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SYSTEMATIC REVIEW

Biosimilars for the Treatment of Chronic Inflammatory Diseases: A Systematic Review of Published Evidence

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Abstract

Background Clinicians are required to assimilate, critically evaluate, and extrapolate information to support appropriate use of biosimilars across indications.

Objectives The objective of this study was to systematically collate all published data in order to assess the weight (quantity and quality) of available evidence for each molecule and inform and support healthcare decision-making in chronic inflammatory diseases.

Methods MEDLINE®, EMBASE®, and ISI Web of Science® were searched to September 2015. Selected conference proceedings were searched from 2012 to July 2015. Studies disclosing biosimilars with unique identifiers were categorized by originator, study type, and indication. Risk of bias assessments were performed. Intended copies were differentiated as commercially available agents without evidence of rigorous comparative biosimilarity evaluations.

Results Proposed biosimilars for adalimumab, etanercept, infliximab, and rituximab are reported in the published literature. Across indications, approved biosimilars infliximab CT-P13, SB2, and etanercept SB4 have published studies involving the largest number of patients or healthy subjects (n = 1405, 743, and 734, respectively), mostly in rheumatoid arthritis. At data cut-off, only CT-P13 had published data in ankylosing spondylitis (n = 250; randomized control trial) and ulcerative colitis/Crohn's disease (n = 336; observational studies). Published data were not available for ongoing studies in psoriasis patients. Four intended copies were identified in published studies (total: n = 1430; n = 1372 in observational studies). Thematic analysis of non-empirical publications showed that indication extrapolation remains an issue, particularly for gastroenterologists.

Conclusions While most agents display a moderate to high degree of similarity to their originator in the published studies identified, large discrepancies persist in the overall amount and type of data available in the public domain. Significant gaps exist particularly for intended copies, reinforcing the need to maintain a clear differentiation between these molecules and true biosimilars.

Key Points

There is a significant body of evidence in the published literature to support infliximab biosimilars CT-P13, SB2, and etanercept biosimilar SB4 for rheumatoid arthritis, but knowledge gaps still exist both in the amount and type of data available. These gaps are more pronounced for other molecules across chronic inflammatory diseases, and most pronounced for intended copies.

Rheumatoid arthritis is the first indication for which biosimilars have been launched and experience here will influence how the broader sector evolves.

Ongoing dissemination of data by all manufacturers is imperative to support adoption of biosimilars.

Leah Isakov was an employee of Pfizer at the time the study was conducted.

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1 Introduction

A biosimilar or follow-on biologic [1] is a biologic medicinal product that contains a version of the active substance of an already authorized original biologic medicinal product [2–4]. Over 700 biosimilar products are reported to be in preclinical and clinical trials [5]. For biosimilar drug approval, data must be generated to establish whether a biosimilar can safely and effectively be used instead of the originator product.

Although highly efficacious, biologic therapy for chronic inflammatory disease is expensive [6]. The expectation among patients, treating physicians, and healthcare providers is that biosimilars should be highly similar in efficacy, comparable in safety, including immunogenicity, but lower in price than their reference products [7]. The introduction of biosimilars can help expand access to safe and effective treatment options for clinicians and patients [6].

Several biosimilars are now available for the treatment of chronic inflammatory diseases. CT-P13 (Remsima®/Inflectra®, an infliximab biosimilar) was the first EU-approved monoclonal antibody (mAb) biosimilar, obtaining market authorization in September 2013 for all approved indications of the innovator drug, including rheumatoid arthritis (RA), ankylosing spondylitis (AS), psoriatic arthritis (PsA), psoriasis, Crohn's disease (CD), and ulcerative colitis (UC). In 2014, Health Canada initially approved CT-P13 for all approved indications of infliximab except for UC and CD [8]; Health Canada subsequently approved CT-P13 for additional indications, including CD, fistulizing CD, and UC [9].The addition of CD, fistulizing CD, and UC to the approved indications was granted on the basis of similarity between CT-P13 and the reference product Remicade® in product quality, mechanism of action, disease pathophysiology, safety profile, dosage regimen, and on clinical experience with the reference product [9]. In February 2016, the US Food and Drug Administration (FDA) Arthritis Advisory Committee approved CT-P13 for all indications of the reference product, making it the first biosimilar mAb therapy to be reviewed by the FDA for licensure in the USA.

In November 2015, the European Medicines Agency (EMA) recommended marketing approval for SB4 (Benepali®, an etanercept biosimilar) for the treatment of RA, AS, PsA, and psoriasis [7]. On 1 June 2016, the EMA Committee for Medicinal Products for Human Use announced a positive opinion on SB2 (Flixabi®, an infliximab biosimilar) for the treatment of RA, CD, UC, AS, PsA, and psoriasis [10]. On 12 July 2016, the FDA advisory panel voted in favor of recommending approval for ABP 501, Amgen's proposed biosimilar of adalimumab, to treat seven chronic inflammatory diseases, including RA, PsA, CD, UC, and plaque psoriasis [11]. Finally, on 13 July 2016, the FDA Arthritis Advisory Committee unanimously voted to recommend approval of Sandoz's GP2015 (an etanercept biosimilar) as the totality of the evidence demonstrated that GP2015 is similar to US-licensed Enbrel® (etanercept) [12].

Similarity to the reference product in terms of quality characteristics, biologic activity, efficacy, and safety must be established before biosimilar products can be marketed in the USA, Europe, or other regulated countries [2]. Numerous batches of the innovator reference product are routinely tested to establish the characteristic range. Manufacturers must provide high-quality evidence of similar efficacy and safety outcomes, including a comprehensive immunogenicity assessment to satisfy the stringent requirements for EMA and FDA approval.

In contrast, 'intended copies' are copies of originator biologics that have not undergone rigorous comparative evaluations as recommended by the leading regulatory authorities, but are nevertheless being sold in some countries. There is a lack of information about the efficacy and safety of intended copies compared with the originator. Furthermore, they may have clinically noticeable differences in quality characteristics, pharmacokinetics, efficacy, or safety. The extent and quality of available data between proposed biosimilars and intended copies often greatly differ [13].

A comprehensive systematic literature review (SLR) was recently undertaken to identify, collate, and summarize all published empirical evidence on named biosimilars and intended copies of originator mAbs and fusion proteins (Jacobs et al. [14]; see page 489 of this issue). The original analysis aimed to summarize the range of available data and number and diversity of publications describing biosimilars (for the treatment of chronic inflammatory disease along with other disease areas, including oncology). Here, we explore in greater depth the findings for biosimilars indicated for chronic inflammatory disease.

2 Methods

2.1 Systematic Literature Review

A detailed description of the methods used in this SLR can be found in Jacobs et al. [14] (see page 489 of this issue). First, the search strategy captured mAb and fusion protein terms; then included the different terminologies for biosimilar products, such as biosimilars, subsequent entry biologics, follow-on biologics, follow-on proteins, biocomparables, biogenerics, similar biotherapeutic products, or intended copies and biobetters (which were analyzed separately). Publications were required to contain both

"mAb/fusion protein" and "biosimilar" terms. Here we report the results of biosimilars indicated for the treatment of RA (active, moderate, severe), psoriasis or plaque psoriasis, PsA, AS, CD, UC, scleroderma, and dermatomyositis. The search results were filtered using the study designs of interest and controlled vocabulary and free-text terms were applied.

MEDLINE®/MEDLINE® In-Process and EMBASE® (searched using the OVIDSP interface), and ISI Web of Science® were searched from database inception to 3 September 2015. The search was carried out on 27 April 2015 and repeated on 3 September 2015 to capture the latest full-text publications. In addition to the publication search and in order to identify recent studies not yet published as full-text articles and/or to provide additional data from previously published studies, a hand search of relevant conference proceedings (17 conferences) was conducted between 1 January 2012 and 31 July 2015 (Electronic Supplementary Material [ESM] Table S1).

The search result was limited to references published in the English language. For this analysis, biosimilars are differentiated from intended copies based on meeting the rigorous regulatory requirements for biosimilarity, as described by major regulatory health authorities such as the EMA, FDA, the World Health Organization (WHO), Health Canada, the Pharmaceuticals Medical Devices Agency/Japan Ministry for Health Labour and Welfare (PMDA/MHLW), or the Korean Ministry of Food and Drug Safety (MFDS) in the Republic of Korea [15, 16]. Guidelines for biosimilar approval have also been issued by Administración Nacional de Medicamentos, Alimentos y Tecnología Médica (ANMAT) in Argentina, Agência Nacional de Vigilância Sanitária (ANVISA) in Brazil, and Comisión Federal para la Protección contra Riesgos Sanitario (COFEPRIS) in Mexico. However, it should be noted that products approved in Latin American countries might not have been authorized following as strict a regulatory process as is required for approval of biosimilars in the USA or EU [17]. The biosimilar approval pathway was recently updated by India's Central Drugs Standard Control Organization (CDSCO) [18]. Other markets have issued guidance on biosimilars, although evaluation of the biosimilar approval pathways by regulatory authorities outside of the major markets was considered beyond the scope of this review.

Results from the SLR were split further into two components: the empirical analysis, which focused on peer-reviewed publications of clinical, pharmacovigilance, and observational empirical data, and the non-empirical analysis, which included opinion pieces or commentaries, publications describing product-related patient support programs, and articles on manufacturing and supply issues. Non-empirical articles were further classified into general thematic categories to summarize key topics being discussed in the field of biosimilar medicines. Empirical studies were also categorized by type: preclinical (including analytical, functional, or nonclinical studies), clinical (pharmacokinetic/safety trials and preliminary or comparative safety/efficacy trials), or observational (prospective, retrospective, and post-marketing) studies. Results of clinical trial searches (from ClinicalTrials.gov) were also included as a separate subsection, and planned or ongoing clinical trials of biosimilars, where results were yet to be published, were explored.

2.2 Risk of Bias (Quality) Assessment

In accordance with the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guidelines, a validated tool matched to the study type was used to assess the strength/validity of the empirical data for each individual study [19, 20]. In cases where multiple publications were retrieved for the same study, quality assessments were only conducted on the first original publication or first full-text publication. Further information on each tool is provided in the ESM.

The assessment of the quality of randomized controlled trials (RCTs) was carried out using recommendations from the National Institute for Health and Care Excellence (NICE) single technology appraisal (STA) manufacturer's template [21] and the Jadad scoring system [22] (ESM Table S2, ESM Fig. S1).

The Downs and Black [23] instrument was used to assess the quality of all non-randomized studies. As studies published as abstracts in conference proceedings have limited information, the Downs and Black instrument was modified to include only the most relevant qualifying parameters ($n = 12$ of 26) for quality assessment, as listed in ESM Tables S3 and S4. Pharmacoeconomic studies were evaluated using Drummond's checklist for assessing economic evaluations [24]. Animal studies were assessed using SYRCLE's (SYstematic Review Centre for Laboratory animal Experimentation) risk of bias tool [25]. Conference abstracts of analytical/nonclinical and economic studies were not evaluated, as suitable tools were not available at the time of analysis. Full-text analytical and cell-based studies were also not evaluated for the same reason.

3 Results

3.1 Literature and Conference Search

The literature search returned 1,991 publications that were identified through title and abstract screening, and those

relevant to the topic of biosimilars were retained (768 publications in total). Of the included references, 301 (39%) addressed biosimilars for the treatment of chronic inflammatory conditions. The numbers of publications included in the analysis are presented in a PRISMA flow diagram (shown in ESM Fig. S2). Of note, in cases where encore (or duplicate) publications were retrieved for studies, the information was compared with the original (first published article) and excluded if no additional data were provided. If new data were identified, encore publications were included along with the original publication. This would be reflected in the overall publication count but not in the overall study count. Named biosimilars (i.e., where a unique identifier was provided) were identified in 55 studies (96 publications) in chronic inflammatory disease (Fig. 1).

3.2 Preclinical and Pharmacokinetic/Safety Data in Healthy Subjects

3.2.1 Adalimumab Biosimilars

Studies of adalimumab biosimilars are presented in Table 1.

ABP 501 (*Amgen*) Pharmacokinetic/safety studies for ABP 501 have been reported [28, 26, 27]. In healthy subjects, ABP 501 was reported to demonstrate pharmacokinetic equivalence to adalimumab and, overall, no safety or immunogenicity concerns were raised. The combined results of analytical and nonclinical in vitro studies suggest a high degree of similarity between ABP 501 and adalimumab, despite some variations reported in structural composition.

Exemptia™ (*Cadila Healthcare*) Bandyopadhyay and coworkers [40] reported on the physicochemical properties and in vivo pharmacokinetic and toxicology profile of Exemptia™ in the journal *Biosimilars* and concluded that the molecule displayed highly similar characteristics to adalimumab. It should be noted that studies from non-indexed publications were not included in this review, and therefore the data from this publication were not extracted. Based on the information from this study and other information which came to the attention of the authors, it seems reasonable to assume that this molecule may be considered a biosimilar and not an intended copy; however, compliance with the EMA, FDA, and WHO requirements is not yet fully transparent.

GP2017 (*Sandoz*) A published nonclinical study found GP2017 to be well-tolerated among tested species (mouse, rabbit, and monkey), and that it displayed a similar pharmacokinetic profile to that of adalimumab [37, 36, 35].

PF-06410293 (*Pfizer*) Analytical/nonclinical studies reporting results of peptide mapping experiments comparing PF-06410293 and adalimumab revealed highly similar primary sequence structures [38].

SB5 (*Samsung Bioepis*) SB5 has been studied in pharmacokinetic/safety studies in healthy volunteers to establish bioequivalence with adalimumab [41]. The pharmacokinetic data were not reported, but all parameters were found to fall within the required range for equivalence. The majority of adverse events (AEs) were mild in severity and comparable to the extent observed in adalimumab-treated healthy subjects.

3.2.2 Etanercept Biosimilars

Studies of etanercept biosimilars are presented in Table 2.

ENIA11 (*TuNEX®*; *Mycenax Biotech/TSH Biopharm Corp*) One pharmacokinetic/safety RCT was identified for ENIA11, wherein 23 healthy male subjects were randomized to study medication and reported similar pharmacokinetic/pharmacodynamic outcomes, with no serious AEs compared with etanercept [43, 42].

HD203 (*Davictrel™; Hanwha Chemical*) In a double-blind RCT comparing HD203 with etanercept in healthy subjects, pharmacokinetic/pharmacodynamic outcomes were similar between the two drugs and no serious AEs were observed [44].

LBEC0101 (*LG Life Sciences*) One pharmacokinetic/safety RCT for LBEC0101 in healthy volunteers was found. It reported similar pharmacokinetic/pharmacodynamic outcomes between this biosimilar and etanercept [47].

SB4 (*Benepali®; Samsung Bioepis*) In a pharmacokinetic/safety trial, pharmacokinetic equivalence was reported and SB4 was well-tolerated in healthy male subjects with a similar safety profile to etanercept [48, 49].

AVG01 (*Avent™; Avesthagen*) One analytical/nonclinical study reported that AVG01 was highly similar to etanercept [52].

GP2015 (*Sandoz*) Two nonclinical studies were identified for GP2015. Both reported that GP2015 was highly similar to etanercept with regard to target binding, antitumor necrosis factor (TNF)-α biologic activity, and pharmacokinetic exposure [51, 53].

3.2.3 Infliximab Biosimilars

Studies of infliximab biosimilars are presented in Table 3.

