across treatment groups in all studies, with the exception of trials for the etanercept biosimilar, SB4, reported in Emery and colleagues' phase 3 trial (36) and Lee and colleagues' phase 1 trial (29) (Appendix Table 5, available at www.annals.org). In Emery and colleagues' trial, only 0.7% of patients developed antidrug antibodies in the biosimilar group compared with 13.1% of those in the reference biologic group. This trial had baseline population characteristics and retention rates similar to the other trials, including patients with RA. Lee and colleagues' study (29) had a similar pattern wherein no patient in the biosimilar group developed antibodies, although between 15% and 20% of patients in the 2 reference groups had positive test results for antidrug antibodies. Of note, Takeuchi and colleagues' phase 1 trial for CT-P13 (32) showed a lower immunogenicity for both treatment groups than other trials of patients with RA.

Table 3. Adverse Effects in Randomized, Controlled Trials Comparing BSM With REF TNF-α Inhibitors*

Study, Year (Reference)	Phase	BSM vs. REF	Patients, *n* (%)						Deaths, *n*	
			With ≥1 Adverse Event		With ≥1 Serious Adverse Event		Who Discontinued Because of Adverse Events		BSM	REF
			BSM	REF	BSM	REF	BSM	REF		
Healthy adults										
Gu et al, 2011 (24)	1	TuNEX vs. etanercept	11 (52.4)	8 (38.1)	1 (4.76)	0 (0)	1 (4.76)	0 (0)	0	0
Yi et al, 2012 (25)	1	HD203 vs. etanercept	16 (43.2)	16 (45.7)	0 (0)	0 (0)	0 (0)	0 (0)	0	0
Park et al, 2015 (26)	1	CT-P13 vs. infliximab (REF for EU) vs. infliximab (REF for US)	37 (52.1)	EU: 21 (29.6) US: 33 (46.5)	1 (1.4)	EU: 0 (0) US: 1 (1.4)	0 (0)	EU: 0 (0) US: 0 (0)	EU: 0 US: 0	EU: 0 US: 0
Shin et al, 2015 (27)	1	SB2 vs. infliximab (REF for EU) vs. infliximab (REF for US)	27 (50.9)	EU: 21 (39.6) US: 23 (43.4)	2 (3.9)	EU: 0 (0) US: 0 (0)	0 (0)	EU: 0 (0) US: 0 (0)	EU: 0 US: 0	EU: 0 US: 0
Lambert et al, 2016 (28)	1	BOW015 vs. infliximab	26 (60.5)	27 (65.9)	0 (0)	1 (2.4)	0 (0)	0 (0)	0	0
Lee et al, 2016 (29)	1	SB4 vs. infliximab (REF for EU) vs. infliximab (REF for US)	41 (44.6)	EU: 33 (35.9) US: 34 (37.0)	0 (0)	EU: 0 (0) US: 0 (0)	2 (4.3)	EU: 0 (0) US: 0 (0)	EU: 0 US: 0	EU: 0 US: 0
Patients with AS										
Park et al, 2016 (31)	1	CT-P13 vs. infliximab	95 (74.2)	82 (67.2)	10 (7.8)	8 (6.6)	11 (8.6)	9 (7.4)	1	1
Patients with RA										
Takeuchi et al, 2015 (32)	1	CT-P13 vs. infliximab	45 (88.2)	46 (86.8)	8 (15.7)	7 (13.7)	9 (17.6)	6 (11.3)	0	1
Yoo et al, 2015 (34)	3	CT-P13 vs. infliximab	213 (70.5)	211 (70.3)	42 (13.9)	31 (10.3)	33 (10.9)	47 (15.7)	0	1
Choe et al, 2015 (35)	3	SB2 vs. infliximab	167 (57.6)	170 (58.0)	26 (9.0)	26 (8.9)	21 (8.5)†	10 (3.9)†	0	1
Emery et al, 2015 (36)	3	SB4 vs. etanercept	165 (55.2)	173 (58.2)	13 (4.3)	13 (4.4)	8 (2.8)‡	14 (5.2)‡	1	0
Jani et al, 2015 (37)	3	ZRC-3197 vs. adalimumab	7 (11.6)	10 (16.6)	2 (3.3)	1 (1.67)	2 (3.3)	0 (0)	0	0
Bae et al, 2016 (38)	3	HD203 vs. etanercept	113 (76.9)	114 (78.1)	19 (12.9)	18 (12.3)	10 (6.8)	11 (7.5)	0	2

AS = ankylosing spondylitis; BSM = biosimilar; EU = European Union; RA = rheumatoid arthritis; REF = reference biologic; TNF-α = tumor necrosis factor-α; US = United States.
* For all studies, the population analyzed for adverse events included all patients who received ≥1 dose of either a BSM or REF TNF-α inhibitor.
† Refers to dropout by week 30. Dropout due to adverse events at week 54 was not given.
‡ Refers to dropout by week 24. Dropout due to adverse events at week 54 was not given.

Observational Studies of Adverse Effects and Effectiveness

All 6 observational studies involved the biosimilar CT-P13 and its reference infliximab, Remicade (39–44) (Appendix Table 6, available at www.annals.org). Participants in these studies were patients with rheumatoid diseases (40, 43) or IBD (39, 41, 42, 44). Two cross-sectional studies (39, 40) examined sera collected from Remicade-treated patients for cross-reactivity to CT-P13. Only sera samples that were positive for antibodies to the reference biologic were cross-reactive to CT-P13.

Four cohort studies (41–44) provided some data on the effectiveness and safety of switching from the reference biologic to CT-P13. The cohorts fully or partially comprised patients who were switched from the reference biologic to CT-P13 during maintenance therapy. All studies reported that most patients who were in remission before switching remained in remission. Studies had small sample sizes, did not have comparator groups of patients who continued to receive the reference drug, and had significant heterogeneity in the times at which patients were switched from the reference biologic to the biosimilar. Because the primary goal of 3 of the studies (41, 42, 44) was to assess the use of CT-P13 in patients with IBD, some patients were infliximab-naive and had received CT-P13 as part of their induction therapy.

Discussion

In this systematic review of the bioequivalence of biosimilar and reference TNF-α inhibitors, we identified 19 eligible studies: 8 phase 1 randomized trials, 5 phase 3 randomized trials, and 6 observational studies. Six of the 8 phase 1 trials studied healthy volunteers; the phase 3 trials enrolled only patients with RA, and the observational studies involved those with RA or IBD. The pharmacokinetic variables in phase 1 trials supported the comparability of reference and biosimilar products, as did most adverse effect variables and all of the major clinical efficacy end points examined in the phase 3 trials. Observational studies showed cross-reactivity between products. The cohort studies of patients switched from reference to biosimilar products indicated similar efficacy at maintaining disease remission.

Although biosimilar and reference products were generally similar, we noted a few differences. For example, trials of the etanercept biosimilar SB4 reported lower immunogenicity in the SB4 group (29, 36). However, because clinical efficacy was equal in the subset of patients without antidrug antibodies, this difference does not preclude SB4 from being classed as a biosimilar (36). Emery and colleagues' trial (36) also reported a relatively higher AUC value for SB4 than the reference product, which the authors speculated may be due to inherently high interpatient variability. Takeuchi and colleagues' trial of CT-P13 (32) showed lower immunogenicity relative to other phase 3 trials that tested an infliximab biosimilar (**Appendix Table 5**), and this difference may have been due to the effect of race and ethnicity on immunogenicity (53). Lastly, of the 5 phase 3 trials in patients with RA, Jani and coworkers' trial (37) for the biosimilar adalimumab ZRC-3197 was unique in terms of its smaller sample size and shorter duration. This shorter duration was justified by the investigators on the basis of an international consensus statement about the length of time required to note significant improvement at appropriate dosing regimens (54).

We searched PubMed for systematic and narrative reviews about biosimilars published in the past 2 years and identified several narrative reviews. A recent review by Dörner and Kay (55) discussed biosimilars that have been approved in the past 3 years and those that are still under development. Another narrative review by Isaacs and colleagues (56) discussed regulatory and clinical issues about CT-P13, which was the first infliximab biosimilar approved for marketing. Papamichael and coworkers (57) reviewed the TNF-α biosimilars and focused on their utility in patients with IBD. Our investigation adds to these reports because we systematically identified studies and discuss the pharmacokinetics, clinical efficacy, adverse events, and immunogenicity of biosimilar TNF-α inhibitors and their respective reference biologics without any restrictions on the study population or design. Our study outlines key details of each trial and contrasts them to highlight the variability across trials. Further, we were not limited to assessing only approved biosimilars, which was the focus of Dörner and Kay's comprehensive review. Instead, we searched for data on all TNF-α biosimilars regardless of regulatory status.

