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SYSTEMATIC REVIEW

Monoclonal Antibody and Fusion Protein Biosimilars Across Therapeutic Areas: A Systematic Review of Published Evidence

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Abstract

Background Despite regulatory efforts to formalize guidance policies on biosimilars, there remains a need to educate healthcare stakeholders on the acknowledged definition of biosimilarity and the data that underpin it.

Objectives The objectives of the study were to systematically collate published data for monoclonal antibodies and fusion protein biosimilars indicated for cancer, chronic inflammatory diseases, and other indications, and to explore differences in the type and weight (quantity and quality) of available evidence.

Methods MEDLINE, Embase, and ISI Web of Science were searched to September 2015. Conference proceedings ($n = 17$) were searched 2012 to July 2015. Included studies were categorized by originator, study type, and indication. To assess data strength and validity, risk of bias assessments were undertaken.

Results Across therapeutic areas, 43 named (marketed or proposed) biosimilars were identified for adalimumab, abciximab, bevacizumab, etanercept, infliximab, omalizumab, ranibizumab, rituximab, and trastuzumab originators. Infliximab CT-P13, SB2, and etanercept SB4 biosimilars have the greatest amount of published evidence of similarity with their originators, based on results of clinical studies involving larger numbers of patients or healthy subjects ($N = 1405$, 743, and 734, respectively). Published data were also retrieved for marketed intended copies of etanercept and rituximab.

Conclusions This unbiased synthesis of the literature exposed significant differences in the extent of published evidence between molecules at preclinical, clinical, and post-marketing stages of development, providing clinicians and payers with a consolidated view of the available data and remaining gaps.

Key Points

The quantity and quality of published preclinical and clinical data for approved or proposed biosimilars and intended copies varies widely.

This synthesis of available evidence provides an unbiased resource to inform and support clinical decision making.

Gregory Finch was an employee of Pfizer at the time the study was conducted.

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1 Introduction

The arrival of biosimilars for a number of key recombinant biologics, including the first approved monoclonal antibodies (mAbs) [1–3], is expected to provide cost savings to healthcare systems and offers the potential to expand patient access to important medicines [4, 5]. Outside of the EU or the USA, experience of the regulatory pathway leading to approval of mAb or fusion protein biosimilars by major health authorities remains limited. Nevertheless, regulatory environments across all markets are evolving rapidly, with extensive global industrial biologic development and manufacturing experience [6, 7], accompanied by rising standards of clinical care. Over the past few years, there has also been a steady increase in the body of evidence—in the form of robust peer-reviewed publications available in the public domain—for biosimilars on the market and in development.

CT-P13 (Remsima™/Inflectra™; Celltrion, South Korea/Hospira, USA) was the first EU-approved mAb infliximab biosimilar, obtaining market authorization in September 2013, across all approved indications of Remicade® for rheumatoid arthritis (RA), Crohn's disease, ulcerative colitis, ankylosing spondylitis, psoriatic arthritis, and psoriasis [8, 9]. In May 2016, SB2 (Flixabi®; Samsung Bioepis), an infliximab biosimilar, was also approved in the EU for the treatment of adults with RA, Crohn's disease, ulcerative colitis, ankylosing spondylitis, psoriatic arthritis, and psoriasis [10]. In January 2016, SB4 (Benepali®; Biogen, Samsung Bioepis, South Korea) became the first etanercept biosimilar to Enbrel® to be approved in the EU for the treatment of adults with moderate to severe RA, psoriatic arthritis, non-radiographic axial spondyloarthritis, and plaque psoriasis [11]. Marketing authorization applications for ABP 501 (adalimumab; Amgen) and GP2015 (etanercept; Sandoz, Switzerland) were submitted to the European Medicines Agency (EMA) in 2015 [12–14] and were still undergoing evaluation at the time of writing this article.

In the USA, the FDA guidance documents on scientific and quality considerations in the demonstration of biosimilarity were finalized in April 2015 [15]. Almost 1 year later, the FDA released draft guidance for industry on the labeling of biosimilar products, which provides an overview of the FDA's recommendations for biosimilar labels and is intended to support the development of draft labeling for submission in proposed biosimilar product applications [16, 17]. In April 2016, the FDA approved the infliximab biosimilar, CT-P13 for multiple indications [18]. CT-P13 is the first mAb biosimilar to be approved in the USA and only the second biosimilar to be granted FDA approval [18, 19]. In July 2016, the FDA Arthritis Advisory Committee unanimously voted to recommend approval of Sandoz's etanercept biosimilar, GP2015 [20]. Also in July 2016, the FDA advisory panel voted in favor of recommending approval for ABP 501, Amgen's proposed biosimilar of adalimumab [21].