BOW015 (*Infimab®; Ranbaxy Laboratories*) A recent announcement from Ranbaxy Laboratories indicates that BOW015 has been discontinued. Prior to this, the pharmacokinetic, safety, and immunogenicity profiles of BOW015 and infliximab were compared in healthy volunteers [54, 55]. Studied pharmacokinetic parameters and safety outcomes were reported to be comparable between

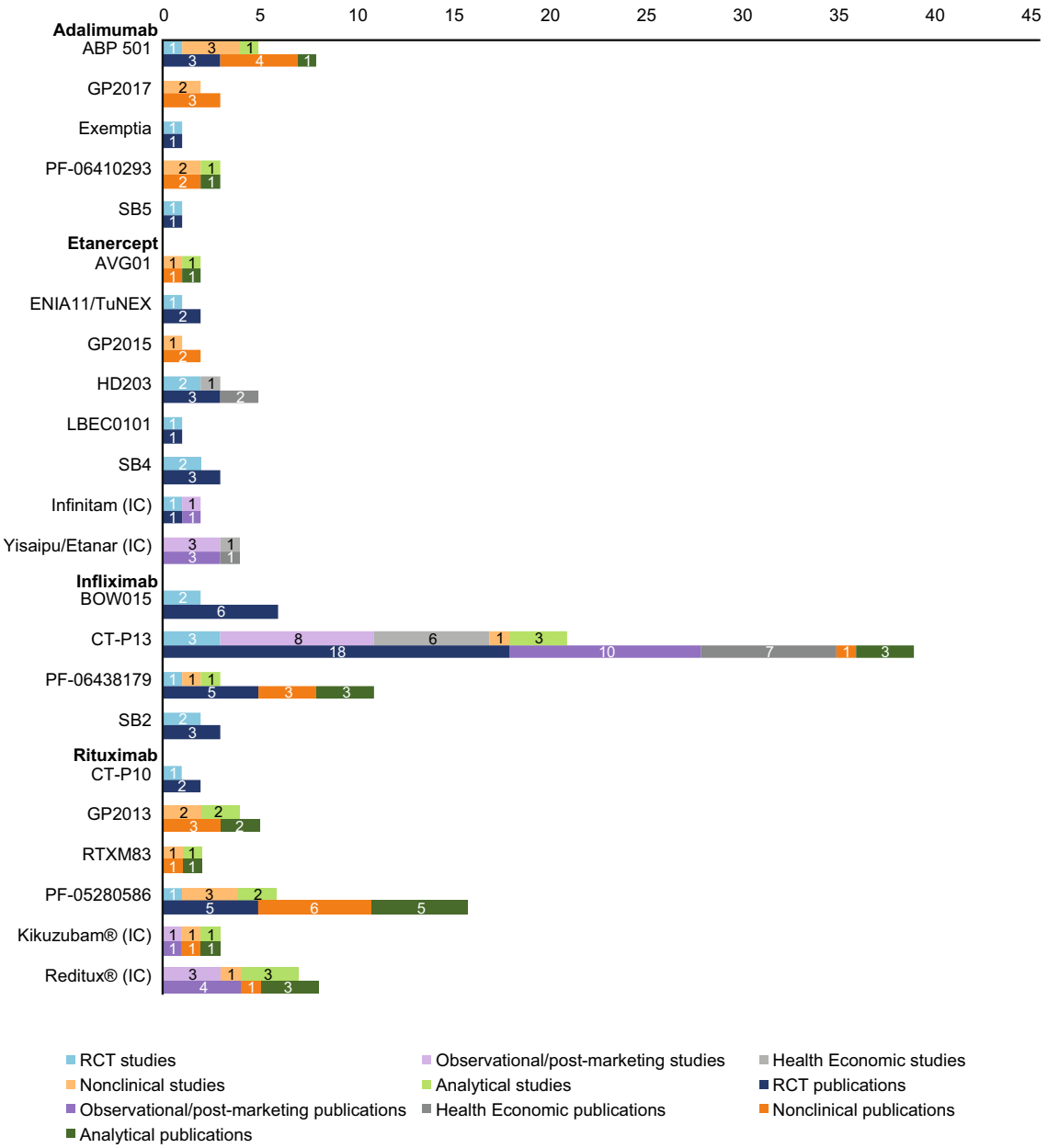

Fig. 1 Frequency of publications of reported named biosimilars in chronic inflammatory diseases. Note: publications were classified into the most relevant category, which in some cases was more than one. Therefore, the number of publications classified into each therapeutic area category does not sum to the total number of publications. For example, overlap in licensed indications for originators/biosimilars led to multiple categorization. Among the empirical references, several (seven) include both nonclinical and human data, and as such have been classified into both categories. *IC* Intended copy, *RCT* randomized controlled trial

the biosimilar and the originator. Within the SLR timeframe, no analytical or nonclinical data had been published or reported for BOW015 to validate its structural and functional biosimilarity to infliximab.

PF-06438179 (*Pfizer*) The pharmacokinetics and safety attributes of PF-06438179 have been evaluated in healthy volunteers [94, 95, 93, 98, 99, 97, 96]. Reports of studies confirmed pharmacokinetic bioequivalence of PF-06438179 as compared with infliximab, with similar incidences of AEs and lower occurrence of immunogenicity in PF-06438179 versus infliximab-treated subjects. The biochemical characteristics and in vitro/in vivo biologic activity of PF-06438179 have been studied and reported. The data suggest that PF-06438179 exhibits high structural and functional similarity to infliximab.

Table 1 Outcomes for adalimumab biosimilars

Study type [patients (*n*)]	Reference(s)	Outcome	Biosimilar[a]	Adalimumab[a]	Statistical comparison	Quality assessment rating
ABP501						
RCT, PK/safety study [healthy adults (136)]	CA [26]; CA [27]; CA [28];	Safety, single dose:				Modified D&B: excellent; score: 11/12
		Serious AEs (%)	0	0		
		ADAb (%)	54	EU: 55; USA: 67		
		PK/PD, single dose:				
		AUC (ng·h/mL)	2137.0	2046.8	Ratio: 1.04 (0.93–1.17)[b]	
		C_{max}, single dose (ng/mL)	3.22	3.37	Ratio: 0.96 (0.89–1.03)[b]	
		$t_{½}$ (h)	190.8	168.0		
Nonclinical study (cell-based)	CA [29]	Functional assessment (in vitro):				Not evaluated[c]
		Immunoassay sensitivity	Comparable	Comparable		
Nonclinical study (cell-based)	CA [30]	Functional assessment (in vitro):				Not evaluated[c]
		Target binding effector function	Highly similar	Highly similar		
		FcRn binding	Highly similar	Highly similar		
Nonclinical study (cell-based)	CA [31]; CA [32]	Functional assessment (in vitro):				Not evaluated[c]
		TNF-binding (pM)	48–52	48–53		
		F(ab)-mediated activity (%)	100–106	100–111		
		Inhibition of TNF activity:				
		Binding to FcRN (%)	86–94	92–114		
		Binding to FcγRIIIa (%)	103–113	92–94		
		Caspase activation (%)	103–107	100–110		
		Cytotoxicity (pM)	390–457	391–544		
		Whole-blood TNF inhibition	Similar	Similar		
		CDC (%)	97	93		
Analytical, nonclinical	CA [30]	Composition:				Not evaluated[c]
		Primary structure	Highly similar	Highly similar		
		Post-translational modifications	Similar	Similar		
		Carbohydrate structure	Not similar	Not similar		
		Higher order structure	Highly similar	Highly similar		

Table 1 continued

Study type [patients (*n*)]	Reference(s)	Outcome	Biosimilar[a]	Adalimumab[a]	Statistical comparison	Quality assessment rating
Exemptia™						
RCT, comparative safety/efficacy study [moderate to severe RA (120)]	[33]	Efficacy (PPS), week 12:				NICE STA: excellent; 1 = unclear, 6 = low risk Jadad: excellent; score: 4/5
		CRP [mean (SD)]	−5.5 (12.66), sig vs. BL	0.7 (26.98)		
		ESR [mean (SD)]	−8.6 (19.76), sig vs. BL	−5.4 (17.35), sig vs. BL		
		DAS28-CRP [mean (SD)]	−2.1 (1.09), sig vs. BL	−2.1 (1.21), sig vs. BL		
		DAS28-ESR [mean (SD)]	−2.0 (1.10), sig vs. BL	−2.1 (1.15), sig vs. BL		
		ACR20 week 12 (%)	82.0	79.3	NS	
		ACR50 week 12 (%)	46.0	43.4	NS	
		ACR70 week 12 (%)	14.0	15.1	NS	
		Safety, week 12:				
		Serious AEs (*n*)	2	1		
		All AEs (*n*)	13	15		
		Infusion reactions (%)	0	0		
		ADAb (*n*)	2	1		
		HR-QOL score, week 12:				
		Pain assessment [mean (SD)]	−30.0 (17.7), sig vs. BL	−28.4 (16.8), sig vs. BL		
		HAQ [mean (SD)]	−0.8 (0.63), sig vs. BL	−0.7 (0.60), sig vs. BL		
SB5						
RCT, PK/safety study [healthy adults (189)]	CA [34]	Safety, single dose:				Modified D&B: excellent; score: 11/12
		Serious AEs (*n*)	2	2		
		PK/PD, single dose:				
		AUC (μg·h/mL)				
		EU	NR	NR	Ratio: 0.990 (0.885–1.108)[b]	
		USA	NR	NR	Ratio: 1.001 (0.890–1.126)[b]	
		Single dose (μg/mL)				
		EU	NR	NR	Ratio: 0.957 (0.870–1.054)[b]	
		USA	NR	NR	Ratio: 0.972 (0.881–1.073)[b]	

Table 1 continued

Study type [patients (*n*)]	Reference(s)	Outcome	Biosimilar[a]	Adalimumab[a]	Statistical comparison	Quality assessment rating
GP2017						
Nonclinical studies (rabbit, cynomolgus monkey, and transgenic mice model)	CA [35]; CA [36]; CA [37]	Functional assessment (mice model):				Not evaluated[c]
		Clinical symptoms	Superimposable	Superimposable		
		Joint morphology	Similar	Similar		
		TNF/IL-6 levels	Similar	Similar		
		PK (rabbit):				
		AUC_{168} (μg·h/mL)	14,146	13,976		
		C_{max} (μg/mL, single dose)	117.2 (108–127)[b]	102.3 (96–108)[b]		
		$t_{½}$ (h)	203	227		
		PK (monkey):				
		AUC_{96}, ratio (%)	NR	NR	Ratio: 0.96	
		C_{max} (μg/mL first dose)	NR	NR	Ratio: 0.96	
		C_{max} (μg/mL second dose)	NR	NR	Ratio: 1.01	
PF-06410293						
Nonclinical (cynomolgus monkey and cell-based)	CA [38]	Functional assessment (in vitro):				Not evaluated[c]
		TNF-induced apoptosis	Similar	Similar		
		PK/PD (monkey):				
		AUC, ratio (%)	NR	NR	Ratio: 1.00–1.20	
		C_{max}, ratio (%)	NR	NR	Ratio: 1.00–1.20	
Nonclinical (cell-based)	CA [39]	Functional assessment (in vitro):				Not evaluated[c]
		Inhibition of TNF-induced cytotoxicity, ADAb (μg/mL)	Human: 0.13	Human: 0.25		
			Rabbit: 1.8	Rabbit: 8.2		
			Mouse: 0.20	Mouse: 0.22		
Analytical, nonclinical	CA [38]	Composition:				Not evaluated[c]
		Peptide mapping	Highly similar	Highly similar		

ACR20, 50, 70 American College of Rheumatology 20, 50, 70% improvement criteria, *ADAb* anti-drug antibodies, *AE* adverse event, *AUC* area under the concentration–time curve, AUC_x area under the concentration–time curve from time zero to *x* h, *BL* baseline, *CA* conference abstract, *CDC* complement-dependent cytotoxicity, C_{max} maximum serum concentration, *CRP* C-reactive protein, *DAS28* Disease Activity Score in 28 joints, *D&B* Downs and Black (tool), *ESR* erythrocyte sedimentation rate, *F(ab)* fragment antigen-binding, *FcγRIIIa* Fc gamma receptor IIIa, *FcRN* neonatal Fc receptor, *HAQ* health assessment questionnaire, *HR-QOL* health-related quality of life, *IL-6* interleukin-6, *NICE STA* National Institute for Health and Care Excellence Single Technology Appraisal (manufacturer's template), *NR* not reported, *NS* not significant, *PD* pharmacodynamic, *PK* pharmacokinetic, *PPS* per protocol set, *RA* rheumatoid arthritis, *RCT* randomized controlled trial, *SD* standard deviation, *sig* significant, $t_{½}$ half-life, *TNF* tumor necrosis factor

[a] Qualitative data for biosimilarity as stated by the corresponding study authors

[b] 90% confidence intervals shown in parentheses

[c] Quality assessment not conducted due to the absence of validated tools specific for the study type, at the time of analysis

Table 2 Outcomes for etanercept biosimilars

Study type [patients (*n*)]	References	Outcome	Biosimilar[a]	Etanercept[a]	Statistical comparison	Quality assessment rating
ENIA11 (TuNEX®)						
RCT, PK/safety study [healthy adults (23)]	[42]; CA [43]	Safety, single dose:				NICE STA: excellent; 1 = high risk, 6 = low risk Jadad: good; score: 3/5
		Serious AEs (%)	0	0		
		All AEs (%)	39	39		
		PK/PD, single dose:				
		AUC_{last} (μg·h/mL)	263.5	268.0		
		AUC_{∞} (μg·h/mL)	276.8	280.92		
		C_{max}, single dose (μg/mL)	1.26	1.28	$p = 0.89$	
		$t_{½}$ (h)	92.7	87.4		
HD203 (Davictrel™)						
RCT, PK/safety study [healthy male adults (37)]	[44]	Safety, single dose:				NICE STA: excellent; 1 = unclear, 6 = low risk Jadad: good; score: 3/5
		C_{max}, single dose (μg/mL)	1.35	1.25	Ratio: 1.076 (1.001–1.156)[b]	
		$t_{½}$ (mean)	134.3	125.9		
		Serious AEs (%)	0	0		
		All AEs (%)	43.2	45.7		
		PK/PD, single dose:				
		AUC (μg·h/mL)	353.8	319.3	Ratio: 1.099 (1.037–1.166)[b]	
		C_{max}, single dose (μg/mL)	1.35	1.25	Ratio: 1.076 (1.001–1.156)[b]	
		$t_{½}$ (mean)	134.3	125.9		
RCT, comparative safety/efficacy study [active RA, insufficient response to MTX (233)]	CA [45]; CA [46]	Efficacy, week 48:				Modified D&B: excellent; score: 11/12
		ACR20, week 48 (%)	87.3	86.5	$p = 0.8626$	
		ACR50, week 48 (%)	68.2	54.5	$p = 0.359$	
		ACR70, week 48 (%)	38.2	33.9	$p = 0.5093$	
		EULAR moderate responder (%)	45.5	47.8	$p = 0.1264$	
		EULAR good responder (%)	50.9	42.3	$p = 0.1264$	
		EULAR non-responder (%)	3.6	9.9	$p = 0.1264$	
		Safety, week 48:				
		All AEs (%)	76.9	78.1	$p = 0.8040$	
		ADAb (%)	Few	Few		
		HR-QOL score, week 48:				
		Δ SF-36, mental, week 48 (SD)	5.02 (11.84)	4.48 (11.28)	$p = 0.9842$	
		Δ SF-36, physical, week 48 (SD)	8.50 (8.66)	8.54 (8.82)	$p = 0.5424$	
		Δ EQ-5D, week 48 (SD)	0.21 (0.31)	0.29 (0.35)	$p = 0.1494$	