Our study has limitations. First, the magnitude of potential publication bias in our analysis is unclear. Although we attempted to mitigate this by searching for unpublished trials, selective reporting in the published studies and selective publication of results favorable to the sponsoring manufacturer remain likely. Most unpublished but completed trials are for as-yet-unapproved biosimilars. An exception is the open-label study sponsored by Nippon Kayaku (JPRN-JapicCTI-142419) (**Appendix Table 7**, available at www.annals.org) that extends the results of a published trial (32) and is marked as being completed. Full-text results for most pivotal trials of the approved drugs were available, except for the phase 3 trial on the infliximab biosimilar BOW015 (approved in India) (13). Furthermore, the FDA and EMA Web sites indicated 2 completed studies of CT-P13 without full-text publications. These studies were small and marked as either pilot studies or studies supporting pivotal trials (58). Of note, our review focused on only primary clinical efficacy outcomes, and thus we did not examine important secondary outcomes, such as quality-of-life assessments, that were included in some trials.

Many questions remain about the use and regulation of biosimilar TNF-α products. For example, phase 3 trials have tested their effects in patients with RA, yet it is unclear how much these studies can be extrapolated to other populations, such as those with IBD or psoriasis. Some evidence supports "indication extrapolation" (59), and some biosimilars have been approved for IBD despite having only been studied among patients with AS or RA (60). On the other hand, different dosing regimens and concomitant medicines may pose barriers to extrapolating information from 1 clinical population to another (57). Many ongoing studies are assessing the performance of biosimilars in patients with IBD (**Appendix Table 7**).

Another important set of questions pertains to the ability to switch patients from biosimilar to originator products and vice versa. Some providers report a hesitancy to switch patients from an originator product without disease-specific evidence about interchangeability (17). Many trials have included an open-label extension phase to assess the ability to switch between reference and biosimilar products. For example, trials by Park and colleagues (61) and Yoo and coworkers (62) were published in late April 2016 and were not captured by our search. These extension studies suggested that switching from the reference biologic to CT-P13, compared with continuing to receive CT-P13 throughout, did not result in any significant difference in adverse events between treatment groups for patients with AS or RA.

Many postmarketing studies have also been initiated to address the issue of switching, such as one in Norway (63) evaluating outcomes from switching patients with RA, IBD, and psoriasis from reference to biosimilar infliximab.

Despite some analogies between standard generic "small-molecule" therapies and biosimilar products, important differences remain. These differences, along with the rapidly growing importance of biologics in pharmaceutical care, have created considerable uncertainty about exactly how interchangeable biologics are and in what context. The core dilemma for patients, caregivers, providers, and health systems is, "To what degree is biosimilar product A interchangeable with originator product A, under what circumstances, and for what population of patients?" Despite the paucity of studies, the existing evidence supports the biosimilarity and interchangeability of these newly developed TNF-α inhibitor products, especially for the treatment of patients with RA.

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Appendix Table 1. Search Strategy

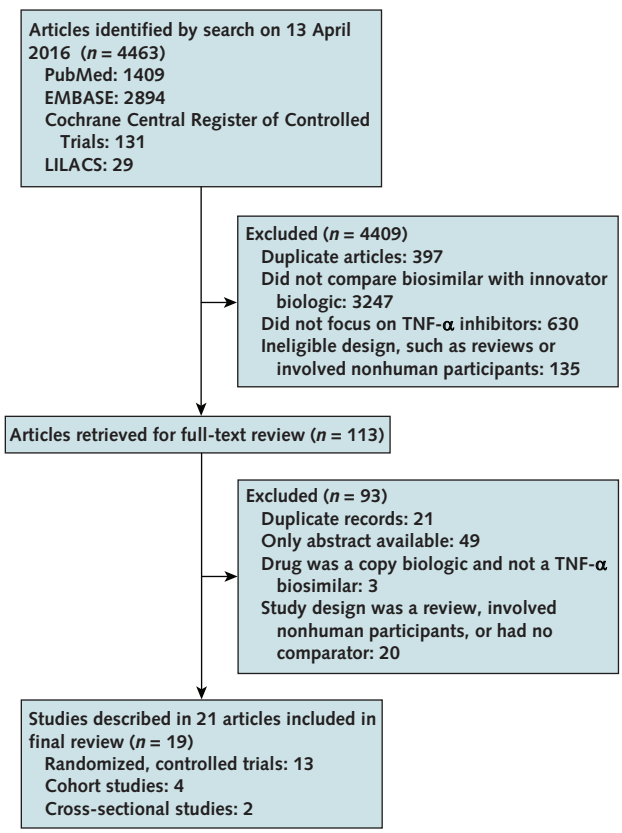
Database	Hits	Search Terms
PubMed Searched on April 13, 2016	1409	1. "CT-P13" [Supplementary Concept] OR "CT-P13"[tw] OR "Remsima"[tw] OR "Inflectra"[tw] OR "Flammegis"[tw] OR "Infliximab BS"[tw] OR "PF-06538179"[tw] OR "Infimab"[tw] OR "BOW015" [tw] OR "NI-071"[tw] OR "ABP 710" [tw] OR "BX2922" [tw] OR "Etacept" [tw] OR "CHS-0214" [tw] OR "Davictrel" [tw] OR "HD203" [tw] OR "Intacept" [tw] OR "LBEC 0101" [tw] OR "LBEC0101" [tw] OR "Tunex" [tw] OR "ENIA11" [tw] OR "PRX-106" [tw] OR "GP2015" [tw] OR "Brenzys" [tw] OR "Etanar" [tw] OR "Yisaipu" [tw] OR "PF688" [tw] OR "ABP 501"[tw] OR "BOW050" [tw] OR "BI695501" [tw] OR "BI 695501" [tw] OR "CHS-1420" [tw] OR "FKB327" [tw] OR "LBAL" [tw] OR "M923" [tw] OR "ONS-3010" [tw] OR "PF-06410293" [tw]OR "GP2017" [tw] OR "Exemptia" [tw] OR "ZRC-3197" [tw] 2. "Biosimilar Pharmaceuticals"[Mesh] OR Biosimilar*[tw] OR "Follow-on biologic"[tw] OR "Follow-on biologics"[tw] OR "Follow-on biological"[tw] OR "Follow-on biologicals"[tw] OR "Subsequent entry biologic"[tw] OR "Subsequent entry biologics"[tw] OR "Subsequent entry biological"[tw] OR "Subsequent entry biologicals"[tw] OR "Similar biotherapeutic"[tw] OR "Similar biotherapeutics"[tw] OR "Similar biologicals"[tw] OR "Similar biologics"[tw] OR Biogeneric*[tw] OR "Me-too biologic"[tw] OR "Me-too biologics"[tw] OR "Me-too biological"[tw] OR "Me-too biologicals"[tw] OR "Non-innovator biologic"[tw] OR "Non-innovator biologics"[tw] OR "Non-innovator biological"[tw] OR "Non-innovator biologicals"[tw] 3. #1 OR #2 4. ("animals"[MeSH Terms]) NOT ("humans"[MeSH Terms]) 5. #3 NOT #4
EMBASE Searched on April 13, 2016	2894	1. ("CT-P13" OR "Remsima" OR "Inflectra" OR "Flammegis" OR "Infliximab BS" OR "PF-06538179" OR "Infimab" OR "BOW015" OR "NI-071" OR "ABP 710" OR "BX2922" OR "Etacept" OR "CHS-0214" OR "Davictrel" OR "HD203" OR "Intacept" OR "LBEC 0101" OR "LBEC0101" OR "Tunex" OR "ENIA11" OR "PRX-106" OR "GP2015" OR "Brenzys" OR "Etanar" OR "Yisaipu" OR "PF688" OR "ABP 501" OR "BOW050" OR "BI695501" OR "BI 695501" OR "CHS-1420" OR "FKB327" OR "LBAL" OR "M923" OR "ONS-3010" OR "PF-06410293" OR "GP2017" OR "Exemptia" OR "ZRC-3197"):ti,ab,tn 2. 'biosimilar agent'/exp OR (Biosimilar* OR "Follow-on biologic" OR "Follow-on biologics" OR "Follow-on biological" OR "Follow-on biologicals" OR "Subsequent entry biologic" OR "Subsequent entry biologics" OR "Subsequent entry biological" OR "Subsequent entry biologicals" OR "Similar biotherapeutic" OR "Similar biotherapeutics" OR "Similar biologicals" OR "Similar biologics" OR Biogeneric* OR "Me-too biologic" OR "Me-too biologics" OR "Me-too biological" OR "Me-too biologicals" OR "Non-innovator"):ti,ab 3. #1 OR #2 4. ('animal'/exp) NOT ('human'/exp) 5. #3 NOT #4
Cochrane Library Searched on April 13, 2016	131	1. "CT-P13" OR "Remsima" OR "Inflectra" OR "Flammegis" OR "Infliximab BS" OR "PF-06538179" OR "Infimab" OR "BOW015" OR "NI-071" OR "ABP 710" OR "BX2922" OR "Etacept" OR "CHS-0214" OR "Davictrel" OR "HD203" OR "Intacept" OR "LBEC 0101" OR "LBEC0101" OR "Tunex" OR "ENIA11" OR "PRX-106" OR "GP2015" OR "Brenzys" OR "Etanar" OR "Yisaipu" OR "PF688" OR "ABP 501" OR "BOW050" OR "BI695501" OR "BI 695501" OR "CHS-1420" OR "FKB327" OR "LBAL" OR "M923" OR "ONS-3010" OR "PF-06410293" OR "GP2017" OR "Exemptia" OR "ZRC-3197" 2. MeSH descriptor: [Biosimilar Pharmaceuticals] explode all trees 3. Biosimilar* OR "Follow-on biologic" OR "Follow-on biologics" OR "Follow-on biological" OR "Follow-on biologicals" OR "Subsequent entry biologic" OR "Subsequent entry biologics" OR "Subsequent entry biological" OR "Subsequent entry biologicals" OR "Similar biotherapeutic" OR "Similar biotherapeutics" OR "Similar biologicals" OR "Similar biologics" OR Biogeneric* OR "Me-too biologic" OR "Me-too biologics" OR "Me-too biological" OR "Me-too biologicals" OR "Non-innovator" 4. #1 or #2 or #3
LILACS (Latin American and Caribbean Health Sciences) Searched on April 13, 2016	29	Biosimilar$ OR Biosimilare$ORBiossimilare$ OR MH:D20.215.261$ OR "Follow-on biologics" OR "Follow-on biological" OR "Follow-on biologicals" OR "Subsequent entry biologic" OR "Subsequent entry biologics" OR "Subsequent entry biological" OR "Subsequent entry biologicals" OR "Similar biotherapeutic" OR "Similar biotherapeutics" OR "Similar biologicals" OR "Similar biologics" OR Biogeneric* OR "Me-too biologic" OR "Me-too biologics" OR "Me-too biological" OR "Me-too biologicals" OR "Non-innovator" OR "CT-P13" OR "Remsima" OR "Inflectra" OR "Flammegis" OR "Infliximab BS" OR "PF-06538179" OR "Infimab" OR "BOW015" OR "NI-071" OR "ABP 710" OR "BX2922" OR "Etacept" OR "CHS-0214" OR "Davictrel" OR "HD203" OR "Intacept" OR "LBEC 0101" OR "LBEC0101" OR "Tunex" OR "ENIA11" OR "PRX-106" OR "GP2015" OR "Brenzys" OR "Etanar" OR "Yisaipu" OR "PF688" OR "ABP 501" OR "BOW050" OR "BI695501" OR "BI 695501" OR "CHS-1420" OR "FKB327" OR "LBAL" OR "M923" OR "ONS-3010" OR "PF-06410293" OR "GP2017" OR "Exemptia" OR "ZRC-3197"
ClinicalTrials.gov Searched on April 30, 2016	203	"CT-P13" OR "Remsima" OR "Inflectra" OR "BOW015" OR "NI-071" OR "ABP 710" OR "BX2922" OR "Etacept" OR "CHS-0214" OR "Davictrel" OR "HD203" OR "Intacept" OR "LBEC 0101" OR "LBEC0101" OR "ENIA11" OR "GP2015" OR "Yisaipu" OR "PF688" OR "ABP 501" OR "BOW050" OR "BI695501" OR "BI 695501" OR "CHS-1420" OR "FKB327" OR "LBAL" OR "M923" OR "ONS-3010" OR Biosimilar OR "Similar biologicals" No studies found for the following terms: "Flammegis" OR "Infliximab BS" OR "PF-06538179" OR "Infimab" OR "Tunex" OR "PRX-106" OR "Brenzys" OR "Etanar" OR "PF-06410293" OR "GP2017" OR "Exemptia" OR "ZRC-3197" OR "Follow-on biologic" OR "Follow-on biologics" OR "Follow-on biological" OR "biosimilar agent" OR "Follow-on biologicals" OR "Subsequent entry biologic" OR "Subsequent entry biologics" OR "Subsequent entry biological" OR "Subsequent entry biologicals" OR "Similar biotherapeutic" OR "Similar biotherapeutics" OR "Similar biologics" OR Biogeneric* OR "Me-too biologic" OR "Me-too biologics" OR "Me-too biological" OR "Me-too biologicals" OR "Non-innovator"