Biosimilars are thus required to meet rigorous regulatory standards on biosimilarity and, as such, the term 'biosimilars' is applied to products that meet these standards. In contrast, the terms 'intended copies' or 'non-comparable biologics' are applied to products that have not undergone rigorous similarity exercises but are marketed nevertheless [1, 22, 23]. The published data available on these products are insufficient to provide robust evidence compared with the originator product [24].

Despite regulatory efforts across major markets to formalize guidance policies on biosimilars, there remains an ongoing need to inform and educate healthcare professionals and payers on the acknowledged definition of biosimilarity and to keep stakeholders abreast of any developments regarding the labeling, substitution, and indication extrapolation of biosimilar candidates. Payers and clinicians would benefit from more information on the weight and breadth of evidence available for proposed or approved biosimilars to support more informed prescribing and coverage decisions.

Currently, no published reviews are available that have systematically summarized all of the available studies on biosimilars across all stages of development and across multiple therapeutic areas. With these considerations in mind, a comprehensive literature review was undertaken to identify, collate, and summarize published empirical evidence on proposed or approved mAb and fusion protein biosimilars indicated for cancer, chronic inflammatory diseases, and other indications. The intent of this research was to provide a robust overview of biosimilar molecules currently in development, in human clinical trials, or on the market, and to explore differences in the type and weight of evidence. The results presented in this study represent findings from the published literature (up to the analysis cut-off date for this article, 3 September 2015) and provide insight on the dataset available for these classes of biosimilars. The authors also reviewed planned, ongoing, or completed trials with currently unpublished data (up to the analysis cut-off date for this article, 21 September 2015).

This work is intended to provide an introduction to the field of biosimilars and reports on the methodology and high-level findings of the systematic literature review (SLR). A detailed analysis of the full study data and remaining knowledge gaps for each therapeutic area will be presented in a series of follow-on manuscripts currently in development and will include all reported outcomes across the identified empirical study types, quality assessment results, and a thematic analysis of the retrieved non-empirical publications.

2 Methods

2.1 Systematic Literature Review

The MEDLINE/Medline in process and Embase electronic databases were searched using the OVIDSP interface from database inception to 3 September 2015. The ISI Web of Science database was searched up to 3 September 2015. The search strategy was executed on 27 April 2015 and was refreshed on 3 September 2015 to capture recent full-text publications. First, search terms were used that capture 'mAb', 'fusion protein', or 'interleukin-1 receptor-antagonist' terms. Second, search terms were used that encompass the different terminologies for biosimilar products, including, for example, 'biosimilars', 'subsequent entry biologics', 'follow-on biologics', 'follow-on proteins', 'biocomparables', 'biogenerics', 'similar biotherapeutic products', and 'intended copies' or 'biobetters' (which were analyzed separately). Controlled vocabulary and free-text terms were used, and the search results were filtered using the study designs of interest. The final search result from each database was limited to references published in the English language. Included publications were required to contain both a 'mAbs/fusion protein' term and a 'biosimilars' term. To capture the latest studies not yet published as full-text articles and/or supplement results of previously published studies, a hand-search of key conference proceedings ($n = 17$) was conducted for the period of 1 January 2012 to 31 July 2015. The complete list of conference proceedings can be found in Table S1 in the Electronic Supplementary Material (ESM) and includes disease-specific (i.e., for oncology or chronic inflammatory disease), health economics and outcomes research, regulatory/payer-focused, and manufacturing/development-themed meetings that were prioritized on the basis of the quantity and quality of biosimilar content in 2014. Searches were also conducted using the US National Library of Medicine (NLM) ClinicalTrials.gov registry to identify biosimilars in development that did not appear in the published literature or in the identified congresses. Hand-screening was used to identify relevant records due to the limited extent of the searches available for ClinicalTrials.gov.

2.2 Eligibility Criteria

All publication types with a 'biosimilar' and either a 'mAb' and/or 'fusion protein' term were included, with the exception of case studies/case reports, short news reports, or congress overviews. The publication types of interest were empirical publications of studies (i.e., analytical, functional, or nonclinical [collectively referred to as preclinical]), clinical (i.e., pharmacokinetics [PK]/safety trials in healthy subjects or patients and comparative safety/efficacy trials), observational (prospective, retrospective, and post-marketing), and non-empirical publications including publications reporting manufacturing or supply topics and themes, review articles, opinion pieces or commentaries, regulatory/policy-related content and published descriptions of product-related patient support programs, and any other non-empirical publication type relevant to biosimilars meeting the inclusion criteria.