Table 2 continued

Study type [patients (*n*)]	References	Outcome	Biosimilar[a]	Etanercept[a]	Statistical comparison	Quality assessment rating
LBEC0101						
RCT, PK/safety study [healthy subjects (48)]	CA [47]	Safety, single dose:				Modified D&B: excellent; score: 9/12
		All AEs	Tolerated	Tolerated		
		PK/PD, single dose:				
		AUC (μg·h/mL)	345.86	348.14	Ratio: 0.96 (0.87–1.06)[c]	
		C_{max} (μg/mL)	1.77	1.71	Ratio: 1.02 (0.92–1.13)[c]	
SB4 (Benepali®)						
RCT, comparative safety/efficacy study [RA (596)]	CA [48]; [49]	Efficacy, week 24:				NICE STA: excellent; 7 = low risk Jadad: excellent; score: 5/5
		ACR20 (%)	78.1	80.3	Adjusted difference: −2.22 (−9.41 to 4.98)[b]	
		ACR50 (%)	46.6	42.3	Adjusted difference: 4.79 (−3.92 to 13.49)[b]	
		ACR70 (%)	25.5	22.6	Adjusted difference: 3.02 (−4.47 to 10.51)[b]	
		DAS28 improvement (score)	2.6	2.5	Not stated (−0.14 to 0.28)[b]	
		EULAR good responders (%)	32.1	29.8		
		EULAR moderate responders (%)	55.1	58.5		
		EULAR non-responders (%)	12.9	11.8		
		EULAR low disease activity score (%)	31.4	27.6		
		EULAR remission (%)	16.7	16.2		
		Safety, week 24:				
		All AEs (%)	55.2	58.2		
		Serious AEs (%)	4.3	4.4		
		Infusion reactions (%)	3.7	17.2	$p < 0.001$	
		PK/PD, week 24:				
		AUC (μg·h/mL)	676.4	520.9		
RCT, PK/safety study [healthy male subjects (138)]	CA [50]	Safety, single dose:				Modified D&B: excellent; score: 10/12
		All AEs (%)	39.1 vs. EU; 50.0 vs. USA	EU: 34.8; USA: 43.5		
		PK/PD, single dose:				
		AUC (μg·h/mL)	NR	NR	Ratio: 1.011 (0.958–1.067)[c]	
		C_{max} (μg/mL)	NR	NR	Ratio: 1.044 (0.977–1.114)[c]	

Table 2 continued

Study type [patients (*n*)]	References	Outcome	Biosimilar[a]	Etanercept[a]	Statistical comparison	Quality assessment rating
GP 2015						
Nonclinical	CA [51]	Functional (in vivo):				Not evaluated[d]
		Binding to TNF-α	Comparable	Comparable		
		Bioactivity	Comparable	Comparable		
		Clinical response	Comparable	Comparable		
		Histological	Comparable	Comparable		
Nonclinical	CA [51]	PK/PD (rabbit and monkey):				Not evaluated[d]
		AUC (μg·h/mL)	Comparable	Comparable		
		C_{max} (μg/mL)	Comparable	Comparable		
AVG01 (Avent™)						
Analytical	[52]	Composition:				SYRCLE's risk of bias: moderate; 1 = high risk, 17 = unclear, 4 = low risk
		Peptide mapping	Similar	Similar		
		Intact molecular mass	Similar	Similar		
		Glycosylation profile	Comparable	Comparable		
		Sialic acid analysis	35	35		
		Stability analysis	Comparable	Comparable		

Δ difference, *ACR20, 50, 70* American College of Rheumatology 20, 50, 70% improvement criteria, *ADAb* anti-drug antibodies, *AE* adverse event, *AUC* area under the concentration–time curve, AUC_{∞} area under the concentration–time curve from time zero to infinity, AUC_{last} area under the concentration–time curve from time zero to time of last measurable concentration, *CA* conference abstract, C_{max} maximum concentration, *D&B* Downs and Black (tool), *DAS28* Disease Activity Score in 28 joints, *EQ-5D* EuroQoL–five dimensions questionnaire, *EULAR* European League Against Rheumatism, *HR-QOL* health-related quality of life, *MTX* methotrexate, *NICE STA* National Institute for Health and Care Excellence Single Technology Appraisal (manufacturer's template), *PD* pharmacodynamic, *PK* pharmacokinetic, *RA* rheumatoid arthritis, *RCT* randomized controlled trial, *SD* standard deviation, *SF-36* short-form-36, *SYRCLE* SYstematic Review Centre for Laboratory animal Experimentation, $t_{½}$ half-life, *TNF* tumor necrosis factor

[a] Qualitative data for biosimilarity as stated by the corresponding study authors

[b] 95% confidence intervals shown in parentheses

[c] 90% confidence intervals shown in parentheses

[d] Quality assessment not conducted due to the absence of validated tools specific for the study type, at the time of analysis

Table 3 Outcomes for infliximab biosimilars

Study type [patients (*n*)]	References	Outcome	Biosimilar[a]	Infliximab[a]	Statistical comparison	Quality assessment rating
BOW015 (Infimab®)						
RCT, PK/safety study [healthy males (84)]	CA [54]; CA [55]	Safety, week 46:				Modified D&B: excellent; score: 10/12
		All AEs (%)	60.5	66.9		
		Serious AEs (%)	0	2.44		
		ADAb (%)	18.6	24.4		
		PK/PD, week 16:				
		$AUC_{0-\infty}$ (μg·h/mL)	36,775	34,801	Not stated (0.98–1.15)[b]	
		C_{max} (μg/mL)	142.47	126.74	Not stated (0.98–1.14)[b]	
		$t_{½}$ (h)	307.96	280.22		
		t_{max} [h (range)]	3.97 (2–8)	2.05 (2–12.02)		
RCT, comparative efficacy/safety [RA (189)]	CA [56]; CA [54]; CA [57]	Preliminary safety/efficacy studies:				Modified D&B: excellent; score: 10/12
		Efficacy, week 16:				
		Δ CRP, double-blind (mL/L)	−13.4	−16.48		
		Δ CRP, open-label (mL/L)	−13.9	NR		
		Δ ESR (mm/h)	−26.5	−23.7		
		Δ DAS28-CRP [score (SD)]	−2.6 (1.3)	−2.5 (1.3)		
		ACR20, PPS, week 16 (%)	89.9	86.4		
		ACR20, ITT, week 16 (%)	85.0	85.5		
		ACR20, week 54 (%)	72.03	75.42		
		Safety, week 54:				
		All AEs, double-blind (%)	40.94	48.39		
		All AEs, open-label (%)	52.83	NR		
		Serious AEs, double-blind (%)	7.1	6.5		
		Serious AEs, open-label (%)	6.7	5.7		
		ADAb, week 14 (%)	29	38	$p = 0.055$	
		ADAb, week 54 (%)	53.5	56.5		
		HR-QOL score, week 54:				
		Δ HAQ (SD)	−0.945 (0.632)	−0.826 (0.712)	NS	
		Δ PGA, double-blind	−3.5	−3.1		
		Δ PGA, double-blind	−4	NR		

Table 3 continued

Study type [patients (*n*)]	References	Outcome	Biosimilar[a]	Infliximab[a]	Statistical comparison	Quality assessment rating
CT-P13 (Remsima®/Inflectra®)						
RCT, PK/safety and comparative safety/efficacy [AS (250)]	CA [58]; [59]; [60]; CA [61]; CA [62]; CA [63]; CA [64]; CA [65]; CA [66]	AS patients:				NICE STA: excellent; 7 = low risk
		Efficacy:				Jadad: excellent; score: 4/5
		Δ CRP, week 30 (mL/dL)	−0.7	−0.8	NS	
		Δ ESR, week 30 (mm/h)	−21.0	−19.5	NS	
		ASAS20, week 14 (%)	62.6	64.8	OR: 0.91	
		ASAS20, week 30 (%)	70.5	72.4	OR: 0.91	
		ASAS20, week 54 (%)	70.5	75.6		
		ASAS20, week 102 (%)	80.7	76.9		
		ASAS40, week 14 (%)	41.7	45.9	OR: 0.85	
		ASAS40, week 30 (%)	51.8	47.4	OR :1.19	
		ASAS40, week 54 (%)	54.7	49.1		
		ASAS40, week 102 (%)	63.9	51.5		
		Δ ASDAS-CRP, week 14 [score (SD)]	−1.8 (1.1)	−1.8 (1.1)	NS	
		Δ ASDAS-CRP, week 30 [score (SD)]	−1.8 (1.2)	−1.7 (1.2)	NS	
		Δ ASDAS-CRP, week 102 (score)	−2.03	−1.81		
		Δ BASDAI, week 14 (score)	−2.7	−2.7		
		Δ BASDAI, week 30 (score)	−3.1	−2.5		
		BASDAI, week 54 (score)	3.78	3.70		
		BASDAI50, week 54 (%)	44.3	46.3	NS	
		ASAS partial remission, week 102 (%)	27.7	28.2		
		Safety:				
		All AEs, week 102 (%)	48.9	71.4		
		Serious AEs, week 54 (%)	7.8	6.6		
		Infusion reactions, week 54 (%)	3.1	9.0		
		ADAb, week 30 (%)	27.4	22.5		

Table 3 continued

Study type [patients (*n*)]	References	Outcome	Biosimilar[a]	Infliximab[a]	Statistical comparison	Quality assessment rating
		ADAb, week 102 (%)	25.0	30.7		
		PK/PD:				
		$AUC_{0-\infty}$ (μg·h/mL)	32,765	31,359	Ratio: 1.045 (94.3–115.8)[b]	
		C_{max} (μg/mL)	147.0	144.8	Ratio: 1.015 (94.7–08.9)[b]	
		$t_{½}$ [h (SD)]	292.2 (32.2)	298.3 (37.3)		
		Clearance [mL/h/kg (SD)]	12.7 (73.1)	14.2 (77.7)		
		Volume of distribution [mL/kg (SD)]	3830 (30.8)	4294 (78.3)		
		t_{max} [h (range)]	3.0 (2–359)	3.0 (2–168)		
		HR-QOL score:				
		SF-36, mental, week 30	6.5	5.2		
		SF-36, physical, week 30	7.6	8.5		
RCT, comparative safety/efficacy [RA (606)]	CA [67]; CA [68]; [69]; CA [70]; CA [71]; CA [72]; CA [73]; CA [63]	RA patients:				NICE STA: excellent; 2 = unclear, 5 = low risk
		Efficacy:				Jadad: good; score: 3/5
		Δ CRP, week 14 [mL/L (SD)]	−0.6 (2.5)	−0.8 (1.9)	$p = 0.413$	
		Δ CRP, week 30, [mL/L (SD)]	−0.6 (2.0)	−0.8 (1.9)	$p = 0.323$	
		ESR, week 30 (mm/h)	30.6	32.1		
		Δ DAS28-ESR score, week 102	−2.6	−2.7		
		DAS28-CRP LDA (%)	40.9	39.0		
		EULAR-CRP response, week 30 (%)	85.8	87.1	RR: 0.98	
		EULAR-CRP response, week 102 (%)	81.5	76.8		
		EULAR-ESR response, week 30 (%)	84.5	82.3	NS	
		EULAR-ESR response, week 102 (%)	81.5	81.0		
		ACR20, PPS, week 30 (%)	60.9	58.69	Difference: 2%	
		ACR20, ITT, week 30 (%)	73.4	69.7	Difference: 4%	
		ACR20, week 54 (%)	71.5	78.2		
		ACR20, week 102 (%)	72.2	71.8		

Table 3 continued

Study type [patients (*n*)]	References	Outcome	Biosimilar[a]	Infliximab[a]	Statistical comparison	Quality assessment rating
		ACR50, PPS, week 30 (%)	42.3	40.6	Difference: 2%	
		ACR50, week 54 (%)	33.1	31.6		
		ACR50, week 102 (%)	48.3	51.4		
		ACR70, PPS, week 30 (%)	20.2	17.9	Difference: 2%	
		ACR70, week 54 (%)	21.3	23.9		
		ACR70, week 102 (%)	24.5	26.1		
		DAS28-CRP remission, week 54 (%)	26.4	27.8		
		ACR/EULAR remission (%)	6.7	6.8		
		Δ CDAI, week 30 score (SD)	−25.2 (13.3)	−23.6 (13.0)	$p = 0.182$	
		Δ SDAI, week 30 score (SD)	−25.8 (14.0)	−24.4 (13.6)	$p = 0.247$	
		SDAI remission (%)	9.7	9.6		
		Joint progression (imputed)	1.3	0.7	$p = 0.3171$	
		Total Sharpe score, week 54	70.4	73		
		Δ Total Sharpe score, week 54	1.0	0.6		
		Δ Erosion score, week 54	0.7	0.0		
		Δ JSN score, week 54	0.4	0.7		
		Safety:				
		All AEs, week 102 (%)	53.5	53.8		
		Serious AEs, week 54 (%)	13.9	10.3		
		Infusion reactions, week 54 (%)	7.6	10.3		
		ADAb, week 54 (%)	52.3	49.5		
		PK/PD:				
		C_{max}, week 30 (μg/mL)	83.9–111.9	83.8–105.1		
		C_{max}, week 54 (μg/mL)	66.1–112.2	60.3–104.5		

Table 3 continued

Study type [patients (*n*)]	References	Outcome	Biosimilar[a]	Infliximab[a]	Statistical comparison	Quality assessment rating
		t_{max} [h (range)]	3.0 (2–3.25)	2.25 (2–4.50)		
		HR-QOL score:				
		Δ HAQ-DI, week 30 (SD)	−0.6 (0.6)	−0.5 (0.5)	$p = 0.082$	
		HAQ-DI, week 54	0.99	1.02	$p = 0.657$	
		SF-36, mental, week 30 (SD)	7.1 (10.0)	6.6 (10.4)	$p = 0.561$	
		SF-36, physical, week 30 (SD)	7.1 (7.9)	6.5 (7.6)	$p = 0.372$	
		Δ PGA, week 30 (SD)	−35.6 (20.6)	−35.3 (21.2)	$p = 0.910$	
RCT, PK/safety [healthy subjects (213)]	CA [63]	Safety, week 54:				Modified D&B: excellent; score: 11/12
		All AEs (%)	39.4	USA: 42.3; EU: 23.9		
		Serious AEs (%)	0	0		
		PK/PD, week 54:				
		$AUC_{0-\infty}$ (μg·h/mL)	33,212	USA: 34,363; EU: 32,986		
		C_{max} (μg/mL)	127.6	USA: 119.9; EU: 121.3		
prospective [CD (59) and UC/ prospective [UC (12)]	CA [74]	Efficacy, week 6:				Modified D&B: fair; score: 4/12
		Clinical response (%)	58	NA		
		Mucosal healing ($n = 9$) (%)	78	NA		

Table 3 continued

Study type [patients (*n*)]	References	Outcome	Biosimilar[a]	Infliximab[a]	Statistical comparison	Quality assessment rating
prospective [CD (59) and UC/ prospective [CD (59) and UC (51)]	CA [75]; [76]	Efficacy:				D&B: good; score: 13/26
		CRP, CD, week 2 [mg/dL (SD)]	1.05 (2.07)			
		CRP, CD, week 30 [mg/dL (SD)]	0.56 (0.82)			
		CRP, UC, week 2 [mg/dL (SD)]	0.40 (0.60)			
		CRP, UC, week 30 [mg/dL (SD)]	0.51 (0.71)			
		ESR, CD, week 2 [mm/h (SD)]	32 (58)			
		ESR, CD, week 30 [mm/h (SD)]	22 (22)			
		ESR, UC, week 2 [mm/h (SD)]	23 (16)			
		ESR, UC, week 30 [mm/h (SD)]	17 (16)			
		CD activity index, week 2 [score (SD)]	127 (46)			
		CD activity index, week 30 [score (SD)]	109 (83)			
		Partial Mayo, UC, week 2 [score (SD)]	3.7 (2.3)			
		Partial Mayo, UC, week 30 [score (SD)]	1.9 (1.7)			
		CD activity index <150 (%)	75.0			
		Partial Mayo ≤1	50.0			
		Safety:				
		All AEs (%)	11.8			
		Infusion reaction (*n*)	1			
prospective [CD (59) and UC/ retrospective [CD (8) and UC (9)]	CA [77]; [78]	Efficacy, week 8:				D&B: good; score: 13/26
		Clinical response (biologic-naïve)	$n = 7$ of 8	NA		
		Clinical response (switchers)	$n = 8$ of 9	NA		
		All AEs (biologic-naïve)	$n = 0$ of 8	NA		
		All AEs (switchers)	$n = 1$ of 9	NA		