Continued on following page

Appendix Table 1–Continued

Database	Hits	Search Terms
World Health Organization International Clinical Trials Registry Platform (ICTRP) http://apps.who.int/trialsearch/ Searched on April 30, 2016	2790	"CT-P13" OR "Remsima" OR "Inflectra" OR "BOW015" OR "NI-071" OR "ABP 710" OR "BX2922" OR "Etacept" OR "CHS-0214" OR "Davictrel" OR "HD203" OR "Intacept" OR "LBEC 0101" OR "LBEC0101" OR "ENIA11" OR "GP2015" OR "Yisaipu" OR "PF688" OR "ABP 501" OR "BOW050" OR "BI695501" OR "BI 695501" OR "CHS-1420" OR "FKB327" OR "LBAL" OR "M923" OR "ONS-3010" OR Biosimilar OR "Similar biologicals" OR "Flammegis" OR "Infliximab BS" OR "PF-06538179" OR "Infimab" OR "Tunex" OR "PRX-106" OR "Brenzys" OR "Etanar" OR "PF-06410293" OR "GP2017" OR "Exemptia" OR "ZRC-3197" OR "Follow-on biologic" OR "Follow-on biologics" OR "Follow-on biological" OR "biosimilar agent" OR "Follow-on biologicals" OR "Subsequent entry biologic" OR "Subsequent entry biologics" OR "Subsequent entry biological" OR "Subsequent entry biologicals" OR "Similar biotherapeutic" OR "Similar biotherapeutics" OR "Similar biologics" OR Biogeneric* OR "Me-too biologic" OR "Me-too biologics" OR "Me-too biological" OR "Me-too biologicals" OR "Non-innovator"
European Inion Clinical Trials Register www.clinicaltrialsregister.eu Searched on April 30, 2016	510	"CT-P13" OR "Remsima" OR "Inflectra" OR "BOW015" OR "NI-071" OR "ABP 710" OR "BX2922" OR "Etacept" OR "CHS-0214" OR "Davictrel" OR "HD203" OR "Intacept" OR "LBEC 0101" OR "LBEC0101" OR "ENIA11" OR "GP2015" OR "Yisaipu" OR "PF688" OR "ABP 501" OR "BOW050" OR "BI695501" OR "BI 695501" OR "CHS-1420" OR "FKB327" OR "LBAL" OR "M923" OR "ONS-3010" OR Biosimilar OR "Similar biologicals" OR "Flammegis" OR "Infliximab BS" OR "PF-06538179" OR "Infimab" OR "Tunex" OR "PRX-106" OR "Brenzys" OR "Etanar" OR "PF-06410293" OR "GP2017" OR "Exemptia" OR "ZRC-3197" OR "Follow-on biologic" OR "Follow-on biologics" OR "Follow-on biological" OR "biosimilar agent" OR "Follow-on biologicals" OR "Subsequent entry biologic" OR "Subsequent entry biologics" OR "Subsequent entry biological" OR "Subsequent entry biologicals" OR "Similar biotherapeutic" OR "Similar biotherapeutics" OR "Similar biologics" OR Biogeneric* OR "Me-too biologic" OR "Me-too biologics" OR "Me-too biological" OR "Me-too biologicals" OR "Non-innovator"

Appendix Figure 1. Evidence search and selection.



TNF-α = tumor necrosis factor-α.