2.3 Study Categorization

A stepwise approach was undertaken to categorize publications by biosimilar molecule, indication, reference product, and study type (ESM Table S2). Two independent reviewers separated empirical publications disclosing 'candidate development' or brand names of biosimilars (collectively referred to as 'named biosimilars' hereafter) from non-empirical publications and from those that did not disclose the name of a biosimilar. For the empirical studies, one reviewer extracted information regarding the reference biologic (where available), the named biosimilar, indication, study type, study characteristics, study outcomes, and parameters assessed. A blinded second reviewer classified a 10% sample of these; in the event of finding a 5% discrepancy, the database was re-evaluated. Any discrepancies were resolved by consensus among reviewers. A similar approach was taken for categorization of non-empirical publications.

In this analysis, biosimilars are differentiated from marketed 'intended copies' based on whether they meet the established rigorous regulatory requirements for biosimilarity as outlined by major regulatory health authorities such as the EMA, FDA, Health Canada, Pharmaceuticals Medical Devices Agency/Japan Ministry for Health Labour and Welfare (PMDA/MHLW), or the Korean Ministry of Food and Drug Safety (MFDS). Unless identified as an approved biosimilar or a marketed intended copy, all molecules presented in this review are considered development candidates (or 'proposed biosimilars'), with final determination of their status pending.

2.4 Risk of Bias Assessment

A risk of bias assessment was undertaken for each individual study using a validated tool matched to study type to assess the strength/validity of the empirical data in accordance with the preferred reporting items for systematic reviews and meta-analyses (PRISMA) guidelines [25, 26]. An assessment of the quality for the reporting of randomized controlled trials (RCTs) was carried out using

recommendations from the UK National Institute for Health and Care Excellence (NICE) single technology appraisal (STA) manufacturer's template [27]. In addition, the Jadad scoring system was used for all included RCTs [28]. The quality of all included non-randomized/observational studies was assessed using the Downs and Black instrument [29]. As abstracts from conference proceedings report limited information on studies, the Downs and Black instrument was modified to include only the 12 most critical qualifying parameters (of 26) for quality assessment. Detailed parameters related to process were excluded as these data were not available in abstract formats, e.g., suitability of statistical method employed. Animal studies were assessed using the SYRCLE's Risk of Bias tool [30], and pharmacoeconomic studies were evaluated using Drummond's checklist for assessing economic evaluations [31].

3 Results

3.1 Literature and Conference Search

Results of the systematic search and screening of the biosimilars literature are presented in a PRISMA diagram [32, 33] for the empirical studies, with a separate designation in the diagram for non-empirical publications (e.g., commentaries, reviews, manufacturing/supply topics) (Fig. 1).

The search strategy yielded 1991 publications from the title and abstract screen, and those relevant to the topic of biosimilars (as defined by our criteria) were retained (768 publications in total). Of the 768 included publications, 244 (32%) were identified as empirical publications, 491 (64%) were non-empirical publications (i.e., review or opinion articles), and 33 (4%) corresponded to payer or healthcare professional surveys. The number of publications is higher than the number of studies, as some studies were disseminated in more than one publication (Fig. 1).

The number of publications included in the analysis are presented in Fig. 2. Of the included references, 147 (19%) reported mAb or fusion protein biosimilars for use in oncology and 301 (39%) addressed biosimilars for the treatment of chronic inflammatory conditions. A total of 12 (2%) publications were classified as 'other', and a further 465 (61%) could not be classified by indication and were categorized as 'not specified'. A degree of overlap in the reported indications was also noted. For example, rituximab biosimilar publications were reported for both the oncology and inflammatory disorders categories, where relevant, as rituximab is indicated for both therapeutic areas.

3.1.1 Empirical Publications

Of the identified 244 empirical publications (and prior to data extraction), 64 (26%) were classified as analytical, 55 (23%) as nonclinical, and five (2%) as 'other'. In total, 83 publications (34%) reported RCTs, and 31 (13%) were classified within the observational/post-marketing category; 13 (5%) were relevant to health economics and seven reported both nonclinical and human clinical studies (Fig. 2). Since a handful of references included both nonclinical and human clinical data and were reported in more than one category, the publication counts do not sum to totals. Named biosimilars were identified in 90 unique studies (reported across 148 publications); 23 studies were reported in 36 publications in oncology, 55 studies (96 publications) in chronic inflammatory disease, ten studies (14 publications) in oncology and inflammatory diseases, and two studies (two publications) in 'other' diseases.

3.1.2 Non-Empirical Publications

Of the total number of included publications, 491 were categorized as non-empirical, of which 176 (36%) were overview articles, 139 (28%) covered regulatory issues and/or safety, 109 (22%) were regarding development and production, and 54 (11%) were related to market analysis and uptake and 13 (3%) review or opinion articles covered other topics that were not classified (Fig. 2).