Table 3 continued

Study type [patients (*n*)]	References	Outcome	Biosimilar[a]	Infliximab[a]	Statistical comparison	Quality assessment rating
prospective [CD (59) and UC/ retrospective [CD and UC (36)]	CA [79]	Efficacy:				Modified D&B: good; score: 6/12
		Surgery rates (%)	29	0	$p = 0.02$	
		Hospital readmission rates (%)	80	5	$p = 0.00004$	
		Requiring steroids (%)	50	8	$p = 0.0007$	
		CRP increase (%)	93	0	$p < 0.001$	
Observational/retrospective [CD (18) and UC (21)]	[80]	Efficacy:				D&B: good; score: 12/26
		Responders, CD, CDAI score (SD)	222 (12.8)	NA		
		Non-responders, CD, CDAI score	242	NA		
		Responders, UC, pMayo score	3	NA		
		Remission, UC, pMayo score (SD)	0.5 (0.27)	NA		
		Non-responders, UC, pMayo score (SD)	7.5 (0.5)	NA		
		Safety:				
		All AEs, CD (*n*)	1	NA		
		All AEs, UC (*n*)	2	NA	–	
		ADAb, CD (*n*)	3	NA	–	
		ADAb, UC (*n*)	1	NA	–	
Observational/prospective [CD (57) and UC (33)]	CA [81]	Efficacy:				Modified D&B: fair; score: 4/12
		CDAI (score)	NR, $p < 0.001$ vs. baseline	NA	–	
		pMayo score, UC, week 2 (score)	3.7	NA	–	
		pMayo score, UC, week 6 (score)	3.6	NA	–	
		Safety:				
		Allergic reactions (*n*)	4	NA	–	
Observational/prospective [CD (32)]	CA [82]	Efficacy:				Modified D&B: good; score: 6/12
		CRP (mg/dL)	0.6	1.2	–	
		ESR (mm/h)	13	13	–	
		Safety:				
		All AEs	Similar	Similar	–	

Table 3 continued

Study type [patients (*n*)]	References	Outcome	Biosimilar[a]	Infliximab[a]	Statistical comparison	Quality assessment rating
Health economics [CD (UK, Italy, and France)]	CA [83]	Budget impact (year: €; 000s):				Not evaluated[c]
		Cost savings for 10% scenarios	2015: 10,210; 2016: 12,240; 2017: 14,730; 2018: 17,670; 2019: 21,220			
		Cost savings for 20% scenarios	2015: 20,420; 2016: 26,560; 2017: 34,570; 2018: 44,930; 2019: 58,440			
		Cost savings for 30% scenarios	2015: 30,640; 2016: 42,900; 2017: 60,120; 2018: 84,180; 2019: 117,890			
		Total 5-year savings (10%; 20%; 30%)	76,070; 184,920; 335,730			
Health economics [RA (Bulgaria, the Czech Republic, Hungary, Poland, Romania, Slovakia)]	[84]	Budget impact (€; 000s) [*n* = 17,257]:				Drummond's checklist: good; score: 23/36
		Cost savings for scenario 1	Year 1: 945; Year 2: 4782; Year 3: 9612; Total: 15,340			
		Cost savings for scenario 2	Year 1: 2394; Year 2: 6968; Year 3: 11,463; Total: 20,826			
Health economics [CD (Bulgaria, the Czech Republic, Hungary, Poland, Romania, Slovakia)]	CA [85]	Budget impact (€; 000s) [*n* = 4625]:				Not evaluated[c]
		Cost savings for non-interchangeable scenario	Total: 7842			
		Cost savings for interchangeable scenario	Total: 16,635			
Health economics [RA, AS, CD, UC, PsA, psoriasis patients in Germany, Italy, Belgium, The Netherlands, and the UK]	CA [86]; [87]	Budget impact (€; 000,000s):				Drummond's checklist: good; score: 23/36
		Cost savings for 10% scenarios, €	Year 1:17.8; GER: 11.3; UK: 3.6; IT: 4.6; NL: 3.4; BL: 2.9			
		Cost savings for 20% scenarios, €	Year 1: 35.5; GER: 22.5; UK: 7.2; IT: 9.3; NL: 6.8; BL: 5.8			
		Cost savings for 30% scenarios, €	Year 1: 53.3; GER: 33.8; UK: 10.9; IT: 13.9; NL: 10.2; BL: 8.7			
		Total 5-year savings (10%; 20%; 30%)	132.8; 322.8; 532.8			
Health economics [RA (UK, Italy, France, Germany)]	CA [88]	Budget impact (year: €; 000s):				Not evaluated[c]
		Cost savings for 10% scenarios	2015: 12,880; 2016: 15,450; 2017: 18,560; 2018: 22,260; 2019: 26,710			
		Cost savings for 20% scenarios	2015: 25,750; 2016: 33,490; 2017: 43,550; 2018: 56,610; 2019: 73,300			
		Cost savings for 30% scenarios	2015: 38,630; 2016: 64,630; 2017: 75,740; 2018: 106,050; 2019: 148,470			
		Total 5-year savings (10%; 20%; 30%)	95,860; 233,000; 433,520			

Table 3 continued

Study type [patients (*n*)]	References	Outcome	Biosimilar[a]	Infliximab[a]	Statistical comparison	Quality assessment rating
Health economics [RA (Ireland)]	CA [89]	Budget impact:				Not evaluated[c]
		Total 5-year savings	Year 1: 3776 patients (13% receive biosimilar)			
		Total cost per patient (€)	Year 1: 15,754; subsequent years: 12,789			
		Annual budget savings (€)	Year 1: 579; Year 2: 1165; Year 3: 1177; Year 4: 1189; Year 5: 1201; Cumulative: 5313			
Analytical/nonclinical (cell-based)	[90]	Functional assessment (in vitro):				Not evaluated[c]
		TNF binding [% (range)]	101 (92–10)	100 (90–112)	Equivalent	
		TNF neutralization [% (range)]	102 (95–107)	104 (98–110)	Equivalent	
		Apoptosis [% (range)]	101 (91–105)	101 (92–110)	Equivalent	
		Composition	Similar	Similar		
Analytical/nonclinical	CA [91]	NA				Not evaluated[c]
Analytical	CA [91]	NA				Not evaluated[c]
Analytical/nonclinical (cell-based)	[90]	Composition:	Similar	Similar		Not evaluated[c]
		Peptide mapping	NR	NR		
		DSC	NR	NR		
		Antibody conformational array	NR	NR		
Analytical	CA [92]	NA				Not evaluated[c]
PF-06438179						
RCT, PK/safety [healthy subjects (146)]	CA [93]; CA [94]; CA [95]; CA [96]; CA [97]; CA [98]; CA [99]	Safety, up to week 12:				Modified D&B: excellent; score: 10/12
		All AEs	Comparable	Comparable		
		ADAb (%)	16.2	USA: 28.2; EU: 32.6		
		PK/PD, up to week 8	Comparable	Comparable	Ratio: 0.80–1.25	
RCT, PK/safety/analytical, and nonclinical	CA [93]; CA[94]; CA [95]; CA [96]; CA [97]; CA [98]; CA [99]	Composition:				Modified D&B: excellent; score: 10/12
		Peptide mapping	Superimposable	Superimposable		
Analytical/PK/safety, analytical, and nonclinical (rats and cell-based)	CA [93]; CA [94]; CA [95]; CA [96]; CA [97]; CA [98]; CA [99]	PK/PD (rat):				Modified D&B: excellent; score: 10/12
		Systemic exposure	Similar	Similar		
		ADAb	Superimposable	Superimposable		
		Functional (in vitro):	0.88–1.16	0.88–1.16		
		Inhibition of apoptosis	Similar	Similar		

Table 3 continued

Study type [patients (*n*)]	References	Outcome	Biosimilar[a]	Infliximab[a]	Statistical comparison	Quality assessment rating
SB2 (Flixabi®)						
RCT, PK/safety [healthy subjects (159)]	CA [41]	Safety, single dose:				Modified D&B: excellent; score: 11/12
		All AEs	Comparable	Comparable	–	
		Serious AEs (*n*)	1	0	NS	
		ADAb (%)	Similar	Similar		
		PK/PD:				
		C_{max} (μg/mL)	NR	NR	Ratio: 0.985 (0.942–1.030)[b]	
RCT, comparative safety/efficacy [RA (584)]	CA [100]; [101]	Efficacy, week 30:				NICE STA: excellent; 7 = low risk Jadad: excellent; score: 5/5
		Δ CRP [mg/dL (SD)]	−3.7 (21.6)	−5.2 (19.9)		
		Δ ESR [mm/h (SD)]	−15.4 (19.8)	−15.5 (22.7)		
		Δ DAS28 [score (SD)]	−2.3 (1.4)	−2.3 (1.5)		
		Δ CDAI [score (SD)]	−23.3 (13.7)	−23.1 (14.2)		
		Δ SDAI [score (SD)]	−23.5 (14.1)	−23.6 (14.5)		
		ACR20, PPS (%)	64.1	66.0	Adjusted difference: −1.88 (−10.26 to 6.51)[b]	
		ACR50, PPS (%)	35.5	38.1	Adjusted difference: −2.13 (−10.69 to 6.43)[b]	
		ACR70, PPS (%)	18.2	19.0	Adjusted difference: −0.025 (−7.26 to 6.75)[b]	
		EULAR moderate response (%)	58.1	54.7		
		EULAR good response (%)	25.7	25.7		
		DAS28 LDA (%)	11.1	9.8		
		DAS28 remission (%)	14.6	15.9		

Table 3 continued

Study type [patients (*n*)]	References	Outcome	Biosimilar[a]	Infliximab[a]	Statistical comparison	Quality assessment rating
		Safety, up to week 48:				
		All AEs (%)	21.4	20.1		
		Serious AEs (%)	9.0	8.9		
		Infusion reaction (%)	5.2	4.4		
		ADAb (%)	55.1	49.7		
		PK/PD:				
		C_{max}, week 6 (μg/mL)	13.37	12.04		
		HR-QOL score:				
		Δ HAQ, week 30 (SD)	−0.5 (0.6)	−0.5 (0.6)		
		PGA (SD)	−32.7 (20.7)	−32.8 (22.2)		

Δ difference, *ACR20, 50, 70* American College of Rheumatology 20%, 50%, 70% improvement criteria, *ADAb* anti-drug antibodies, *AE* adverse event, *AS* ankylosing spondylitis, *ASAS* Assessment in Ankylosing Spondylitis, *ASDAS* ankylosing spondylitis Disease Activity Score, $AUC_{0-\infty}$ area under the concentration–time curve from time zero to infinity concentration, *BASDAI* Bath Ankylosing Spondylitis Disease Activity Index, *BL* baseline, *BE* Belgium, *CA* conference abstract, *CD* Crohn's disease, *CDAI* Clinical Disease Activity Index, C_{max} maximum concentration, *CRP* C-reactive protein, *D&B* Downs and Black (tool), *DAS28* Disease Activity Score in 28 joints, *DSC* differential scanning calorimetry, *ESR* erythrocyte sedimentation rate, *EULAR* European League Against Rheumatism, *GER* Germany, *HAQ-DI* health assessment questionnaire disability index, *HR-QOL* health-related quality of life, *IT* Italy, *ITT* intention-to-treat analysis, *JSN* joint space narrowing, *LDA* low disease activity, *NA* not available, *NICE STA* National Institute for Health and Care Excellence Single Technology Appraisal (manufacturer's template), *NL* The Netherlands, *NR* not reported, *NS* non-significant, *OR* odds ratio, *PGA* Patient Global Assessment of disease, *PD* pharmacodynamic, *PK* pharmacokinetic, *PPS* per protocol set, *PsA* psoriatic arthritis, *RA* rheumatoid arthritis, *RCT* randomized controlled trial, *RR* relative risk, *SD* standard deviation, *SDAI* Simple Disease Activity Index, *SF-36* 36-Item Short Form Health Survey, $t_{½}$ half-life, t_{max} time taken to reach the maximum concentration, *TNF* tumor necrosis factor, *UC* ulcerative colitis

[a] Qualitative data for biosimilarity as stated by the corresponding study authors

[b] 95% confidence intervals shown in parentheses

[c] Quality assessment not conducted due to the absence of validated tools specific for the study type, at the time of analysis

SB2 (*Flixabi®; Samsung Bioepis*) The pharmacokinetics, safety, and immunogenicity profiles were reportedly similar between SB2 and infliximab in healthy volunteers [41]. No analytical or nonclinical studies comparing structural or functional similarity of SB2 versus infliximab had been published at the time of review.

CT-P13 (*Remsima®/Inflectra®; Celltrion*) CT-P13 was evaluated in healthy human volunteers and demonstrated similar safety and pharmacokinetic profiles as those for infliximab [63]. The physicochemical properties of CT-P13 were also characterized using combined analytical techniques [91, 90]. The results, overall, demonstrated that CT-P13 has comparable structural properties to that of infliximab. A nonclinical cell-based study has also been reported, confirming bioequivalence in vitro.

3.2.4 Rituximab Biosimilars

Studies of rituximab biosimilars are presented in Table 4.

GP2013 (*Sandoz*) The functional similarity and pharmacokinetic properties of GP2013 compared with rituximab have been assessed both in vitro (using lymphoma cell lines) [117] and in vivo (mouse xenograft models and cynomolgus monkeys) [117, 115]. The studies also included structural comparability assessments using a combination of biochemical techniques. These studies suggest high levels of similarity between GP2013 and the originator rituximab.

PF-05280586 (*Pfizer*) Comparative nonclinical studies have been published for PF-05280586 and rituximab, based on in vitro functional assessments and evaluation of safety or pharmacokinetic in vivo (monkeys) [114, 109, 111, 113, 108, 112]. In vitro data (complement-dependent cytotoxicity assays and biologic activity) provide evidence of functional similarity to the originator. The safety, tolerability, and pharmacokinetic/pharmacodynamic profile of PF-05280586 in monkeys is reported to be comparable to rituximab. These studies also included comprehensive analytical assessments of the primary and higher-order structure, and concluded high similarity between the biosimilar and the originator.

RTXM83 (*Mabxience*) The biological potency and pharmacokinetic/pharmacodynamic properties of RTXM83 have been evaluated in a single preclinical study (unspecified cell line or cynomolgus monkeys) [118]. The results of the study suggest functional similarity and analogous pharmacokinetic/pharmacodynamic properties between the biosimilar and originator.

3.3 Clinical Evidence in Rheumatoid Arthritis (RA)

3.3.1 Adalimumab Biosimilars in RA

Studies of adalimumab biosimilars are presented in Table 1.

Exemptia™ (*Cadila Healthcare*) The safety and efficacy of Exemptia™ versus adalimumab have been reported in a comparative safety/efficacy trial in patients (n = 120) with moderate-to-severe RA [33]. The results demonstrated no significant difference in any of the parameters (with respect to efficacy, tolerability, and safety) at the end of the study between the two treatment groups. No analytical or nonclinical study data evaluating the structural composition or functional similarity of Exemptia™ with respect to adalimumab were extracted during this literature review.

3.3.2 Etanercept Biosimilars in RA

Studies of etanercept biosimilars are presented in Table 2.

HD203 (*Davictrel™; Hanwha Chemical*) In a comparative safety/efficacy trial comparing HD203 with etanercept in patients with active RA (n = 233) and insufficient response to methotrexate, the proportion of patients achieving American College of Rheumatology (ACR) improvement of 20% (ACR20) at week 24 was not significantly different between HD203 and etanercept. Similar trends were seen for ACR improvement of 50% (ACR50) and of 70% (ACR70) [46, 45].

SB4 (*Benepali®; Samsung Bioepis*) One comparative safety/efficacy RCT for SB4 was found for patients with RA (n = 596), which reported that SB4 was equivalent to etanercept in terms of efficacy and had a comparable safety profile [48, 49].

3.3.3 Infliximab Biosimilars in RA

Studies of infliximab biosimilars are presented in Table 3.