Appendix Table 2. Characteristics of the Intervention in Randomized, Controlled Trials Comparing BSM With REF TNF-α Inhibitors

Study, Year (Reference); Phase	Drug	Completed/Enrolled, *n/N*	Dose	Frequency	Duration and Route
Study population: healthy adults					
Gu, 2011 (24); phase 1	TuNEX and REF etanercept	19/25*	25 mg	Single administration per dosing period	Subcutaneous injection
Yi, 2012 (25); phase 1	HD203 and REF etanercept	35/37*			
Park, 2015 (26); phase 1	CT-P13	70/71	5 mg/kg	Single administration at start of study	2-h IV infusion
	REF infliximab (EU)	71/71			
	REF infliximab (US)	70/71			
Shin, 2015 (27); phase 1	SB2	53/53	5 mg/kg	Single administration at start of study	2-h IV infusion
	REF infliximab (EU)	53/53			
	REF infliximab (US)	53/53			
Lambert, 2016 (28); phase 1	BOW015	43/43	5 mg/kg	Single administration at start of study	2-h IV infusion
	REF infliximab	40/41			
Lee, 2016 (29); phase 1	SB4/REF etanercept (EU)	45/46†	50 mg	Single administration per dosing period	
	SB4/REF etanercept (US)	45/46†			
Study population: AS patients					
Park, 2013 (30); phase 1 (PLANETAS)	CT-P13	106/125‡	5 mg/kg	Week 0, 2, 6, then every 8 wk until week 30	2-h IV infusion
	REF infliximab	104/125‡			
Study population: RA patients					
Takeuchi, 2015 (32); phase 1	CT-P13	39/50	3 mg/kg	Week 0, 2, 6, then every 8 wk until week 54	2-h IV infusion
	REF infliximab	39/51			
Yoo, 2015 (34); phase 3 (PLANETRA)	CT-P13	233/302‡	3 mg/kg	Week 0, 2, 6, then every 8 wk until week 30	2-h IV infusion
	REF infliximab	222/304‡			
Choe, 2015 (35); phase 3	SB2	246/291§	3 mg/kg	Week 0, 2, 6, then every 8 wk until week 54	2-h IV infusion
	REF infliximab	259/293§			
Emery, 2015 (36); phase 3	SB4	283/299	50 mg	Once weekly for 52 wk	Subcutaneous injection
	REF etanercept	268/297			
Jani, 2015 (37); phase 3	ZRC-3197	60/60	40 mg	Week 0, 2, 4, 8, 12	Subcutaneous injection
	REF adalimumab	59/60			
Bae, 2016 (38); phase 3	HD203	102/147	25 mg	Twice weekly	Subcutaneous injection
	REF etanercept	105/147			

AS = ankylosing spondylitis; BSM = biosimilar; EU = European Union; IV = intravenous; PLANETAS = Programme Evaluating the Autoimmune Disease Investigational Drug CT-P13 in Ankylosing Spondylitis Patients; PLANETRA = Programme Evaluating the Autoimmune Disease Investigational Drug CT-P13 in Rheumatoid Arthritis Patients; RA = rheumatoid arthritis; REF = reference biologic; TNF-α = tumor necrosis factor-α; US = United States.

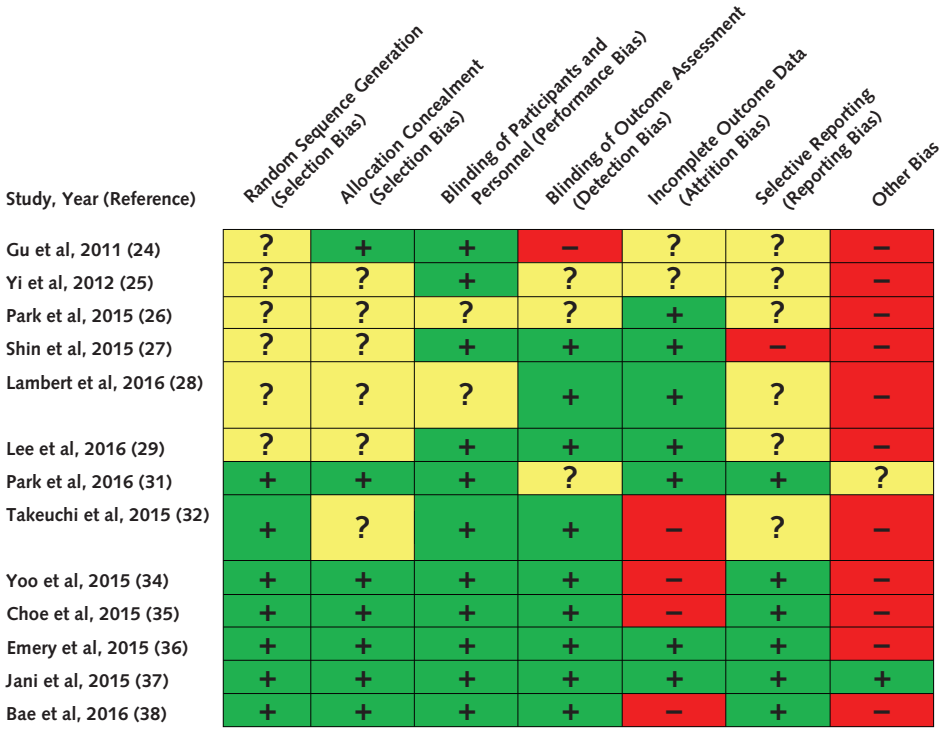
* Number completed refers to the number of participants who completed both dosing periods.

† All dropouts occurred during the first dosing period.

‡ Number completed for PLANETAS and PLANETRA trials refer to those who completed all 54 wk.

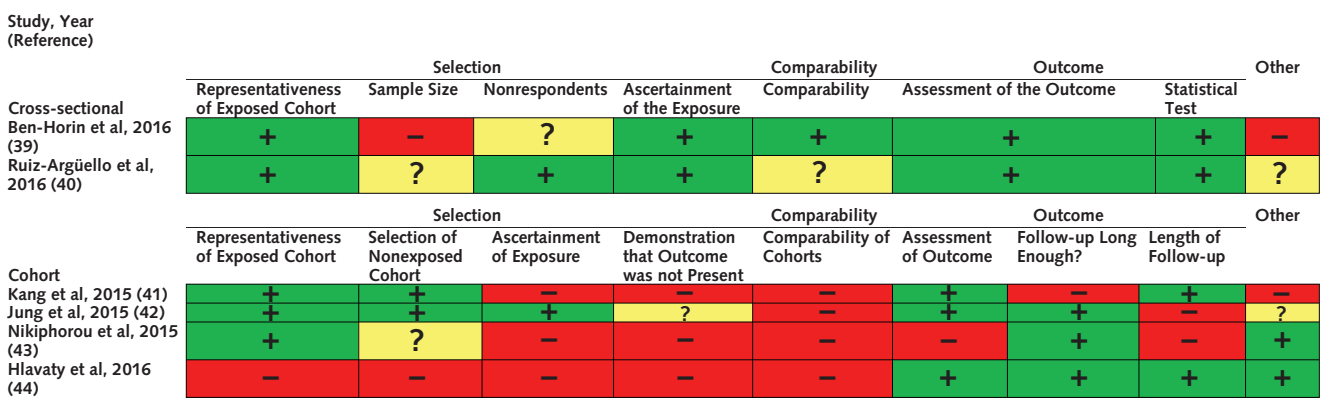
§ Number completed refers to those who completed up to week 30.

Appendix Figure 2. Risk of bias in randomized, controlled trials.



Attrition bias based on primary end point identified by authors. Specific end points identified in Table 3. Other biases include the risk of bias due to conflict of interest (for example, authors employed by, held stock in, or received funds from manufacturer). Green boxes with a plus sign indicate low risk of bias. Yellow boxes with a question mark indicate unclear risk of bias. Red boxes with a minus sign indicate high risk of bias.

Appendix Figure 3. Risk of bias in observational studies.



Other biases include the risk of bias due to conflict of interest (for example, authors employed by, held stock in, or received funds from the manufacturer); lack of temporality for cross-sectional studies; heterogeneity when patients were switched between originator and biosimilar products; and small sample size. Green boxes with a plus sign indicate low risk of bias. Yellow boxes with a question mark indicate unclear risk of bias. Red boxes with a minus sign indicate high risk of bias.