Within the overview category, the most common publications were 'general' overview articles ($n = 83$ [17%]), and a further 74 publications provided an overview of a given therapy area ($n = 74$ [15%]). The majority of publications on regulation and safety were concerned with regulatory and/or policy topics ($n = 121$ [25%]). Among the publications concerning development and production, most focused on biosimilar development ($n = 42$ [9%]) or quality or analysis methods ($n = 43$ [9%]). Market analysis and/or commercial uptake articles were predominantly concerned with economics or pricing ($n = 21$ [4%]) (Fig. 2).

3.2 Named Biosimilars of Monoclonal Antibody (mAb) and Fusion Protein Originators Across Therapy Areas

3.2.1 Overview of Biosimilars in Development: Key Manufacturers

In total, 21 different mAb or fusion protein originators were identified relevant to the topic of biosimilars (ESM Table S3). Figure 3 shows the number of molecules reported to be in development for each manufacturer classified by originator and therapy area. Across therapy areas, named biosimilars were reported for the following

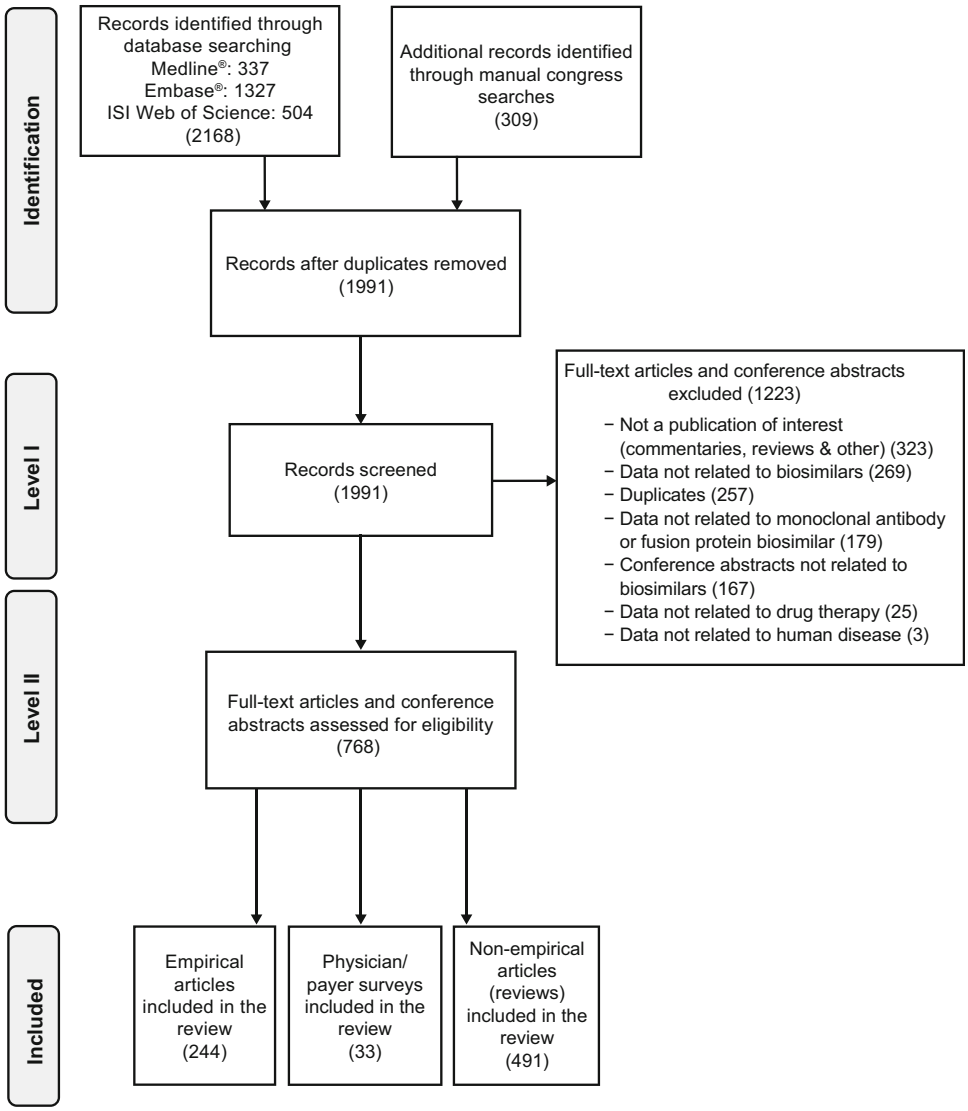

Fig. 1 PRISMA flow diagram showing the high-level breakdown of the publication counts. Where duplicates were retrieved for studies, originals (first published article) were retained if no additional data were provided in encore publications. If new data were identified, subsequent publications were included together with the original publication. This affected overall publication count but not overall study count. Note: Of the total 244 empirical publications, 90 empirical studies of named biosimilars or intended copies were identified, reported across 148 publications (23 studies in 36 publications in oncology, 55 studies in 96 publications in chronic inflammatory diseases, ten studies in 14 publications in oncology and chronic inflammatory diseases, two studies in two publications in 'other' diseases) and 96 empirical publications did not name the biosimilar being evaluated