BOW015 (*Infimab®; Ranbaxy Laboratories*) Prior to discontinuation, BOW015 was investigated in a comparative safety/efficacy equivalence study in patients with RA (n = 189). Results of the study implied similarity with respect to efficacy (disease activity and physical function) and safety compared with infliximab [54, 119, 57, 56, 120].

SB2 (*Flixabi®; Samsung Bioepis*) SB2 has been studied in a comparative safety/efficacy study to demonstrate equivalence of efficacy, safety, immunogenicity, and pharmacokinetic outcomes versus infliximab in patients with moderate to severe RA (n = 584) [100, 101]. SB2 demonstrated equivalent efficacy to infliximab in regards to ACR20 response. The pharmacokinetic, safety, and immunogenicity profiles were also reportedly similar to infliximab.

CT-P13 (*Remsima®/Inflectra®; Celltrion*) In the PLANETRA (Programme evaLuating the Autoimmune disease iNvEstigational drug cT-p13 in RA patients) comparative safety/efficacy study, CT-P13 displayed equivalent efficacy to infliximab, was well-tolerated, and had a comparable pharmacokinetic, safety, and immunogenicity profile, as

Table 4 Outcomes for rituximab biosimilars

Study type [patients (*n*)]	Reference	Outcome	Biosimilar[a]	Rituximab[a]	Statistical comparison	Quality assessment rating
CT-P10						
RCT, PK/safety [RA (154)]	CA [102]; CA [103]	Efficacy, week 24:				Modified D&B: excellent; score: 9/12
		ACR20 (%)	63.0	66.7		
		ACR50 (%)	37.0	31.3		
		ACR70 (%)	16.0	14.6		
		Safety, week 24:				
		All AEs (*n*)				
		Treatment AEs	166	88		
		Infections (%)	23.5	25.5		
		Infusion reactions (%)	16.7	19.6		
		Serious AEs (%)	16.7	17.6		
		Serious AEs RTX Abs +ve (%)	11.1	22.2		
		Serious AEs RTX Abs –ve (%)	15.6	16.2		
		ADAb (%)	17.6	17.6		
		PK/PD, week 24:				
		C_{max} (μg/mL)	465.9	477.5	Ratio: 0.976 (0.92–1.035)[b]	
		AUC (μg·day/mL)	7870.8	8010.4	Ratio: 0.983 (0.896–1.078)[b]	
		AUC of B cell count (cells/μL)	20.8	20.4	Ratio: 1.02 (0.98–1.06)[b]	
PF-05280586						
RCT, PK/safety, preliminary safety/efficacy [RA (220)]	CA [104]; CA [105]; CA [106]; CA [107]	Efficacy, week 16:				Modified D&B: good; score: 7/12
		ACR20, 50, and 70 (%)	Improved	Improved		
		DAS28-CRP	Improved	Improved		
		CRP (mg/L)	Improved	Improved		
		Safety, week 16:				
		Serious AEs (*n*)	5	6		
		PK/PD, week 16:				
		C_{max} (μg/mL)	Similar	Similar		
		AUC (μg·day/mL)	Similar	Similar		
		$t_{½}$ (h)	Similar	Similar		
		Clearance (mL/h/kg)	Similar	Similar		
		Volume of distribution (mL/kg)	Similar	Similar		

Table 4 continued

Study type [patients (*n*)]	Reference	Outcome	Biosimilar[a]	Rituximab[a]	Statistical comparison	Quality assessment rating
Nonclinical (cynomolgus monkeys and cell-based)	[108]; CA [109]; CA [110]	Functional assessment (in vitro):				SYRCLE'S risk of bias: moderate; unclear = 9, low risk = 13
		CDC	Similar	Similar		
		Safety (monkey):	Similar	Similar		
		ADAb, single-dose (%)	100	100		
		ADAb, repeated-dose, day 22 (%)	71	36		
		ADAb, repeated-dose, day 114 (%)	50	50		
		PK/PD (monkey):				
		AUC, 2 mg/kg [μg·h/mL (SD)]	4720 (966.0)	4940 (890.0)		
		AUC, 10 mg/kg [μg·h/mL (SD)]	34,700 (8650.0)	37,100 (6010.0)		
		AUC, 20 mg/kg [μg·h/mL (SD)]	64,000 (14,600.0)	51,700 (11,900.0)		
		AUC, repeated-dose, day 1 [μg·h/mL (SD)]	56,800 (15,400.0)	54,600 (8,800.0)		
		AUC, repeated-dose, day 22 [μg·h/mL (SD)]	53,200 (18,700.0)	79,500 (39,900.0)		
		C_{max}, 2 mg/kg [μg/mL (SD)]	74.0 (15.5)	80.3 (7.95)		
		C_{max}, 10 mg/kg [μg/mL (SD)]	481.0 (70.4)	497.0 (62.2)		
		C_{max}, 20 mg/kg [μg/mL (SD)]	912.0 (198.0)	726.0 (138.0)		
		C_{max}, repeated-dose, day 1 [μg/mL (SD)]	848.0 (241.0)	903.0 (292.0)		
		C_{max}, repeated-dose, day 22 [μg/mL (SD)]	966.0 (966.0)	1230.0 (313.0)		
		$t_{½}$, 2 mg/kg [h (SD)]	1.22 (2.37)	0.08 (0.0)		
		$t_{½}$, 10 mg/kg [h (SD)]	0.24 (0.37)	0.24 (0.37)		
		$t_{½}$, 20 mg/kg [h (SD)]	0.24 (0.37)	0.39 (0.47)		
		$t_{½}$, repeated-dose [h (SD)]	0.70 (1.57)	0.35 (0.43)		
		$t_{½}$, repeated-dose [h (SD)]	0.48 (0.47)	0.67 (0.46)		
		t_{max}	Similar	Similar		
		Reduction in splenic weight (%)	12–42	15–44		
		Single-dose:				
		CD3–CD20+, 2 mg; 10 mg; 20 mg, day 4 (%)	99.3; 99.7; 99.2	98.4; 99.5; 99.0		
		CD3–CD20+, 2 mg; 10 mg; 20 mg, day 15 (%)	92.1; 97.4; 98.7	89.5; 99.7; 97.0		
		CD3–CD20+, 2 mg; 10 mg; 20 mg, day 92 (%)	27.7; 28.7; 35.1	27.8; 18.3; 24.1		
		CD3–CD20+CD40+, 2 mg; 10 mg; 20 mg, day 4 (%)	100; 100; 100	100; 100; 100		
		CD3–CD20+CD40+, 2 mg; 10 mg; 20 mg, day 15 (%)	91.1; 97.0; 100	89.0; 99.2; 95.0		
		CD3–CD20+CD40+, 2 mg; 10 mg; 20 mg, day 92 (%)	29.1; 8.3; 27.5	40.0; –15.5; 18.8		

Table 4 continued

Study type [patients (*n*)]	Reference	Outcome	Biosimilar[a]	Rituximab[a]	Statistical comparison	Quality assessment rating
		CD3–CD19+, 2 mg; 10 mg; 20 mg, day 4 (%)	86.3; 90.2; 90.5	83.5; 85.2; 87.1		
		CD3–CD19+, 2 mg; 10 mg; 20 mg, day 15 (%)	81.0; 85.6; 91.1	74.6; 88.7; 83.1		
		CD3–CD19+, 2 mg; 10 mg; 20mg, day 92 (%)	9.8; 2.1; 29.6	6.2; –5.2; –8.4		
		CD3–CD40+, 22 mg; 10 mg; 20 mg, day 4 (%)	85.9; 91.4; 92.6	88.0; 87.3; 88.3		
		CD3–CD40+, 2 mg; 10 mg; 20 mg, day 15 (%)	81.0; 84.8; 94.9	78.4; 88.2; 88.0		
		CD3–CD40+, 2 mg; 10 mg; 20 mg, day 92 (%)	25.3; 1.5; 18.7	25.5; –30.0; 5.3		
		Repeated-dose:				
		CD3–CD20+, 2 mg; 10 mg; 20 mg, day 4 (%)	100	100		
		CD3–CD20+, 2 mg; 10 mg; 20 mg, day 15 (%)	99.9	99.7		
		CD3–CD20+, 2 mg; 10 mg; 20 mg, day 121 (%)	75.5	80.9		
		CD3–CD20+CD40+, 2 mg; 10 mg; 20 mg, day 4 (%)	100	90.1		
		CD3–CD20+CD40+, 2 mg; 10 mg; 20 mg, day 15 (%)	99.9	99.4		
		CD3–CD20+CD40+, 2 mg; 10 mg; 20 mg, day 121 (%)	76.1	80.5		
		CD3–CD19+, 2 mg; 10 mg; 20 mg, day 4 (%)	96.1	92.1		
		CD3–CD19+, 2 mg; 10 mg; 20 mg, day 15 (%)	90.3	89.6	–	
		CD3–CD19+, 2 mg; 10 mg; 20 mg, day 121 (%)	80.1	84.0	–	
		CD3–CD40+, 2 mg; 10 mg; 20 mg, day 4 (%)	97.3	86.0	–	
		CD3–CD40+, 2 mg; 10 mg; 20 mg, day 15 (%)	97.3	96.8		
		CD3–CD40+, 2 mg; 10 mg; 20 mg, day 121 (%)	74.3	77.1		
Nonclinical (cell-based)	CA [111]	Functional assessment (in vitro):				Not evaluated[d]
		Biologic activity (%)	93–114	USA/EU: 79–135		
Nonclinical (cell-based)	CA [112]	Functional assessment (in vitro):				Not evaluated[d]
		ADCC dose-response curve	Superimposable	Superimposable		
		CDC dose-response curve	Superimposable	Superimposable		
		Binding to FcγRIIIa	Similar	Similar		

Table 4 continued

Study type [patients (*n*)]	Reference	Outcome	Biosimilar[a]	Rituximab[a]	Statistical comparison	Quality assessment rating
Analytical/nonclinical (cynomolgus monkeys and cell-based)	CA [113]; [108]; CA [109]; CA [114]	Composition:				SYRCLE'S risk of bias: moderate; unclear = 9, low risk = 13
		Tryptic peptide mapping	Superimposable	Superimposable		
Analytical/nonclinical (cell-based)	CA [111]	Composition:	Similar	Similar		Not evaluated[d]
		Proteolytic peptide mapping	Similar	Similar		
		Glycan quantification	Similar	Similar		
		Purity	NR	NR		
		Charge heterogeneity	NR	NR		
		Major post-translational modification	NR	NR		
		Hydrodynamic size heterogeneity	NR	NR		
		High molecular mass species (%)	0.5–0.7	USA/EU: 0.9–1.6		
Analytical/nonclinical (cell-based)	CA [112]	Composition:				Not evaluated[d]
		Peptide mapping	Similar	Similar		
GP2013						
Nonclinical (cynomolgus monkeys, mouse xenograft models, and cell-based)	[115]; CA [116]	Functional assessment (in vitro):				SYRCLE's risk of bias: moderate; 12 = unclear, 10 = low risk
		ADCC	Overlapping	Overlapping	NS	
		Efficacy (mouse model):	Similar	Similar		
		Tumor growth inhibition, 3 mg, SU-DHL			Ratio: 1.07 (0.82–1.38)[c]	
		Tumor growth inhibition, 30 mg, SU-DHL			Ratio: 1.08 (0.70–1.69)[c]	
		Tumor growth inhibition, 0.1 mg, Jeko-1 [cell-line]			Ratio: 1.06 (0.74–1.51)[c]	
		Tumor growth inhibition, 0.3 mg, Jeko-1 [cell-line]			Ratio: 0.95 (0.53–1.71)[c]	
		Safety:				
		ADAb (days)	>9	>9		
		PK/PD (monkey):				
		AUC (%)	0.80–1.25	0.80–1.25		
		C_{max}	13% lower	13% higher		
		CD20 levels (%)	80–125	80–125		
		Composition:	Similar	Similar		
		Glycan quantification	NR	NR		
		Charge variation	NR	NR		
		Specific amino acid modifications	NR	NR		
		Size heterogeneity	NR	NR		
Nonclinical (cell-based)	[117]	Functional assessment (in vitro):			Bioequivalent	Not evaluated[d]
		Cell-based competitive binding (%)	97–108	96–100	$p < 0.0001$	
		ADCC (%)	86–105	70–132	$p < 0.0001$	
		CDC (%)	99–111	95–127	$p < 0.0001$	
		Apoptosis (%)	88–99	88–102	$p < 0.0001$	

Table 4 continued

Study type [patients (*n*)]	Reference	Outcome	Biosimilar[a]	Rituximab[a]	Statistical comparison	Quality assessment rating
Analytical (cynomolgus monkeys, mouse models, and cell-based)	[115] CA [116]	Composition:	Similar	Similar		SYRCLE's risk of bias: moderate; 12 = unclear, 10 = low risk
		Glycan quantification	NR	NR		
		Charge variation	NR	NR		
		Specific amino acid modifications	NR	NR		
		Size heterogeneity	NR	NR		
Analytical/nonclinical (cell-based)	[117]	Composition:				Not evaluated[d]
		Primary structure	Identical	Identical		
		Higher order structure	Expected pattern			
		Stability	Superimposable			
		Free thiol analysis	Comparable			
		Deamidation, deamidated L28H [peptide] (%)	0.5	1.0		
		Glycation (%)	2–3	2–3		
		Glycosylation site analysis	Similar			
		Purity, aggregate and particle levels	Similar			
RTXM83						
Nonclinical (cynomolgus monkeys and cell-based)	CA [118]	Functional assessment (in vitro):				Not evaluated[d]
		ADCC, binding	Similar	Similar		
		CDC, potency	Similar	Similar		
		PK/PD (monkey):				
		AUC (%)	80–120			
		C_{max} (%)	80–120			
		$t_{½}$, repeated-dose (%)	80–120			
		CD20 and CD40 depletion	Similar	Similar		
Analytical/nonclinical (cell-based)	CA [118]	Composition:				Not evaluated[d]
		Peptide mapping	Similar	Similar		
		Glycan quantification and charge variant	Similar	Similar		

Abs antibodies, *ACR20, 50, 70* American College of Rheumatology 20, 50, 70% improvement criteria, *ADAb* anti-drug antibodies, *ADCC* antibody-dependent cell-mediated cytotoxicity, *AE* adverse event, *AUC* area under the plasma concentration–time curve, *CA* conference abstract, *CDC* complement-dependent cytotoxicity, C_{max} maximum concentration, *CRP* C-reactive protein, *D&B* Downs and Black (tool), *DAS28* Disease Activity Score in 28 joints, *FcγRIIIa* Fc gamma receptor IIIa, *NR* not reported, *NS* not significant, *PD* pharmacodynamic, *PK* pharmacokinetic, *RA* rheumatoid arthritis, *RCT* randomized controlled trial, *RTX* rituximab, *SD* standard deviation, *SU-DHL* Southwestern University Diffuse Histiocytic Lymphoma, *SYRCLE* SYstematic Review Centre for Laboratory animal Experimentation, $t_{½}$ half-life, t_{max} time to maximum concentration, *+ve* positive, *–ve* negative

[a] Qualitative data for biosimilarity as stated by the corresponding study authors

[b] 90% confidence intervals shown in parentheses

[c] 95% confidence intervals shown in parentheses

[d] Quality assessment not conducted due to the absence of validated tools specific for the study type, at the time of analysis

compared with infliximab in patients with RA (n = 606) [66, 121, 67, 72, 69, 102, 71]. An observational cross-sectional study, which included RA patients from Romania who were treated with biologic agents, assessed efficacy and safety data after 2 years of treatment with infliximab, CT-P13, etanercept, adalimumab, or rituximab [122].

3.3.4 Rituximab Biosimilars in RA

Studies of rituximab biosimilars are presented in Table 4.