Appendix Table 3. Pharmacokinetic Outcomes in Randomized, Controlled Trials Comparing BSM With REF TNF-α Inhibitors

Study, Year (Reference); Phase; BSM vs. REF	Definition of Analysis Population	BSM, *n*	REF, *n*	Outcome	Time Point	Geometric Mean Ratio (%) BSM/REF (90% CI)
Study population: healthy adults						
Gu, 2011 (24); phase 1; TuNEX vs. REF etanercept	Participants who completed at least 1 treatment period	21	21	AUC	0-t	95.0 (79.0–113.0)
					0-∞	95.0 (80.0–113.0)
				C_{max}	Not applicable	99.0 (83.0–117.0)
Yi, 2012 (25); phase 1; HD203 vs. REF etanercept	All participants who completed both treatment periods without major protocol deviations	35	35	AUC	0-t	112.7 (104.9–121.1)
					0-∞	109.9 (103.7–116.6)
				C_{max}	Not applicable	107.6 (100.1–115.6)
Park, 2015 (26); phase 1; CT-P13 vs. REF infliximab (EU) vs. REF infliximab (US)	All participants who received study treatment, provided at least 1 PK sample with a concentration above the lower limit of quantification, and had no major protocol violation	70	EU:71	AUC	0-t	101.8 (96.4–107.6)
					0-∞	100.8 (94.4–107.6)
				C_{max}	Not applicable	105.0 (100.6–109.6)
		70	US:70	AUC	0-t	98.4 (93.2–104.0)
					0-∞	96.5 (90.4–103.0)
				C_{max}	Not applicable	106.3 (101.9–111.0)
Shin, 2015 (27); phase 1 SB2 vs. REF infliximab (EU) vs. REF infliximab (US)	All participants (no randomized participants discontinued the study)	53	EU:53	AUC	0-t	99.4 (91.5–107.9)
					0-∞	98.6 (89.7–108.3)
				C_{max}	Not applicable	100.7 (96.4–105.2)
		53	US:53	AUC	0-t	98.1 (90.4–106.4)
					0-∞	97.9 (89.4–107.2)
				C_{max}	Not applicable	98.5 (94.2–103.0)
Lambert, 2016 (28); phase 1; BOW015 vs. REF infliximab	All participants (no randomized participants discontinued the study)	43	41	AUC	0-t	106.0 (98.0–114.0)
					0-∞	106.0 (98.0–115.0)
				C_{max}	Not applicable	113.0 (107.0–118.0)
Lee, 2016 (29); phase 1; SB4 vs. REF infliximab (EU) vs. REF infliximab (US)	Participants who completed the study and did not have non-0 baseline concentrations greater than 5% of C_{max}	SB4/REF infliximab (EU): 42		AUC	0-t	98.6 (94.17–103.28)
					0-∞	99.0 (94.71–103.58)
				C_{max}	Not applicable	103.7 (98.46–109.25)
		SB4/REF infliximab (US): 44		AUC	0-t	101.0 (95.37–106.87)
					0-∞	101.1 (95.75–106.73)
				C_{max}	Not applicable	104.4 (97.74–111.41)
Study population: AS patients						
Park, 2013 (30); phase 1; CT-P13 vs. REF infliximab	Patients who received at least the first 5 doses ≥1, provided ≥1 posttreatment PK sample, and had no major protocol deviations	113	110	AUC	Steady state at weeks 22-30	104.5 (94.3–115.8)
		113	110	C_{max}	Steady state at weeks 22-30	101.5 (94.7–108.9)
Study population: RA patients						
Takeuchi, 2015 (32); phase 1; CT-P13 vs. REF infliximab	Patients who receive ≥1 dose of study drug and did not develop infliximab antibodies before week 14	39	39	AUC	Steady state at weeks 6-14	111.62 (100.24–124.29)
				C_{max}	Steady state at weeks 6-14	104.09 (92.12–117.61)
Yoo, 2013 (33); phase 3; CT-P13 vs. REF infliximab	Patients who received either CT-P13 or REF and had at least 1 PK value	Not specified		C_{max}	Across all doses	**Range of Geometric Means**
						CT-P13: 83.9–111.9; REF: 83.8–105.1
Choe, 2015 (35); phase 3; SB2 vs. REF infliximab	Approximately the first enrolled 50% of the study population	Not specified		C_{trough}	Weeks 0-30	SB2 0.0–17.96; REF 0.0–16.95
Emery, 2015 (36); phase 3; SB4 vs. REF etanercept	Subset of 79 patients from predesignated sites who had at least 1 PK sample collected	41	38	AUC	Week 8	**Ratio Not Calculated**
						SB4: 676.4; REF: 520.9
				C_{trough}	Weeks 2-24	**Range of Geometric Means**
						SB4: 2.419–2.886; REF: 2.066–2.635

AS = ankylosing spondylitis; AUC = area under the curve (presented in μgh/mL); BSM = biosimilar; C_{max} = maximum serum levels of the drug (presented in μg/mL); C_{trough} = minimum serum levels of the drug (presented in μg/mL); EU = European Union; PK = pharmacokinetic; RA = rheumatoid arthritis; REF = reference biologic; TNF-α = tumor necrosis factor-α; US = United States.

Appendix Table 4. Study Populations in Randomized, Controlled Trials Comparing BSM With REF TNF-α Inhibitors

Study, Year (Reference)	Drug Group (Sample Size)	Mean Age (SD), y*	Male, %	Race/Ethnicity, %			BMI or BW	Clinical Baseline Values				
				Asian	Caucasian	Other						
Study population: healthy adults												
Gu, 2011 (24)	TuNEX/REF etanercept (*n* = 12)	25.1 (2.6)	100	100	0.0	0.0	Mean BW (SD): 67.7 (9.4) kg	–				
	REF etanercept/TuNEX (*n* = 11)	26.6 (5.8)	100	100	0.0	0.0	Mean BW (SD): 73.5 (7.9) kg	–				
Yi, 2012 (25)	Total (*n* = 35)	24.8 (3.7)	100	100	0.0	0.0	Mean BW (SD): 67.8 (5.7) kg	–				
Park, 2015 (26)	CT-P13 (*n* = 70)	41.0 (22-55)†	85.9	‡	100	0.0	Median BMI (range): 25.0 (18.8-29.7) kg/m^2	–				
	REF infliximab (EU) (*n* = 71)	45.0 (24-55)†	85.9	‡	97.2	2.8	Median BMI (range): 25.3 (18.6-29.6) kg/m^2	–				
	REF infliximab (US) (*n* = 70)	41.0 (18-55)†	85.9	‡	98.6	1.4	Median BMI (range): 24.5 (18.8-29.7) kg/m^2	–				
Shin, 2015 (27)	SB2 (*n* = 53)	40.7 (9.7)	92.5	‡	96.2	3.8	Mean BMI (SD): 24.6 (2.1) kg/m^2	–				
	REF infliximab (EU) (*n* = 53)	40.3 (9.7)	96.2	‡	98.1	1.9	Mean BMI (SD): 25.4 (2.1) kg/m^2	–				
	REF infliximab (US) (*n* = 53)	39.4 (9.9)	94.3	‡	98.1	1.9	Mean BMI (SD): 24.8 (2.1) kg/m^2	–				
Lambert, 2016 (28)§	BOW015 (*n* = 43)	29.5 (6.4)	100		Not specified		Mean BMI (SD): 23.81 (2.02) kg/m^2	–				
	REF infliximab (*n* = 41)	28.5 (7.0)	100				Mean BMI (SD): 23.23 (1.95) kg/m^2	–				
Lee, 2016 (29)	SB4/REF infliximab (EU) (*n* = 46)	39.0 (10.2)	100	‡	100	0.0	Mean BMI (SD): 24.4 (2.3) kg/m^2	–				
	SB4/REF infliximab (US) (*n* = 46)	40.0 (9.5)	100	‡	97.8	2.2	Mean BMI (SD): 24.5 (2.3) kg/m^2					
								Mean ASDAS (SD)	**BASDAI Stratification 4~≤8, %**	**Median BASMI (0-10) Score (Range)**	**Median BASFI (0-10) Score (Range)**	
Study population: AS patients												
Park, 2013 (30) Park, 2016 (31)	CT-P13 (*n* = 125)	38.0 (18-69)†	79.2	12.8	77.6	9.6	Median BMI (range): 24.39 (18.0-38.7) kg/m^2	3.8 (0.8)	73.6	4.0 (0.0-9.0)	6.3 (0.7-9.8)	
	REF infliximab (*n* = 125)	38.0 (18-66)†	82.4	10.4	73.6	16.0	Median BMI (range): 25.64 (17.5-42.0) kg/m^2	3.9 (1.1)	76.0	4.0 (0.0-9.0)	6.3 (0.1-10)	
								Mean TJC 68 (SD)	**Mean SJC 66 (SD)**	**RF, %**	**Mean DAS28-CRP (SD)**	**Mean HAQ (SD)**
Study population: RA patients												
Takeuchi, 2015 (32)	CT-P13 (*n* = 50)	54.4 (13.0)	20.0	100	0.0	0.0	Mean BW (SD): 57.1 (10.9) kg	14.7 (11.0)	12.1 (7.6)	86.0	5.2 (1.0)	1.0 (0.7)
	REF infliximab (*n* = 51)	53.8 (13.4)	19.6	100	0.0	0.0	Mean BW (SD): 53.4 (10.1) kg	17.8 (12.3)	12.8 (7.0)	88.2	5.3 (0.9)	1.1 (0.7)
Yoo, 2013 (33) Yoo, 2015 (34)	CT-P13 (*n* = 302)	50 (18-75)†	18.9	11.3	72.8	15.9	Median BMI (range): 26.3 (13.9-49.8) kg/m^2	25.6 (13.9)	16.2 (8.7)	‖	5.9 (0.8)	1.6 (0.6)
	REF infliximab (*n* = 304)	50 (21-74)†	15.8	12.2	73.0	14.8	Median BMI (range): 25.4 (15.0-53.1) kg/m^2	24.0 (12.9)	15.2 (8.3)	‖	5.8 (0.9)	1.6 (0.6)
Choe, 2015 (35)	SB2 (*n* = 291)	51.6 (11.9)	20.3	‡	86.6	13.4	Mean BMI (SD): 26.6 (5.3) kg/m^2	23.6 (12.3)	14.6 (7.8)	73.9	Not given	1.5 (0.6)
	REF infliximab (*n* = 293)	52.6 (11.7)	19.5	‡	86.7	13.3	Mean BMI (SD): 26.5 (6.0) kg/m^2	24.0 (12.2)	14.9 (7.7)	71.0	Not given	1.5 (0.6)
Emery, 2015 (36)	SB4 (*n* = 299)	52.1 (11.72)	16.7	3.7	93.3	3.0	Mean BMI (SD): 26.8 (5.51) kg/m^2	23.5 (11.9)	15.4 (7.5)	79.3	Not given	1.5 (0.6)
	REF etanercept (*n* = 297)	51.6 (11.63)	14.8	4.4	91.9	3.7	Mean BMI (SD): 26.3 (5.3) kg/m^2	23.6 (12.6)	15.0 (7.3)	77.8	Not given	1.5 (0.6)
Jani, 2015 (37)	ZRC-3197 (*n* = 60)	45 (11.06)	15.0	100	0.0	0.0	Mean BW (SD): 55.2 (10.51) kg	¶	¶	95.0	5.9 (0.9)	1.7 (0.6)
	REF adalimumab (*n* = 60)	45 (10.92)	20.0	100	0.0	0.0	Mean BW (SD): 55.9 (11.79) kg	¶	¶	100	6.0 (0.8)	1.6 (0.6)
Bae, 2016 (38)	HD203 (*n* = 147)	51.0 (12.0)	12.2	100	0.0	0.0	Mean BMI (SD): 22.5 (3.4) kg/m^2	17.4 (11.2)	12.5 (7.3)	81.7	6.1 (0.84)	1.1 (0.7)
	REF etanercept (*n* = 147)	51.3 (12.4)	14.4	100	0.0	0.0	Mean BMI (SD): 22.8 (3.5) kg/m^2	17.5 (10.7)	12.2 (6.4)	91.5	6.2 (0.85)	1.1 (0.7)