nine identified originators: adalimumab, abciximab, bevacizumab, etanercept, infliximab, omalizumab, ranibizumab, rituximab, and trastuzumab. Marketed intended copies were identified for etanercept and rituximab. In total, 43 named biosimilars (and a further four marketed intended copies) were identified from 27 different manufacturer/development partnerships (Fig. 3).

3.2.2 Biosimilars in Oncology

For bevacizumab, four proposed biosimilars (ABP 215 [Amgen/Allergan], BCD-021 [Biocad], PF-06439535 [Pfizer], and RPH-001 [Alphamab]) were identified in empirical and non-empirical publications, of which ABP 215 was cited the most frequently, in two empirical studies reported across four publications. The following proposed trastuzumab biosimilars were reported: BCD-022 (Biocad), CT-P6 (Celltrion/Hospira), FTMB/ABP 980 (Amgen/Synthon/Allergan), and PF-05280014 (Pfizer), of which PF-05280014 was referenced the most frequently, in five empirical studies reported across 11 publications. Although the originator mAb cetuximab was referenced in empirical and non-empirical publications ($n = 7$ and $n = 2$, respectively), no named biosimilars were identified in these reports. Publications that did not disclose unique names of biosimilars were categorized as 'biosimilars without unique identifiers' (ESM Table S3).

3.2.3 Biosimilars in Chronic Inflammatory Diseases

Within the chronic inflammatory disease category, 14 different mAb or fusion protein originators were identified from the retrieved biosimilar publications. Named biosimilars were found for originators adalimumab, etanercept, and infliximab. For adalimumab, five proposed biosimilars were found: ABP 501 (recommended for FDA approval), ZRC-3197

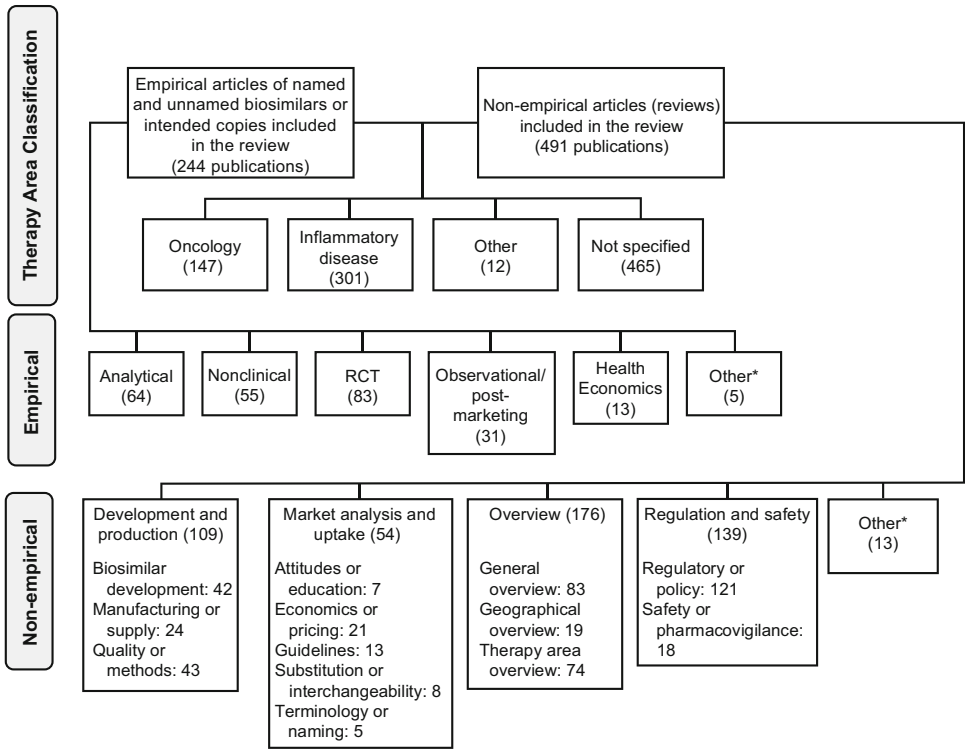

Fig. 2 Categorization of publication type. *Other category includes any other publication on the topic of biosimilars provided it is not one of the excluded empirical/ non-empirical publication types. Note: Publications were classified into the most relevant category, which in some cases was more than 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 ($n = 7$) include both nonclinical and human data, and as such have been classified into both categories. *RCT* randomized controlled trial