CT-P10 (*Celltrion*) CT-P10 was evaluated in a pharmacokinetic/safety trial in patients with active RA and an inadequate response or intolerance to prior anti-TNF agents (n = 154) [102, 103]. The published findings of the study concluded equivalence in terms of efficacy, safety, and pharmacokinetic/pharmacodynamic outcomes compared with rituximab. There was some indication, however, that antidrug antibodies-positive patients in the rituximab group may have been at greater risk of serious AEs than those in the CT-P10 group.

PF-05280586 (*Pfizer*) Data from a pharmacokinetic/safety study on PF-05280586 in patients with active RA on methotrexate and with prior inadequate response to anti-TNF therapies (n = 220) also inferred equivalence of efficacy, safety, and pharmacokinetic/pharmacodynamic performance compared with rituximab.

3.4 Clinical Evidence in Ankylosing Spondylitis (AS)

3.4.1 Infliximab Biosimilars in AS

Studies of infliximab biosimilars are presented in Table 3.

CT-P13 (*Remsima®/Inflectra®; Celltrion*) CT-P13 has been evaluated in a pharmacokinetic/safety study (PLANETAS) study [63, 59, 58, 61, 123, 62]. The pharmacokinetic profiles of CT-P13 and infliximab were equivalent in patients with active AS (n = 250). CT-P13 was well-tolerated, with an efficacy and safety profile comparable with that of infliximab over the duration of the study.

3.5 Clinical Evidence in Ulcerative Colitis (UC) and Crohn's Disease (CD)

3.5.1 Infliximab Biosimilars in UC/CD

Studies of infliximab biosimilars are presented in Table 3.

CT-P13 (*Remsima®/Inflectra®; Celltrion*) Several observational (post-marketing) studies have been reported for CT-P13 that investigated the efficacy and impact of switching from the biologic originator to CT-P13 in patients with UC or CD (n = 336) [80, 81, 76, 77, 78, 74, 79, 75, 82]. In one study of 110 patients with CD or UC, the clinical response to the treatment at 8 weeks was 87% in patients who had not been previously treated with an anti-TNF agent and 67% in those who had switched from another anti-TNF [76]. Another prospective study in 90 patients with CD or UC found decreases in scores of disease activity after 6 weeks of treatment with the biosimilar [81]. One of these observational cohort studies explored the use of CT-P13 in pediatric patients with CD (n = 32) [82]. The results of these studies should be interpreted with a degree of caution based on the underlying limitations of the study designs.

3.6 Health Economics Evidence: Infliximab Biosimilars

Studies of infliximab biosimilars are presented in Table 3.

CT-P13 (*Remsima®/Inflectra®; Celltrion*) Following the launch of CT-P13 in several major European countries, health economic studies have emerged evaluating the budget impact and cost effectiveness (from a payer or patient perspective) of introducing the biosimilar into the chronic inflammatory disease market [84, 85, 86, 87, 88, 83, 89]. Published studies to date have explored the potential cost savings realized from substituting the originator with CT-P13 for the treatment of CD, UC, RA, AS, and PsA across multiple European countries. The totality of evidence from these studies points towards substantial cost savings, with the degree of budget impact dependent on the rate of interchangeability, patient number, and eligibility of treatment with the biosimilar (i.e., whether patients are treatment-naïve or treatment-experienced), along with the acquisition cost of the biosimilar. These authors have attempted to quantitatively demonstrate that the introduction of a biosimilar may provide additional budget to treat more patients (including, for example, those with earlier-stage disease) on an annual basis, which could potentially alleviate both the short- and longer-term cost burden among healthcare payers and providers.

3.7 Preclinical and Clinical Data on Intended Copies

3.7.1 Intended Copies of Etanercept

Studies of etanercept intended copies are presented in Table 5.

Infinitam® (*Probiomed*) One preliminary safety/efficacy RCT for Infinitam® in patients with moderate to severe RA (n = 58) was identified [124]. The results suggested similar efficacy, safety, and pharmacokinetic/pharmacodynamic outcomes between Infinitam® and etanercept at 24 weeks. An observational study investigating Infinitam®, Yisaipu® (etanercept intended copy), or Kikuzubam® (rituximab intended copy) in patients with rheumatic diseases reported that a large proportion of patients experienced AEs, with more than one-third of AEs reportedly occurring on the same day as first treatment [125].

Yisaipu® (*Shanghai CP Guojian Pharmaceutical Co.*) An observational retrospective cohort study was performed

Table 5 Outcomes for etanercept intended copies

Study type [patients (*n*)]	Reference	Outcome	Intended copy[a]	Etanercept[a]	Statistical comparison	Quality assessment rating
Infinitam®						
RCT, preliminary safety/efficacy study [moderate and severe RA (58)]	CA [124]	Efficacy, week 24:				Modified D&B: excellent; score: 9/12
		DAS28 (score)	2.8	2.4		
		Safety	Similar	Similar		
		PK/PD	NR	NR	$p = 0.355$	
Observational [rheumatic diseases (219)]	CA [125]	Safety:				Modified D&B: fair; score: 4/12
		All AEs (Infinitam®/ Yisaipu®)	$n = 10$ of 14	NA		
		All AEs (Kikuzubam®)	$n = 101$ of 205	NA		
Yisaipu®						
Observational [RA (802)]	CA [48]	NA				Modified D&B: good; score: 5/12
Observational [RA (158)]	CA [126]	Efficacy:		[Study did not compare etanercept originator]		Modified D&B: good; score: 7/12
		DAS28 low score, BL (%)	11.2	ADA: 13.1; IFX: 8.5	NS	
		DAS28 low score, week 104 (%)	16.1	ADA: 11.4; IFX: 17.1	NS	
		DAS28 moderate score, BL (%)	51.6	ADA: 45.9; IFX: 34.2	NS	
		DAS28 moderate score, week 104 (%)	9.6	ADA: 11.4; IFX: 14.2	NS	
		DAS28 high score, BL (%)	9.6	ADA: 8.2; IFX: 28.5	NS	
		DAS28 high score, week 104 (%)	6.4	ADA: 4.9; IFX: 0	NS	
Health economics [RA (China)]	[127]	Costs:	[Strategy 9][b]	[vs. MTX, Strategy 1]		Drummond's checklist: good; score: 29/36
		Lifetime costs (US$)	18,574	12,735.4		
		LYs gained (years)	23.50	23.5		
		QALYs gained (years)	9.76	9.1		
		ICERs	8680			

ADA adalimumab, *AE* adverse event, *BL* baseline, *CA* conference abstract, *D&B* Downs and Black (tool), *DAS28* Disease Activity Score in 28 joints, *ICER* incremental cost-effectiveness ratio, *IFX* infliximab, *LY* life-year, *MTX* methotrexate, *NA* not available, *NR* not reported, *NS* non-significant, *PD* pharmacodynamic, *PK* pharmacokinetic, *QALY* quality-adjusted life-year, *RA* rheumatoid arthritis, *RCT* randomized controlled trial

[a] Qualitative data for biosimilarity as stated by the corresponding study authors

[b] Nine strategies evaluated. Most cost-effective strategy is shown

in 158 patients with active RA treated with Yisaipu® (etanercept intended copy) ($n = 62$), adalimumab ($n = 61$), or infliximab ($n = 35$) [126]. Similar decreases in Disease Activity Score in 28 joints (DAS28) were seen at 24 months. No statistically significant differences were seen in the number of patients achieving remission. The authors noted that fewer AEs were present in the Yisaipu® treatment group than in the adalimumab- and infliximab-treated patients. Only one health economics study was identified for etanercept biosimilars/intended copies [127]. This study assessed the cost effectiveness of reduced doses or discontinuation of Yisaipu® in patients with moderately active RA. Strategies starting with Yisaipu® 50 mg/week for 9 months followed by Yisaipu® 25 or 50 mg/week maintenance showed the greatest number of quality-adjusted life-years (QALYs) gained. The incremental cost-

Table 6 Outcomes for rituximab intended copies

Study type [patients (*n*)]	Reference	Outcome	Intended copy[a]	Rituximab[a]	Statistical comparison	Quality assessment rating
Reditux™						
Observational/retrospective [RA and failed DMARD therapy (39)]	CA [128]; CA [129]	Efficacy, week 24:				Modified D&B: good; score: 5/12
		DAS-CRP	NR	NA	$p < 0.0001$	
		DAS-ESR	NR	NA	$p < 0.0001$	
		ACR20 (%)	97	NA		
		Safety, week 24:				
		All SAEs (*n*)	0			
Observational/ prospective [diffuse large B cell lymphoma, RA, scleroderma, dermatomyositis (133)]	CA [130]	Safety:				Modified D&B: fair; score: 4/12
		All AEs (%)	14.3	NA		
		Chills (%)	20	NA		
		Headache (%)	16.7	NA		
		Fever (%)	13.0	NA		
		Urticaria (%)	10.0	NA		
		All treatment-related AEs (%)	73.0	NA		
		Mild AEs (%)	90.0	NA		
		Moderate AEs (%)	6.7	NA		
		Severe AEs (%)	3.3	NA		
		Mortality (%)	0	NA		
Observational/prospective [biologic-naïve RA (21)]	[131]	Efficacy:				D&B: good; score: 11/26
		DAS28-ESR score	2.54, $p <$ 0.0001 vs. BL	NA		
		DAS28 LDA (year 1) (%)	33	NA		
		DAS28 LDA (year 3) (%)	43	NA		
		DAS28 remission (year 1) (%)	57	NA		
		DAS28 remission (year 3) (%)	47	NA		
		Safety:				
		Serious AEs (*n*)	0	NA		
		Infusion reactions (%)	10	NA		
Nonclinical (cell-based)	[132]	Functional assessment (in vitro):				Not evaluated[b]
		ADCC (%)	80–125	80–125	NS	
		CDC (3 batches) (%)	81; 111; 108	NR		
Nonclinical (cell-based)	CA [133]	Safety (rat and rabbit cell-lines):				Not evaluated[b]
		ADAb	Comparable	Comparable (USA/EU)		
Analytical/nonclinical (cell-based)	[132]	Composition:				Not evaluated[b]
		Peptide mapping	Same	Same		
		Glycan quantification	Same	Same		
		Mass spectrometry, intact mass	Heterogeneous	Heterogeneous		
		DSC analysis	Similar	Similar		
		Cation exchange, acid (%)	7.0	22.1		
		Cation exchange, main (%)	20.6	68.5		
		Cation exchange, basic (%)	72.4	9.4		
		Hydrophobic interaction (main isoform) (%)	<24.1	<2.0		
		Multi-angle laser light scattering	Similar	Similar		

Table 6 continued

Study type [patients (*n*)]	Reference	Outcome	Intended copy[a]	Rituximab[a]	Statistical comparison	Quality assessment rating
Analytical	CA [134]	Composition:				Not evaluated[b]
		IdeS digestion	Similar	Similar		
		Peptide mapping (trypsin and pepsin)	Similar	Similar		
		Isotope	Similar	Similar		
Analytical	CA [135]	Composition:				Not evaluated[b]
		SDS-PAGE	Similar	Similar		
		iCE	NR	NR	Significant	
		CE	NR	NR	Significant	
		CEX-HPLC	NR	NR	Significant	
Kikuzubam®						
Nonclinical (cell-based)	[132]	Functional assessment (in vitro):				Not evaluated[b]
		ADCC (%)	80–125	80–125	NS	
		CDC (3 batches) (%)	98; 102; 112	NR/81; 111; 108	NS	
Analytical/nonclinical (cell-based)	[132]	Composition:				Not evaluated[b]
		Peptide mapping	Same	Same		
		Glycan quantification	Same	Same		
		Mass spectrometry, intact mass	Heterogeneous	Heterogeneous		
		DSC analysis	Similar	Similar		
		Cation exchange, acid (%)	37.8	22.1/7.0		
		Cation exchange, main (%)	56.6	68.5/20.6		
		Cation exchange, basic (%)	5.6	9.4/72.4		
		Hydrophobic interaction (main isoform) (%)	<3.0	<2.0/<24.1		
		Multi-angle laser light scattering	Similar	Similar		

ACR20 American College of Rheumatology 20% improvement criteria, *ADAb* anti-drug antibodies, *ADCC* antibody-dependent cell-mediated cytotoxicity, *AE* adverse event, *BL* baseline, *CA* conference abstract, *CDC* complement-dependent cytotoxicity, *CE* capillary electrophoresis, *CEX-HPLC* cation-exchange chromatography high-performance liquid chromatography, *CRP* C-reactive protein, *D&B* Downs and Black (tool), *DAS* Disease Activity Score, *DAS28* Disease Activity Score in 28 joints, *DMARD* disease-modifying antirheumatic drug, *DSC* differential scanning calorimetry, *ESR* erythrocyte sedimentation rate, *iCE* imaged capillary electrophoresis isoelectric focusing, *IdeS* Immunoglobulin-degrading enzyme from Streptococcus pyogenes, *LDA* low disease activity, *NA* not available, *NR* not reported, *PPS* per protocol set, *RA* rheumatoid arthritis, *SDS-PAGE* sodium dodecyl sulfate polyacrylamide gel electrophoresis

[a] Qualitative data for biosimilarity as stated by the corresponding study authors

[b] Quality assessment not conducted due to the absence of validated tools specific for the study type, at the time of analysis

effectiveness ratio (ICER) was most sensitive to the acquisition cost of Yisaipu®.

3.7.2 Intended Copies of Rituximab

Studies of rituximab intended copies are presented in Table 6.

Kikuzubam® (*Probiomed*) The biochemical characterization and in vitro biological activity of Kikuzubam® (and Reditux™) versus rituximab have been assessed in a preclinical study [132]. Study findings provided evidence of similar potency to rituximab. As previously mentioned, an observational study investigating Kikuzubam® (or Infinitam®/Yisaipu®) in patients with rheumatic diseases reported that a large proportion of patients experienced AEs [125].

Reditux™ (*Dr Reddy's Laboratories*) Reditux™ has been evaluated in two independent nonclinical studies, wherein the drug was reported to exhibit similar biological effects in vitro to rituximab (in cell-based assays) [132, 133]. Two nonclinical studies examined structural attributes of Reditux™ and reported heterogeneity between it and rituximab with respect to theoretical mass and secondary/tertiary structure [132, 135, 134]. Three observational trials were identified that assessed clinical outcomes for Reditux™ [130, 128, 129, 131]. Although none of these studies provided a comparator, there is some evidence supporting the efficacy and safety of Reditux™

in the treatment of chronic inflammatory disease and, in particular, for treatment of RA.

3.8 Quality Assessment of the Studies

The quality of all included randomized and non-randomized studies were assessed using validated instruments.

3.8.1 National Institute for Health and Care Excellence (NICE) Single Technology Appraisal (STA) Manufacturer's Template

Seven RCTs were assessed using the NICE STA manufacturer's template [42, 44, 49, 33, 101, 69, 59] (Tables 1, 2, 3, ESM Fig. S3a); all were considered excellent quality overall. The RCTs provided information to assess the randomization process, subject withdrawals, outcome selection, reporting bias, and statistical analyses, which were adequately reported in all studies. The bias of allocation concealment process was unclear in three studies (Jani et al. [33], Yi et al. [44], and Yoo et al. [69]). The blinding process was unclear in one study (Yoo et al. [69]) and assessed as high risk for unblinding in one study (Gu et al. [42]).

3.8.2 Jadad Scoring Tool

Seven RCTs were evaluated using the Jadad scoring tool (Tables 1, 2, 3, ESM Fig. S3b). Choe et al. [101] and Emery et al. [49] scored high for reporting on the five scored regions of randomization, blinding, methodology, withdrawals, and dropouts (total score 5 points). Gu et al. [42] reported an open-label study and, therefore, scored the maximum possible 3 points [42]; Jani et al. [33] and Park et al. [59] both failed to report on the method of blinding, and therefore scored 4 points each; Yi et al. [44] and Yoo et al. [69] failed to report on both the randomization and blinding methods, thereby scoring 3 points each.