AS = ankylosing spondylitis; ASDAS = Ankylosing Spondylitis Disease Activity Score; BASDAI = Bath Ankylosing Spondylitis Disease Activity Index; BASFI = Bath Ankylosing Spondylitis Functional Index; BASMI = Bath Ankylosing Spondylitis Metrology Index; BMI = body mass index; BSM = biosimilar; BW = body weight; DAS28-CRP = disease activity score in 28 joints–C-reactive protein; EU = European Union; HAQ = Health Assessment Questionnaire; RA = rheumatoid arthritis; REF = reference biologic; RF = rheumatoid factor positive; SJC 66 = swollen joint score (0-66); TJC 68 = tender joint score (0-68); US = United States.

* Except where indicated.

† Median (range).

‡ Percentage of Asian patients not given (e.g., listed as Caucasian or other).

§ Four participants were of Hispanic origin, but the authors do not explicitly state the distribution of race for the study population.

‖ Rheumatoid factor stated but given as the mean levels of IgG, IgM and IgA rheumatoid factor.

¶ Only TJC 28 (0–28) and SJC 28 (0–28) are given.

Appendix Table 5. Immunogenicity in Randomized, Controlled Trials Comparing BSM With REF TNF-α Inhibitors

Study, Year (Reference); Phase; BSM vs. REF	Immunogenicity		
	Time Point	BSM, %*	REF, %*
Gu, 2011 (24); phase 1; TuNEX vs. REF etanercept	Not measured		
Yi, 2012 (25); phase 1; HD203 vs. REF etanercept	Not measured		
Park, 2015 (26); phase 1; CT-P13 vs. REF infliximab (EU) vs. REF infliximab (US)	Not measured		
Shin, 2015 (27); phase 1; SB2 vs. REF infliximab (EU) vs. REF infliximab (US)	Week 4	3.8	EU: 0.0 US: 1.9
	Week 10	47.2	EU: 37.7 US: 37.7
Lambert, 2016 (28); phase 1; BOW015 vs. REF infliximab	Week 12	18.6	24.4
Lee, 2016 (29); phase 1; SB4 vs. REF infliximab (EU) vs. REF infliximab (US)	Week 4 (after first dosing period)	0.0	EU: 15.6 US: 22.7
Park, 2013 (30) and Park, 2016 (31); phase 1; CT-P13 vs. REF infliximab	Week 14	8.6	10.7
	Week 30	25.0	20.5
	Week 54	19.5	23.0
Takeuchi, 2015 (32); phase 1; CT-P13 vs. REF infliximab	Week 14	19.6	15.1
	Week 30	25.5	26.4
	Week 54	25.5	32.1
Yoo, 2013 (33) and Yoo, 2015 (34); phase 3; CT-P13 vs. REF infliximab	Week 14	25.4	25.8
	Week 30	48.4	48.2
	Week 54	41.1	36.0
Choe, 2015 (35); phase 3; SB2 vs. REF infliximab	Week 30	55.1	49.7
Emery, 2015 (36); phase 3; SB4 vs. REF etanercept	Week 24	0.7	13.1
Bae, 2016 (38); phase 3; HD203 vs. REF etanercept	Week 48	5.4	2.0
Jani, 2015 (37); phase 3; ZRC-3197 vs. REF adalimumab	At week 12, antidrug antibodies were observed in 2 samples from patients treated with BSM ZRC-3197 and in 1 sample from a patient treated with REF adalimumab (titer values 25 and 800; authors do not specify which titer value corresponds to which patient). However, low-level antidrug antibodies were also observed in 2 baseline samples (before any drug treatment) which had titer values of 25 and 50.		

BSM = biosimilar; EU = European Union; REF = reference biologic; TNF-α = tumor necrosis factor-α; US = United States.
* Proportion of patients who have developed antidrug antibodies against the BSM or REF.