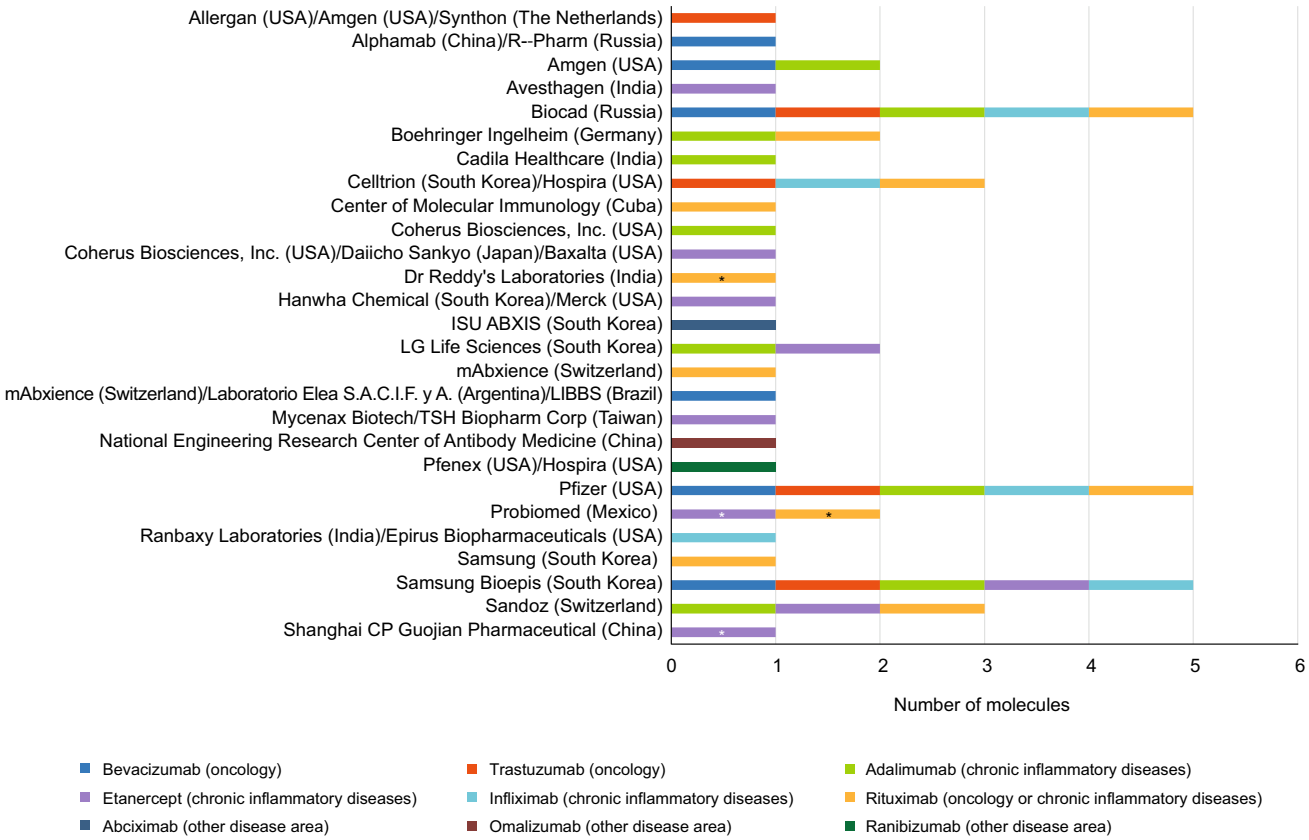

Fig. 3 Biosimilar development pipeline: key manufacturers, country, and number of biosimilar agents categorized by originator and therapy area. Includes manufacturers with marketed intended copies (individual products indicated by an *asterisk* on the *bar*)