3.8.3 Downs and Black/Modified Downs and Black Instrument

Four observational studies with full-study reporting were assessed using the Downs and Black scoring tool (Tables 3 and 6, ESM Fig. S4) [80, 76, 78, 131]; all were considered fair quality. The restrictive word count in abstracts from conference proceedings generally provide limited information on study methodologies and outcomes. For this reason, the Downs and Black instrument was adapted to assess the quality of the 22 identified abstracts for additional original studies (Tables 1, 2, 3, 4, 5, 6, ESM Fig. S5) [26, 41, 47, 48, 98, 63, 46, 119, 122, 103, 81, 74, 79, 82, 124, 125, 126, 130, 128, 104, 50, 34]. The average score for the abstract publications was 7.8 out of a possible 12 points. The total score was fair quality (3–4) for four studies [81, 74, 125, 130], good quality (5–8) for seven studies [48, 122, 79, 82, 126, 128, 104], and excellent quality (9–12) for 11 studies [26, 41, 47, 98, 63, 45, 119, 103, 124, 50, 34]. The majority of the studies published as conference abstracts were of good or excellent quality (81.8%).

3.8.4 Drummond's Checklist

Three pharmacoeconomic studies were assessed using Drummond's checklist for assessing economic evaluations (Tables 3 and 5, ESM Fig. S6) [84, 87, 127]; the studies were of good quality. Of a maximum 36 points, Brodszky et al. [84] scored 23 points, Jha et al. [87] scored 23 points, and Wu et al. [127] scored 29 points.

3.8.5 SYRCLE's Risk of Bias Tool

Three animal studies were assessed using SYRCLE's risk of bias tool (Tables 2, 4, ESM Fig. S7) [52, 115, 108]. The three studies were of moderate quality.

3.9 Weight and Breadth of Evidence for Biosimilarity

The final determination of biosimilarity by regulatory authorities (e.g., the FDA [136]) is based on the 'totality of evidence' approach and the degree of residual uncertainty concerning biosimilarity between the proposed biosimilar and the innovator drug. The authorities base their decision on data from the molecular and functional characterization, any nonclinical data obtained, and the safety, pharmacokinetic, immunogenicity, and efficacy clinical trial data provided by the manufacturer. However, given that regulatory submissions are not publically available and the full dataset therein cannot be systematically reviewed, the authors have instead based all analysis in this literature review on information from the peer-reviewed literature.

All comparative publications uncovered in this literature review were carefully assessed to analyze the reported extent of similarity between the originator product and the biosimilar. Biosimilarity (based on combined evidence from all related published studies) for each type of study was graded as comparable, highly similar, similar, or non-similar, which was directly inferred from investigator conclusions (Table 7). The available comparative data from full-text publications of randomized clinical trials are currently limited. However, based on original investigator conclusions from the literature at the time the search was undertaken, the current data from clinical, nonclinical, and observational/post-marketing studies for proposed

Table 7 Summary of evidence for the degree of similarity between biosimilars/intended copies and originators by study type

Biologic originator	Biosimilar/intended copy [name(s); (company)]	Analytical studies	Nonclinical studies	PK/safety studies or preliminary safety/efficacy studies	Comparative safety/efficacy studies	Post-marketing/ observational studies
Adalimumab	ABP 501 (Amgen, USA)	✔ or ✔✔	✔✔	✔✔	NA	NA
	GP2017 (Sandoz, Switzerland)	NA	✔✔	NA	NA	NA
	PF-06410293 (Pfizer, USA)	✔✔	✔✔	NA	NA	NA
	SB5 (Samsung Bioepis, South Korea)	NA	NA	✔✔	NA	NA
	ZRC-3197 (Exemptia™; Cadila Healthcare, India)	NA	NA	NA	✔✔	NA
Etanercept	AVG01 (Avent™; Avesthagen, India)	✔✔	✔✔	NA	NA	NA
	ENIA11 (TuNEX®; Mycenax Biotech/TSH Biopharm Corp., Taiwan)	NA	NA	✔✔	NA	NA
	GP2015 (Sandoz, Switzerland)	NA	✔✔	NA	NA	NA
	HD203 (Davictrel™; Hanwha Chemical, South Korea/Merck, USA)	NA	NA	✔✔	✔✔	NA
	LBEC0101 (LG Life Sciences, South Korea)	NA	NA	✔✔	NA	NA
	SB4 (Benepali®; Samsung Bioepis, South Korea)	NA	NA	✔✔	✔✔	NA
Infliximab	BOW015 (Infimab®; Ranbaxy Laboratories, India/Epirus Biopharmaceuticals, USA)	NA	NA	✔✔	✔✔	NA
	CT-P13 (Remsima®; Inflectra®; Celltrion, South Korea/Hospira, USA)	✔✔ or ✔✔✔	✔✔	✔✔	✔✔	a
	PF-06438179 (Pfizer, USA)	✔✔ or ✔✔✔	✔✔	✔✔	NA	NA
	SB2 (Flixabi®; Samsung Bioepis, South Korea)	NA	NA	✔✔	✔✔	NA
Rituximab	CT-P10 (Celltrion, South Korea/ Hospira, USA)	NA	NA	✔✔	NA	NA
	GP2013 (Sandoz, Switzerland)	✔✔✔	✔	NA	NA	NA
	PF-05280586 (Pfizer, USA)	✔✔ or ✔✔✔	✔✔	✔✔	NA	NA
	RTXM83 (mAbxience, Switzerland)	✔	✔	NA	NA	NA
Intended copies	Infinitam® (Probiomed, Mexico)	NA	NA	✔✔	NA	a
	Yisaipu® (Etanar®; Shanghai CP Guojian Pharmaceutical, China)	NA	NA	NA	NA	a
	Reditux™ (Dr Reddy's Laboratories, India)	✖ or ✔✔	✔	NA	NA	a
	Kikuzubam® (Probiomed, Mexico)	✖ or ✔✔✔	✔✔	NA	NA	a

NA not applicable, evidence from published studies not available, *PK* pharmacokinetic, *SAE* serious adverse events, ✔✔✔ identical (based on combined evidence from all related published studies), ✔✔ highly similar (based on combined evidence from all related published studies), ✔ similar (based on combined evidence from all related published studies), ✖ non-similar (based on combined evidence from all related published studies)

[a] Not possible to draw conclusions from published studies, due to the lack of direct comparative data with the originator

biosimilars indicate moderate to high levels of biosimilarity to the comparator products (Table 7).

In order to summarize findings, the total number of studied variables and total reported patient numbers were extracted from the identified analytical/nonclinical and clinical studies, respectively. These parameters were then mapped (Fig. 2a, b) against the 'degree of similarity' (as observed by the study investigator) in an effort to depict the

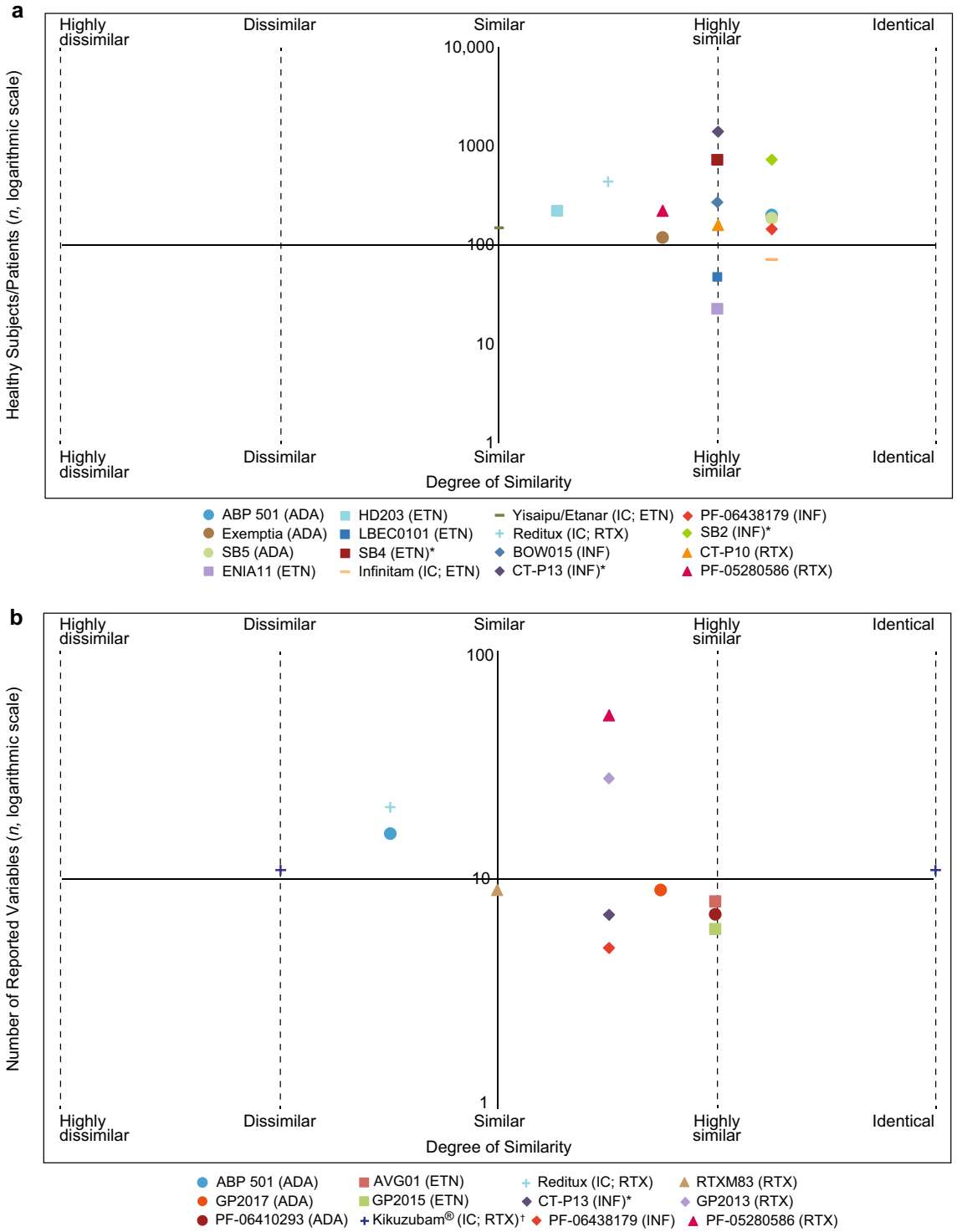

Fig. 2 Biosimilarity and **a** total treated patients for named biosimilars and intended copies in published clinical trials and **b** breadth of data for named biosimilars and intended copies in published analytical and nonclinical studies. 'Degree of similarity' for biosimilars and intended copies is inferred from the totality of evidence provided from all available published studies (up to 3 September 2015), and is based on the original conclusions made by the study investigators. The scale of reference used by each investigator was not accounted for, as it was not uniformly reported. * refers to agents that have already met the European Medicines Agency and/or US Food and Drug Administration requirements and have been approved as biosimilars. † based on different author interpretations of study data, intended copy Kikuzubam® purportedly exhibits some highly dissimilar and some identical physicochemical characteristics compared with the originator. *ADA* adalimumab, *ETN* etanercept, *IC* intended copy, *INF* infliximab, *RTX* rituximab

overall quantity of available evidence for each agent. Most biosimilars have published clinical data on fewer than 100 human subjects, whereas studies of CT-P13 have involved more than 1000 subjects (Fig. 2a). Studies of 13 biosimilars identified included 4522 patients or healthy subjects. Approved biosimilars CT-P13 (infliximab biosimilar Remsima®/Inflectra®), SB2 (infliximab biosimilar, Flixabi®), and SB4 (etanercept biosimilar, Benepali®) reported the largest combined study populations from pharmacokinetic/safety, comparative efficacy/safety, and observational studies (1405, 743, and 734 patients, respectively). Four intended copies were identified in studies including a total of 1430 patients.

When considering the breadth of data available for preclinical studies (based on the number of variables studied in structural, functional, and nonclinical studies) for named biosimilars, there is an inconsistent amount of reported information available across studies (Fig. 2b). PF-05280586 (rituximab) and GP2013 (rituximab) were found to have a larger number of investigated variables for analytical and nonclinical biosimilarity. Of note, Flores-Ortiz et al. [132] reported that the mass spectrometry and cation exchange findings were heterogeneous for the intended copy Kikuzubam® in comparison to its rituximab originator, while other variables (differential scanning calorimetry analysis, peptide mapping, glycan quantification, etc.) were reported to be the same. Thus, the positioning on the *x* axis (Fig. 2b) was determined to be both dissimilar and identical across selected variables.

Although the original study investigators concluded that the majority of agents exhibited biosimilarity to their originator, it is worth noting that comparative data were not provided for all attributes studied.

3.10 Non-Empirical Publications

A summary of information from the non-empirical publications is shown in ESM Table S5. Within the 34 identified empirical publications, 16 were therapy area overviews (in RA, AS, UC/CD, and dermatology) and 11 articles discussed regulatory policy. Other topics included biosimilar development, national guidelines, safety/pharmacovigilance, and substitution/interchangeability. One theme that was discussed in many of the articles (at least 17 of the 34 publications) was the extrapolation of clinical data from clinical trials of biosimilars between different indications. In many of the 17 publications, the extrapolation of clinical trial data of the biosimilar infliximab CT-P13 (Remsima®/Inflectra®) from RA patients to patients with UC/CD was discussed in detail due to the fact that CT-P13 was originally approved by the EMA, but not the Canadian authorities, for the treatment of UC/CD. Whilst the EMA considered that "high similarity" in preclinical studies together with clinical data from two trials in AS and RA warrant the "extrapolation" for CD and UC, Canadian authorities did not initially accept extrapolation, based on differences in glycosylation (fucosylation) in irritable bowel syndrome. However, CT-P13 has now been approved by Health Canada for additional indications, including CD and UC.

3.11 Additional Planned and Ongoing Trials of Adalimumab, Etanercept, Infliximab, and Rituximab Biosimilars

The ClinicalTrials.gov registry was consulted to identify planned or ongoing trials not yet reported in the published literature. Trials were listed for biosimilars for adalimumab in a total of 14 studies (ESM Table S6). The clinical trials search also identified biosimilars of adalimumab not yet appearing in the published literature. Biosimilars produced by Coherus Biosciences, Inc. (USA), LG Life Sciences (South Korea), Boehringer Ingelheim (Germany), and Biocad (Russia) were identified for adalimumab (CHS-1420, LBAL, BI 695501, and BCD-057, respectively).

A total of nine studies were listed in the ClinicalTrials.gov database for named biosimilars of etanercept (ESM Table S6). Trials were also identified for a newly identified biosimilar, CHS-0214 (Coherus Biosciences, Inc.; two studies co-sponsored with Daiichi Sankyo Co. Ltd. and one with Baxalta US Inc.).

A total of three clinical trials were retrieved from the search for named biosimilars of infliximab in ClinicalTrials.gov (ESM Table S6). An additional biosimilar, BCD-055 (Biocad), was identified from this search, which was not identified in the published literature search.

Seven trials were identified in the ClinicalTrials.gov search for named biosimilars of rituximab for the treatment of RA only (ESM Table S6). One biosimilar (BI 695500) that had not been reported in the published literature was identified from this search.

Although the majority of patient studies listed for development candidates of adalimumab, etanercept, and infliximab were in RA (for ABP 501 [adalimumab], BI 695501 [adalimumab], PF-06410293 [adalimumab], SB5 [adalimumab], CHS-0214 [etanercept], ENIA11 [etanercept], LCEC0101 [etanercept], and PF-06438179 [infliximab]), several complete or ongoing studies were also identified for psoriasis or plaque psoriasis for ABP 501, CHS-1420 (adalimumab), GP2017 (adalimumab), CHS-0214, and GP2015 (etanercept). In addition, for infliximab biosimilars BCD-055 and CT-P13, studies were recruiting in AS and CD, respectively, at the time of analysis.