Appendix Table 6. Observational Studies

Study, Year (Reference)	BSM/REF	Description of Population					Outcomes	
		Indication	Number	Median Age (Range), *y*	Male, %	Concomitant Medication	Discontinuations and Relevant Adverse Events	Effectiveness/Cross-Reactivity
Cross-sectional studies to assess whether antidrug antibodies to the REF cross-react with the BSM								
Ben-Horin, 2016 (39)	CT-P13/REF infliximab	IBD patients 69% CD 28% UC 3.5% unclassified		31 (4-70)	NA	57% on monotherapy 43% on immunomodulators (thiopurines, MTX, prednisone)	Not applicable	All samples that were positive of REF infliximab ADA cross-reacted to BSM, CT-P13; all samples that were negative of REF infliximab ADA did not cross-react
		Positive for ADA to REF infliximab	56					
		Negative for ADA to REF infliximab	30					
		Infliximab-naive patients (additional controls)	22					
Ruiz-Argüello, 2016 (40)	CT-P13/REF infliximab	RA and SpA patients		52.5 (21-82)	39.8	56.5% on MTX 23.1% on monotherapy 20.4% on other immunomodulators (sulfasalazine, prednisone, leflunomide, AZA, hydroxychloroquine)	Not applicable	All samples that were positive of ADA to the REF infliximab cross-reacted to ADA to BSM, CT-P13 All samples that were negative of REF infliximab ADA did not cross-react
		Positive for ADA to REF infliximab	126					
		Negative for ADA to REF infliximab (matched to be balanced to ADA positive population)	124					
		Infliximab-naive patients (additional controls)	77					
Cohort studies to assess effectiveness and safety of switching from REF to BSM								
Kang, 2015 (41)	CT-P13/REF infliximab Note: Primary objective was to assess CT-P13 in IBD. Also, listed as retrospective case series but has a similar design to other cohort studies.	Patients who switched from REF to CT-P13					Discontinued after switching: *n* = 1 UC patient due to the development of arthralgia	8/9 showed similar clinical outcome compared with originator 1 CD patient lost therapeutic response during study period (Outcome noted as "similar clinical efficacy" with no specific detail)
		CD	5	23 (20-39)	80.0	*n* = 1 on CS and 5-ASA; *n* = 2 on CS, IS, and 5-ASA; *n* = 1 on IS and antibiotics		
		UC	4	39.5 (28-44)	75.0	*n* = 2 on CS and 5-ASA; *n* = 2 on CS		
Jung, 2015 (42)	CT-P13/REF infliximab (retrospective cohort) Note: Primary objective was to assess CT-P13 in IBD.	Patients who switched from REF to CT-P13						(Outcome noted as "similar clinical efficacy" with no specific detail)
		CD	27	24.5 (9.4)*	74.1	*n* = 16 on 5-ASA; *n* = 7 on antibiotics; *n* = 3 on corticosteroids; *n* = 14 on AZA	*n* = 2 due to lack of efficacy	*n* = 25/27 achieved similar clinical efficacy after switching
		UC	9	34.0 (11.1)*	55.6	*n* = 4 on 5-ASA; *n* = 2 on antibiotics; *n* = 2 on corticosteroids; *n* = 4 on AZA	*n* = 1 due to lack of efficacy *n* = 1 wanted to switch to infliximab again *n* = 1 due to adverse event (skin rash and arthralgia)	*n* = 6/9 achieved similar clinical efficacy after switching
Nikiphorou, 2015 (43)	CT-P13/REF infliximab (prospective cohort)	Rheumatic disease patients 38% RA 36% AS 18% PsA 5% JIA 3% chronic reactive arthritis	39	53 (11)*	44.0	79% on MTX Median MTX dose: 20 mg (5-25 mg) 1.17% on monotherapy	11/39 discontinued (after switch): *n* = 3 had ADA to REF infliximab prior to switching (results only obtained after switching) *n* = 3 latent TB reactivation *n* = 1 new onset of neurofibromatosis *n* = 6 gave subjective reasons with no objective deterioration of disease	Mean AUC for patient-reported outcomes (CT-P13/REF infliximab): Pain: 24/26 Fatigue: 24/28 PtGlob: 24/26 PtAct: 24/21 HAQ: 0.61/0.58 DrGlob: 3.8/5.9 ESR: 14/13 CRP: 3.6/3.7 None statistically different (*P* = 0.05)
Hlavaty, 2016 (44)	CT-P13/REF infliximab (retrospective cohort) Note: Primary objective was to assess CT-P13 in IBD	12 patients with IBD taking maintenance therapy					Discontinuation after switching:	Maintained clinical remission at: Week 24: *n* = 12/12 Week 40: *n* = 7/8 (6/7 CD; 1/1 UC) Week 48: *n* = 6/8 (5/7 CD; 1/1 UC)
		CD	10	35.8 (21.5-67.7)	90.0	*n* = 5 on AZA	2/10 CD patients *n* = 1 due to development of psoriasiform dermatitis *n* = 1 lost therapeutic response	
		UC	2	48.7 (43.5-54)	50.0	*n* = 1 on AZA		

5-ASA = 5-aminosalicylic acid; ADA = antidrug antibodies; AS = ankylosing spondylitis; AUC = area under the curve; AZA = azathioprine; BSM = biosimilar; CD = Crohn disease; CRP = C-reactive protein; CS = corticosteroid; DrGlob = doctor global assessment activity score; ESR = erythrocyte sedimentation rate; HAQ = Health Assessment Questionnaire; IBD = inflammatory bowel disease; IS = immunosuppressant; JIA = juvenile idiopathic arthritis; MTX = methotrexate; NA = not available; PsA = psoriatic arthritis; PtAct = patient disease activity score; PtGlob = patient global estimate; RA = rheumatoid arthritis; REF = reference biologic; SpA = spondyloarthritis; TB = tuberculosis; UC = ulcerative colitis.
* Mean age (SD) reported.

Appendix Table 7. List of Registered Trials With TNF-α BSMs

Trial Identification (Primary Sponsor)	Study Design	BSM vs. REF (Status)
Completed: with full-text publications (all publications were included in this review)		
NCT01220518 (Celltrion Inc.)	Phase 1 double-blind, parallel-group trial with AS patients	CT-P13 vs. REF infliximab (completed: June 2012)
NCT01571206 (Celltrion Inc.; extension phase for NCT01220518*)	Phase 1 open-label, single-group trial with AS patients	CT-P13 vs. REF infliximab (completed: July 2013)
NCT01217086 (Celltrion Inc.)	Phase 3 double-blind, parallel-group trial with RA patients	CT-P13 vs. REF infliximab (completed: July 2012)
NCT01571219 (Celltrion Inc.; extension phase for NCT01217086*)	Phase 3 open-label, single-group trial with RA patients	CT-P13 vs. REF infliximab (completed: May 2013)
NCT01865552 (Samsung Bioepis Co., Ltd.)	Phase 1 single-blind, 3-group crossover study with healthy participants	SB4 vs. REF etanercept (EU) vs. REF etanercept (US) (completed: August 2013)
NCT01895309 (Samsung Bioepis Co., Ltd.)	Phase 3 double-blind, parallel-arm trial with RA patients	SB4 vs. REF etanercept (completed: October 2015)
NCT01922336 (Samsung Bioepis Co., Ltd.)	Phase 1 single-blind, 3-group crossover study with healthy participants	SB4 vs. REF infliximab (EU) vs. REF infliximab (US) (completed: October 2013)
NCT01936181 (Samsung Bioepis Co., Ltd.)	Phase 3 double-blind, parallel-group trial with RA patients	SB2 vs. REF infliximab (completed: September 2015
NCT01044836 (Hanwha Chemical)	Phase 1 double-blind crossover trial with healthy participants	HD203 vs. REF etanercept (completed: August 2010)
NCT01270997 (Hanwha Chemical)	Phase 3 double-blind, parallel-group trial with RA patients	HD203 vs. REF etanercept (completed: May 2012)
clinicaltrials.jp: JPRN-JapicCTI-111620 (Nippon Kayaku Co., Ltd.)	Phase 1 double-blind, parallel-group trial with RA patients	CT-P13 vs. REF infliximab (completed: ?)
KCT0000118 (Biotrion)	Phase 1 open-label, crossover trial with healthy participants	TuNEX vs. REF etanercept (completed: 2011)
Completed: no full-text publication available		
NCT01725620 (LG Life Sciences)	Phase 1 double-blind crossover study trial with healthy participants	LBEC0101 vs. REF etanercept (completed: April 2014)
NCT02206867 (LG Life Sciences)	Phase 1 double-blind, parallel-group with healthy participants	LBAL vs. REF adalimumab (completed: February 2015)
NCT01505491 (Boehringer Ingelheim)	Phase 1 open-label, parallel-group trial with healthy participants	BI695501 vs. REF adalimumab (completed: July 2012)
NCT02045979 (Boehringer Ingelheim)	Phase 1 double-blind, 3-group parallel-group trial with healthy participants	BI695501 vs. REF adalimumab (EU) vs. REF adalimumab (US) (completed: June 2014)
NCT01891864 (Sandoz)	Phase 3 double-blind, parallel-group trial with psoriasis patients	GP2015 vs. REF etanercept (completed: March 2015)
NCT01970475 (Amgen)	Phase 3 double-blind, parallel-group with RA patients	ABP 501 vs. REF adalimumab (completed: November 2014)
NCT02114931 (Amgen; extension phase for NCT01970475*)	Phase 3 open-label, single-group trial with RA patients	ABP 501 vs. REF adalimumab (completed: April 2016)
NCT01970488 (Amgen)	Phase 3 double-blind, parallel-group trial with psoriasis patients	ABP 501 vs. REF adalimumab (completed: March 2015)
World Health Organization registry identification: ACTRN12614000903684 (Amgen)	Phase 1 single-blind, 3-group, parallel-group trial with healthy participants	ABP 710 vs. REF infliximab (EU) vs. REF infliximab (US) (completed: ?)
NCT02167139 (Samsung Bioepis Co., Ltd.)	Phase 3 double-blind, parallel-group trial with RA patients	SB5 vs. REF adalimumab (completed: November 2015)
NCT02395055 (Biocad)	Phase 1 double-blind, parallel-group trial with healthy participants	BCD-057 vs. REF adalimumab (completed: October 2015)
NCT02472912 (Mylan Inc.)	Phase 1 double-blind, 3-group, parallel-group trial with healthy participants	BMO-2 vs. REF adalimumab (EU) vs. REF adalimumab (US) (completed: June 2015)
NCT02237729 (Pfizer)	Phase 1 double-blind, 3-group, parallel-group trial with healthy participants	PF-06410293 vs. REF adalimumab (EU) vs. REF adalimumab (US) (completed: March 2015)
NCT01931189 (Nichi-Iko Pharmaceutical Co., Ltd.)	Phase 1 open-label, parallel-group trial with healthy participants	NI-071 vs. REF infliximab (completed: January 2014)
NCT01567358 (Nichi-Iko Pharmaceutical Co., Ltd.)	Phase 1 double-blind, parallel-group trial with RA patients	NI-071 vs. REF infliximab (completed: April 2013)
NCT01927263 (Nichi-Iko Pharmaceutical Co., Ltd.)	Phase 3 double-blind, parallel-group trial with RA patients	NI-071 vs. REF infliximab (completed: March 2016)
NCT01431404 (Hanwha Chemical)	Phase 1 double-blind crossover study with healthy participants	HD203 vs. REF etanercept (completed: June 2013)
ISRCTN: EudraCT 2014-001043-20 (Baxter Innovations GmbH)	Phase 1 double-blind, 3-group, parallel-group trial with healthy participants	M923 vs. REF adalimumab (EU) vs. REF adalimumab (US)(completed: August 2015)
JPRN-JapicCTI-142419 (Nippon Kayaku Co., Ltd.; extension phase for JPRN-JapicCTI-111620*)	Open-label study with RA patients	CT-P13 vs. REF infliximab (completed: ?)
Ongoing		
NCT02096861 (Celltrion Inc.)	Phase 3 double-blind, parallel-group trial with Crohn disease patients	CT-P13 vs. REF infliximab (estimated completion date: February 2017)
NCT02115750 (Coherus Biosciences, Inc.)	Phase 3 double-blind, parallel-group trial with RA patients	CHS-0214 vs. REF etanercept (estimated completion date: May 2016)
NCT02134210(Coherus Biosciences, Inc.)	Phase 3 double-blind, parallel-group trial with psoriasis patients	CHS-0214 vs. REF etanercept (estimated completion date: May 2016)
NCT02486939 (Coherus Biosciences, Inc.; extension phase for NCT02115750 &NCT02134210*)	Phase 3, open-label, single-group trial with patients with RA or psoriasis	CHS-0214 vs. REF etanercept (estimated completion date: June 2017)
NCT02489227 (Coherus Biosciences, Inc.)	Phase 3 double-blind, parallel-group trial with psoriasis patients	CHS-1420 vs. REF adalimumab (estimated completion date: May 2016)
NCT02137226 (Boehringer Ingelheim)	Phase 3 double-blind, parallel-group trial with RA patients	BI695501 vs. REF adalimumab (estimated completion date: October 2016)
NCT02640612 (Boehringer Ingelheim; extension phase for NCT02137226*)	Open-label, single-group study with RA patients	BI695501 vs. REF adalimumab (estimated completion date: October 2017)
NCT02148640† (Diakonhjemmet Hospital)	Phase 4 double-blind, parallel-group study with patients with arthritis, IBD, and psoriasis	CT-P13 vs. REF infliximab (estimated completion date: January 2017)