(Exemptia™; Cadila Healthcare), GP2017 (Sandoz), PF-06410293 (Pfizer), and SB5 (Samsung Bioepis). ABP 501 was reported in four empirical studies, which were reported in seven empirical publications. GP2017 was evaluated in two studies, which were reported in three separate empirical publications. Four biosimilars were identified for infliximab: BOW015; (Ranbaxy Laboratories/Epirus Biopharmaceuticals; development now suspended), CT-P13 (EMA/FDA approved), PF-06438179 (Pfizer), and SB2 (EMA approved). Of these infliximab biosimilars, approved biosimilar CT-P13 was reported by far the most frequently (in 20 studies reported in 38 empirical publications and in 38 non-empirical publications). The following six biosimilars were identified for etanercept fusion protein: AVG01 (Avesthagen), ENIA11 (TuNEX®; Mycenax Biotech/TSH Biopharm Corp), GP2015 (recommended for FDA approval), HD203 (Hanwha Chemical/Merck), LBEC0101 (LG Life Sciences), and SB4 (EMA approved) (ESM Table S3).

3.2.4 *Biosimilars in Both Oncology and Chronic Inflammatory Diseases*

Rituximab was identified in empirical and non-empirical publications (for either cancer or inflammatory conditions

Table 1 Biologic originator rituximab and corresponding named biosimilar agents in oncology and inflammatory disease classified by empirical study type[a]

Biosimilar or IC (name[b], company)	Reference counts for empirical publications (and studies)[c]					
	RCT	Observational/ post-marketing	Nonclinical	Analytical	Health economics	Other
Oncology/inflammatory disease mAbs						
1B8 (Center of Molecular Immunology, Cuba)	–	–	Onc: 1 (1)	Onc: 1 (1)	–	–
Onc: [113]			–	–		
BCD-020 (AcellBia™; Biocad, Russia)	Onc: 3 (1)	–	–	–	–	–
Onc: [38, 114, 115]	–					
CT-P10 (Celltrion, South Korea)/Hospira, USA)	–	–	–	–	–	–
Inflamm: [83, 116]	Inflamm: 2 (1)					
GP2013 (Sandoz, Switzerland)[d]	–	–	Onc: 4 (2)	Onc: 4 (2)	–	–
Onc: [49, 117–119]			Inflamm: 3 (2)	Inflamm: 2 (2)		
Inflamm: [49, 117, 119]						
PF-05280586 (Pfizer, USA)[d]	–	–	Onc: 4 (2)	Onc: 4 (2)	–	–
Onc: [51, 120–122]	Inflamm: 5 (1)		Inflamm: 6 (3)	Inflamm: 5 (2)		
Inflamm: [51, 67, 120–127]						
RTXM83 (mAbxience, Switzerland)[d]	Onc: 1 (1)	–	Onc: 1 (1)	Onc: 1 (1)	–	–
Onc: [41, 128]	–		Inflamm: 1 (1)	Inflamm: 1 (1)		
Inflamm: [128]						
SAIT101 (Samsung BioLogics, South Korea)[d] [44]	Onc: 1 (1)	–	–	–	–	–
IC of rituximab						
Kikuzubam® (IC) (Probiomed, Mexico)[d]	–	–	Onc: 1 (1)	Onc: 1 (1)	–	–
Onc: [90]		Inflamm: 1 (1)	Inflamm: 1 (1)	Inflamm: 1 (1)		
Inflamm: [66, 90]						
Reditux™ (IC) (Dr. Reddy's Laboratories, India)[d]	–	Onc: 5 (3)	Onc: 3 (3)	Onc: 3 (3)	–	–
Onc: [36, 37, 39, 46, 90, 129–133]		Inflamm: 4 (3)	Inflamm: 1 (1)	Inflamm: 3 (3)		
Inflamm: [39, 62, 65, 90, 129–131, 134]						
Biosimilars without unique identifiers	–	3	3	6	–	1

Corresponding indications for study counts for rituximab are labelled with 'Onc' for oncology and 'Inflamm' for chronic inflammatory disease

IC intended copy, *mAbs* monoclonal antibodies, *RCT* randomized controlled trial

[a] Italic font indicates biosimilars that are included in at least one reference naming multiple biosimilars

[b] Alternative names for biosimilars are provided where applicable

[c] Reference counts correspond to the number of identified publications. The number of unique empirical studies reported for named biosimilars is shown in parentheses

[d] Several studies/publications were classified under both oncology and inflammatory disease indications or the disease area was not specified

or, in some cases, for combined indications). Among the rituximab biosimilar publications, seven proposed biosimilars were referenced (the majority in empirical publications): 1B8 (Center of Molecular Immunology, Cuba), BCD-020 (Biocad), CT-P10 (Celltrion/Hospira), GP2013 (Sandoz), PF-05280586 (Pfizer), RTXM83 (mAbxience), and SAIT101 (Samsung BioLogics). For the proposed biosimilars of rituximab, PF-05280586 was most often reported (ESM Table S3), with published data available for two oncology studies (four publications) and five chronic inflammatory disease studies (ten publications).