3.12 Key Journals and Congresses

A total of 98 journals publishing relevant material on biosimilars for chronic inflammatory disease were identified during this review (ESM Table S7). *Annals of the Rheumatic Diseases* published the greatest number of articles on this topic during the search period (ten articles since 2013). Prior to 2011, no journal articles relevant to the topic of MAb or fusion protein biosimilars were published that were relevant to chronic inflammatory diseases and there has been a steady rise since then (two, six, ten, and 14 articles in 2011, 2012, 2013, and 2014, respectively). In the last complete year of the analysis (2014), the *European Journal of Health Economics* published the greatest number of articles related to biosimilars in chronic inflammatory disease (four articles), followed by *Annals of the Rheumatic Diseases* (three articles), and the *Journal of Crohn's and Colitis* (three articles).

A total of 28 congresses were identified that presented abstracts of named biosimilars relevant to chronic inflammatory diseases between January 2010 and August 2015 (ESM Table S8). No congress abstracts were identified in the years preceding 2010. A total of 54 abstracts were published in the year 2014 for these congresses. Of these, the largest number of abstracts were published for dissemination at European League Against Rheumatism (EULAR) (17 abstracts), ACR (13 abstracts), and International Society For Pharmacoeconomics and Outcomes Research (ISPOR) (ten abstracts) congress meetings. The sharp increase in the number of abstract publications from 2013 to 2014 at these congresses (30 to 54 abstracts) highlights the high level of interest in biosimilars for the treatment of chronic inflammatory diseases among clinical, regulatory, and payer stakeholders. The search also captured abstracts published between January and August 2015. A total of 22 abstracts were presented at EULAR and 11 at European Crohn's and Colitis Organisation (ECCO) congress meetings.

4 Discussion

Guidelines require that biosimilars should exhibit close similarity to the originator with respect to structure (primary and higher-order) and many other molecular characteristics, display similar levels of biological potency in vitro or in vivo, and should meet the required thresholds for bioequivalence in safety and pharmacokinetic studies before entering a comparative trial(s) in patients to satisfy efficacy requirements [2]. Robust evidence of similarity provided from analytical, pharmacokinetic, and nonclinical studies is thus equally as important as clinical evidence to demonstrate the safety and efficacy of a biosimilar, and to meet regulatory standards and requirements set by the EMA and FDA for approval [137, 138]. While these data are generated as evidence for approval, ensuring the data are made available in the public domain is also important for promoting education and awareness and encouraging acceptance of biosimilars among physicians and other healthcare professionals.

At the time of data analysis, the totality of evidence for candidate biosimilars with comparative studies in chronic inflammatory disease suggested that the majority of biosimilars demonstrated a moderate to high degree of similarity to their originator. In contrast, there was limited information in the public domain regarding the similarity of intended copies with their originator products.

This SLR revealed several biosimilar molecules that met the required standards. CT-P13 (Remsima®/Inflectra®) is the only commercially available infliximab biosimilar to date that has been launched across 12 European countries and Canada, and approved in the USA. The combined evidence gathered from analytical, nonclinical, and clinical studies (identified in this review of publications to 3 September 2015) supported the premise that CT-P13 is safe and effective [63, 91, 90, 66, 121, 67, 72, 69, 71, 64, 139, 92, 73, 70, 68]. A comparative safety/efficacy study is underway in CD and CT-P13 is also being evaluated in observational studies for multiple other chronic inflammatory conditions (including ankylosing spondyloarthritis, PsA, UC, CD, and chronic psoriasis) [63, 59, 58, 61, 123, 62, 80, 81, 76, 77, 78, 74, 79, 75, 82, 64, 68, 65, 60]. PF-06438179 is another infliximab biosimilar that has exhibited moderate to high structural and functional similarity during analytical and preclinical investigations [94, 95, 93, 98, 99, 97, 96]. At the time of this review, a comparative safety/efficacy trial comparing the efficacy and immunogenicity of PF-06538179 versus infliximab was recruiting patients with RA. Adalimumab biosimilars GP2017 and PF-06410293 both showed similarity to adalimumab in in vitro assays and preclinical studies [37, 36, 35, 38, 39]. At the time of analysis, progression of PF-06410293 into three pharmacokinetic/safety studies and one comparative safety/efficacy trial had been listed on ClinicalTrials.gov and comparative safety/efficacy trials for GP2017 were underway in the treatment of plaque psoriasis. For GP2015, an etanercept biosimilar, published nonclinical (in vitro and in vivo) data revealed close functional similarity compared with its originator [53]. Finally, rituximab biosimilars GP2013 and PF-05280586 both showed adequate degrees of similarity to rituximab during preclinical phases of development [117, 115, 116]. Some pharmacokinetic/safety trials and preliminary safety/efficacy trials for RA have also been reported [114, 109, 111, 113, 108, 112, 104, 106, 107, 105].

For the prescribing physician and key decision-makers, it is important to understand whether the published data on biosimilarity are of sufficient quality to influence prescribing decisions. Therefore, as well as investigating the weight of available data, this review also used validated instruments, such as the NICE STA assessment, Jadad scoring tool, Downs and Black checklist, Drummond scoring system for economic studies, and SYRCLE's risk of bias tool for animal studies to assess the quality of studies. The results were reassuring; of the seven RCTs assessed, all were considered to be of excellent quality by the NICE STA assessment, and all scored between 3 and 5 points using the Jadad scoring tool.

Taken together, the weight and breadth of evidence of comparative studies suggest that biosimilars will soon become a mainstay of treatment in many different chronic inflammatory diseases. The non-empirical publication analysis in this report suggests that the reduced cost of biosimilars and the increased number of available therapeutic options may make access to biologic therapy available to a broader subset of patients. This is particularly important for chronic diseases such as RA, AS, UC, and CD where patients need treatment with costly biologic therapy for long periods of time [6]. Indeed, it has often been shown in these diseases that early aggressive therapy has long-term benefits both for the prevention of joint deterioration (in the case of RA) [140] and quality of life [141, 142]. The availability of relatively low-cost biosimilars may eventually alter the treatment paradigm so that patients are treated for less time with conventional disease-modifying antirheumatic drugs alone, and biologic therapy is initiated earlier in the disease course [143].

Although the number and quality of published studies providing evidence of structural and functional similarity at the preclinical phase may not be sufficient to predict behaviors or performance in humans, these studies form the basis for demonstration of similarity and represent a crucial step in the development program. At the time of analysis, BOW015 (Infimab®; infliximab; Ranbaxy Laboratories, India/Epirus Biopharmaceuticals), CT-P10 (infliximab; Celltrion), SB2 (Flixabi®; infliximab; Samsung Bioepis); SB5 (adalimumab, Samsung Bioepis), and ZRC-3197 (Exemptia™; adalimumab; Cadila Healthcare) had all entered into clinical stages of development (comparative safety/efficacy in RA) without published data or evidence to suggest that they had similar structural or functional resemblance to their originators. This was also true for the majority of etanercept biosimilars (HD203 [Davictrel™; Hanwha Chemical], LBEC0101 [LG Life Sciences], ENIA11 [TuNEX®; Biotech/TSH Biopharm Corp., Taiwan], and SB4 [Benepali®; Samsung Bioepis]), which had all reported comparative safety/efficacy trials in RA with a lack of published analytical or nonclinical data. Although publication of similarity information is not a regulatory requirement for the approval of biosimilars, a lack of information in the public domain will impact on education and awareness and therefore the ability of clinicians to make informed prescribing decisions.

This review also provides information on marketed intended copies (copies of originator biologics that have not undergone rigorous comparative evaluations). Several intended copies are commercially available with very little evidence of biosimilarity. For example, intended copy Kikuzubam® (Probiomed) gained approval in Mexico without published comparative safety/efficacy trials and prior to COFEPRIS releasing official regulatory guidance on 'biocomparables' [17]. In 2012, Kikuzubam® was withdrawn by the regulatory authority due to documented anaphylactic reactions and a lack of clinical data [144]. Intended copy Reditux™ (Dr Reddy's Laboratories) was also commercialized in Latin American countries, India, and Iran without published data to indicate structural or functional similarity or clinical effectiveness as compared with rituximab [145]. Although several observational studies have been reported for Reditux™, no studies for chronic inflammatory conditions included rituximab as a comparator at the time of this review [132, 133, 135, 134, 130, 128, 129, 131]. Intended copy Yisaipu® (etanercept; Shanghai CP Guojian Pharmaceutical Co.) is a fusion protein that is already marketed in China. However, as is evident from this review, no published data are available for comparison with etanercept to determine its biosimilarity. In Colombia, Yisaipu® is marketed under the brand name Etanar®. At the time of this review, only one limited clinical trial (not an equivalence study comparing Yisaipu® with etanercept) had been reported [48, 126, 127]. Finally, at the time that this analysis was completed, there was only one study that assessed the efficacy and safety of intended copy Infinitam®, which is currently marketed in Mexico [124]. Suffice to say, significant data gaps remain for intended copies, reinforcing the need to maintain a clear differentiation between these molecules and true biosimilars.

Non-empirical data analysis suggests that some countries are only just beginning to establish formal regulatory guidelines for the approval of biosimilars to cover requirements for preclinical, clinical, or other analyses that should be used to demonstrate the safety, quality, and effectiveness of a biosimilar. This includes studies required for immunogenicity and AEs, as well as demonstration of similar modes of action or pharmacodynamic properties to that of the originator. Other countries have yet to implement any guidelines. The extrapolation of biosimilarity information across indications was also an issue that was mentioned frequently in the non-empirical publications identified in this report [144, 146, 147,

148, 149, 150, 151, 152, 153, 154, 155, 156, 157, 158, 159, 160]. A common theme of discussion was the fact that RA (where almost all molecules were first investigated) may not be a sensitive clinical model to detect potential differences between biosimilars and originator products that may be observed in UC/CD. It was suggested that the immunogenicity potential of biosimilars is fairly low in RA and even further suppressed by the concomitant use of methotrexate, and that regulatory agencies should grant extrapolated indications to biosimilars based on appropriate scientific justification only after biosimilarity is confirmed [152, 154].

This systematic review aims to provide a comprehensive summary of literature relevant to mAb and fusion protein biosimilars for the treatment of chronic inflammatory diseases. However, there are some inherent weaknesses and limitations to this method of data analysis. As with any systematic review, the search retrieved records citing a particular term (either a mAb or fusion protein biosimilar). Due to a lack of consensus on the naming of biosimilars and intended copies, no consistent nomenclature could be relied upon to identify and correctly classify every possible molecule of interest. Molecules may, for example, have been incorrectly termed biosimilars in the literature without rigorous data to support biosimilarity to the originator product. The authors' determination of biosimilarity for each molecule was limited to using only the specific terms (e.g., "similar" or "highly similar") reported by the investigators. Consequently, the analysis is based purely on the scale of reference used by the original investigators.

In addition, only data from studies disclosing names of biosimilars or intended copies (i.e., utilizing a unique identifier) and from journals or abstracts published in English were extracted. Clinical trial information was taken from the ClinicalTrials.gov database; no other clinical trial registries were consulted in this analysis. It is therefore possible that information on some regional trials may not have been captured.

One of the original aims of our research was to identify gaps in the published literature. With this in mind, the results presented contain only the outcomes data and statistical comparisons available from the published abstracts or full-text articles retrieved from the search. Thus, the information collated may not be representative of the full extent of data available for each study, only that which has been published. It should be noted that the search strategy was designed to capture only articles published by MEDLINE®- or EMBASE®-indexed journals. Therefore, studies published by non-indexed journals were not included. A full Internet search of all online content was not included in the methodology.

It should also be noted that proceedings from only 17 conferences were searched, and thus additional data may be available from other conference proceedings not considered in this analysis. Furthermore, at the time of analysis, only limited outcomes data were available from published conference abstracts, with no full-text publications available at the time of the review.

Lastly, the authors also acknowledge that the delay between regulatory submission and publication of studies may partially explain why there is limited information available for those biosimilars that are newly approved.

A number of biosimilars have newly published data and new molecules (which were not included in this review) may now also be in development for the treatment of chronic inflammatory diseases. For example, at the time of writing, comparative safety/efficacy trials were listed in the ClinicalTrials.gov registry for M923 (adalimumab; Baxalta) for the treatment of chronic plaque-type psoriasis and moderate to severe RA, and for MYL-1401A (adalimumab; Mylan) in patients with psoriasis and PsA. In addition, other studies of biosimilars included in the review have since been listed in the ClinicalTrials.gov registry. For the infliximab biosimilar CT-P13 (Remsima®/Inflectra®), two observational studies (one in RA and one in AS) and one post-marketing study (in RA patients [PERSIST]) have been listed. BCD-055 (infliximab biosimilar) has comparative safety/efficacy trials planned in AS and RA. Three new studies for adalimumab biosimilars have also been added. A multicenter clinical study to evaluate the usability and safety of a pre-filled pen and pre-filled syringe in RA is reportedly complete (SB5), GP2017 has a comparative safety/efficacy RA trial listed (ADMYRA), and there is a comparative safety/efficacy trial planned for BCD-057 in the treatment of plaque psoriasis (CALYPSO). For etanercept biosimilars, GP2015 is being studied (EQUIRA) and LBEC0101 is under evaluation for the treatment of RA. The rituximab biosimilar BCD-020 is being investigated with methotrexate as first-line biologic therapy for patients with active RA (ALTERRA). The number of new biosimilars and clinical trials identified illustrates the speed at which this field of medicine is progressing. This is a highly competitive market, as illustrated by Epirus Biopharmaceuticals suspending development of the biosimilar BOW015 (Infimab®; infliximab) in May 2016, citing the evolving biosimilar competitive and business landscape as the primary reason [161].

As discussed here, there is a need to recognize and maintain a clear distinction between biosimilars and intended copies. However, since it is not always apparent from publicly available sources what manufacturers' intentions are, the term 'proposed biosimilars' is employed in this analysis as a blanket term for all development candidates pending final determination of their status as biosimilars.

There are examples of molecules that are currently marketed as biosimilars in countries outside of the EU or USA: HD203 (Davictrel™; Hanwha Chemical) was approved by the Korean MFDS in 2014 [162] and BOW-015 (Infimab®; infliximab; development now suspended) and ZRC-3197 (Exemptia™; adalimumab) were also approved in India [145]. As noted by Castañeda-Hernández et al. [145], it is not yet known whether other countries will approve these products as biosimilars based on the data currently available.

5 Conclusions

This SLR sought to collate and synthesize publicly available information on biosimilars on the market and in development for chronic inflammatory disease to support healthcare decision-making. As anticipated, at the time of this review, all approved biosimilars had published data providing evidence of biosimilarity from RCT studies. At the analysis cut-off, only CT-P13 had additional published evidence from analytical and nonclinical studies.

A number of proposed biosimilars are also amassing a significant body of evidence from studies across development stages. The majority of agents were found to exhibit a high degree of similarity to their originators, based on investigator conclusions. However, the authors found that significant gaps in the evidence base for some pipeline products remain, and this is also true for all of the intended copies identified. As shown in this review, only one intended copy had published RCT data and this was from a preliminary safety/efficacy study. The implications of these intended copies being marketed without a transparent evidence base are multi-fold and the authors advise caution in the use of these molecules. Apart from the obvious safety issues, this lack of transparency may have a broad impact on adoption of biosimilars in general and cause confusion among healthcare stakeholders. While the authors acknowledge that the existence of data not yet published may potentially address these gaps, if it is not in the public domain it will do little to alleviate these concerns.

RA is the first market in which multiple biosimilars have been launched and, undoubtedly, experience in this market will influence how the broader sector evolves. Therefore, the ongoing dissemination of data by all manufacturers is imperative to instill confidence and support adoption of biosimilars in healthcare practice.

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Compliance with Ethical Standards

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Conflict of interest IJ, DP and KLS are full-time employees and shareholders of Pfizer. LI was a full-time employee of Pfizer Inc. at the time the study was conducted. SL is a full-time employee of Envision Pharma Group, who were paid consultants to Pfizer in connection with the development of the SLR report that forms the basis of this manuscript. He was not compensated for his role in the development of this manuscript.

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