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Appendix Table 7–Continued

Trial Identification (Primary Sponsor)	Study Design	BSM vs. REF (Status)
NCT02357069 (LG Life Sciences)	Phase 3 double-blind, parallel-group trial with RA patients	LBEC0101 vs. REF etanercept (estimated completion date: December 2016)
NCT02715908 (LG Life Sciences; extension phase for NCT02357069*)	Open-label, single-group study with RA patients	LBEC0101 vs. REF etanercept (estimated completion date: May 2018)
NCT02452151 (Onze Lieve Vrouwe Gasthuis)	Phase 4 double-blind, parallel-group study with IBD patients	CT-P13 vs. REF infliximab (estimated completion date: September 2016)
NCT02539368‡ (Hospira, Inc.)	Prospective cohort study with IBD patients	CT-P13 vs. REF infliximab (estimated completion date: June 2019)
NCT02557295‡ (Celltrion Inc.)	Prospective cohort study (patient registry) with RA patients	CT-P13 vs. other anti-tumor necrosis factor drugs (estimated completion date: June 2026)
NCT02557308 (Celltrion Inc.)	Prospective cohort study (patient registry) with AS patients	CT-P13 vs. other anti-tumor necrosis factor drugs (estimated completion date: June 2026)
NCT02581345 (Baxalta US Inc.)	Phase 3 double-blind, factorial-assignment trial with psoriasis patients	M923 vs. REF adalimumab (estimated completion date: May 2017)
NCT02605642‡ (Hospira, Inc.)	Prospective cohort study (patient registry) with RA and AS patients	CT-P13 vs. REF infliximab (estimated completion date: August 2018)
NCT02683564 (Epirus Biopharmaceuticals)	Phase 3 double-blind, parallel-group trial with RA patients	BOW015 vs. REF infliximab (estimated completion date: July 2017)
NCT02714322 (Mylan Inc.)	Phase 3 double-blind, parallel-group trial with psoriasis patients	MYL-1401A vs. REF adalimumab (estimated completion date: November 2016)
NCT02016105 (Sandoz)	Phase 3 double-blind, parallel-group trial with psoriasis patients	GP2017 vs. REF adalimumab (estimated completion date: April 2016)
NCT02638259 (Sandoz)	Phase 3 double-blind, parallel-group trial with RA patients	GP2015 vs. REF etanercept (estimated completion date: July 2017)
NCT02744755 (Sandoz)	Phase 3 double-blind, parallel-group with RA patients	GP2017 vs. REF adalimumab (estimated completion date: October 2017)
NCT02746380 (LG Life Sciences)	Phase 3 double-blind, parallel-group trial with RA patients	LBAL vs. REF adalimumab (estimated completion date: December 2017)
NCT02260791 (Fujifilm Kyowa Kirin Biologics Co., Ltd.)	Phase 3 double-blind, parallel-group trial with RA patients	FKB327 vs. REF adalimumab (estimated completion date: July 2016)
NCT02405780 (Fujifilm Kyowa Kirin Biologics Co., Ltd.; extension study to NCT02260791)	Phase 3 open-label, parallel-group trial with RA patients	FKB327 vs. REF adalimumab (estimated completion date: December 2017)
NCT02480153 (Pfizer)	Phase 3 double-blind, parallel-group trial with RA patients	PF-06410293 vs. REF adalimumab (estimated completion date: November 2017)
NCT01894412 (Hanwha Chemical)	Phase 1 double-blind crossover trial with healthy participants	HD203 vs. REF etanercept (estimated completion date: February 2015)
JPRN-UMIN000021492† (Inoue Hospital)	Open-label, single-group study with RA patients	(Unspecified) BSM infliximab vs. REF infliximab (estimated completion date: ?)
Netherlands Trial Register: NTR5279† (Sint Maartenskliniek Nijmegen)	Prospective cohort study with arthritis patients	CT-P13 vs. REF infliximab (estimated completion date: April 2017)
EudraCT No.: 2014-004904-31 (Mundipharma Pharmaceuticals B.V.)†	Open-label, multicenter, postmarketing study with IBD or RA patients	CT-P13 vs. REF infliximab (estimated completion date: ?)
EudraCT No.: 2015-002809-12 (YL Biologics Ltd)	Phase 3 double-blind parallel-group with RA patients	YLB113 vs. REF etanercept (estimated completion date: ?)

AS = ankylosing spondylitis; BSM = biosimilar; EU = European Union; IBD = inflammatory bowel disease; RA = rheumatoid arthritis; REF = reference biologic; TNF-α = tumor necrosis factor-α; US = United States.
* Presumably includes patients who were originally taking the REF and consequently switched to the BSM.
† Study aim to assess switching from REF to the BSM.
‡ Study population: biologic-naive and those who switch from REF to BSM.