3.2.5 Biosimilars in Other Disease Areas

Within the 'other' disease area category (including cardiovascular disorders, respiratory [allergic] conditions, and eye conditions), three proposed biosimilars, clotinab (ISU ABXIS), CMAB007 (National Engineering Research Center of Antibody Medicine), and PF582 (Pfenex/Hospira), were identified for abciximab (cardiovascular), omalizumab (respiratory/asthma), and ranibizumab (ophthalmology), respectively. Clotinab and CMAB007 were each reported in one empirical study, and PF582 was reported once in a non-empirical publication (ESM Table S3).

3.3 Empirical Publications in Oncology

The reference counts for empirical studies and publications for identified originators in oncology, along with corresponding proposed biosimilars, are shown in Fig. 4. As rituximab is licensed for oncology and chronic inflammatory conditions, the analyses are presented separately. Pfizer's PF-05280014 (trastuzumab) was the most commonly reported proposed biosimilar in oncology (Fig. 4), reported in seven RCT publications (for three unique RCT studies), five nonclinical publications (covering two unique studies), and four analytical publications (describing two unique studies). The second most frequently reported biosimilar was ABP 215, a proposed bevacizumab biosimilar, identified in two RCT publications (one study), four nonclinical publications (two studies), and one analytical publication describing a single study.

At study cut-off, all biosimilars except RPH-001 (Alphamab, China/R-Pharm, Russia) and PF-06439535 had entered into clinical stages of development, with published RCT data available in at least one study. Interestingly, despite entering into clinical development programs, published analytical and nonclinical data were not available for BCD-021, BCD-022, CT-P6, or FTMB/ABP 980.

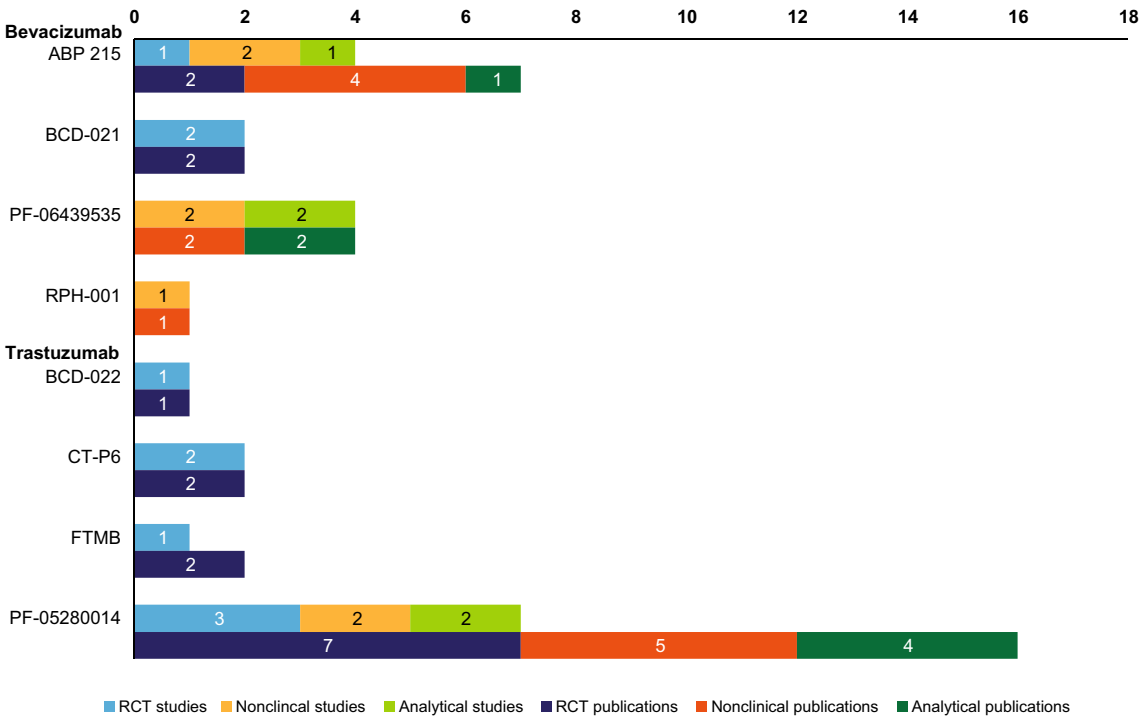

Fig. 4 Frequency of reported named biosimilars in oncology. Excludes data (shown in Table 1) on biosimilars or intended copies of rituximab. *RCT* randomized controlled trial

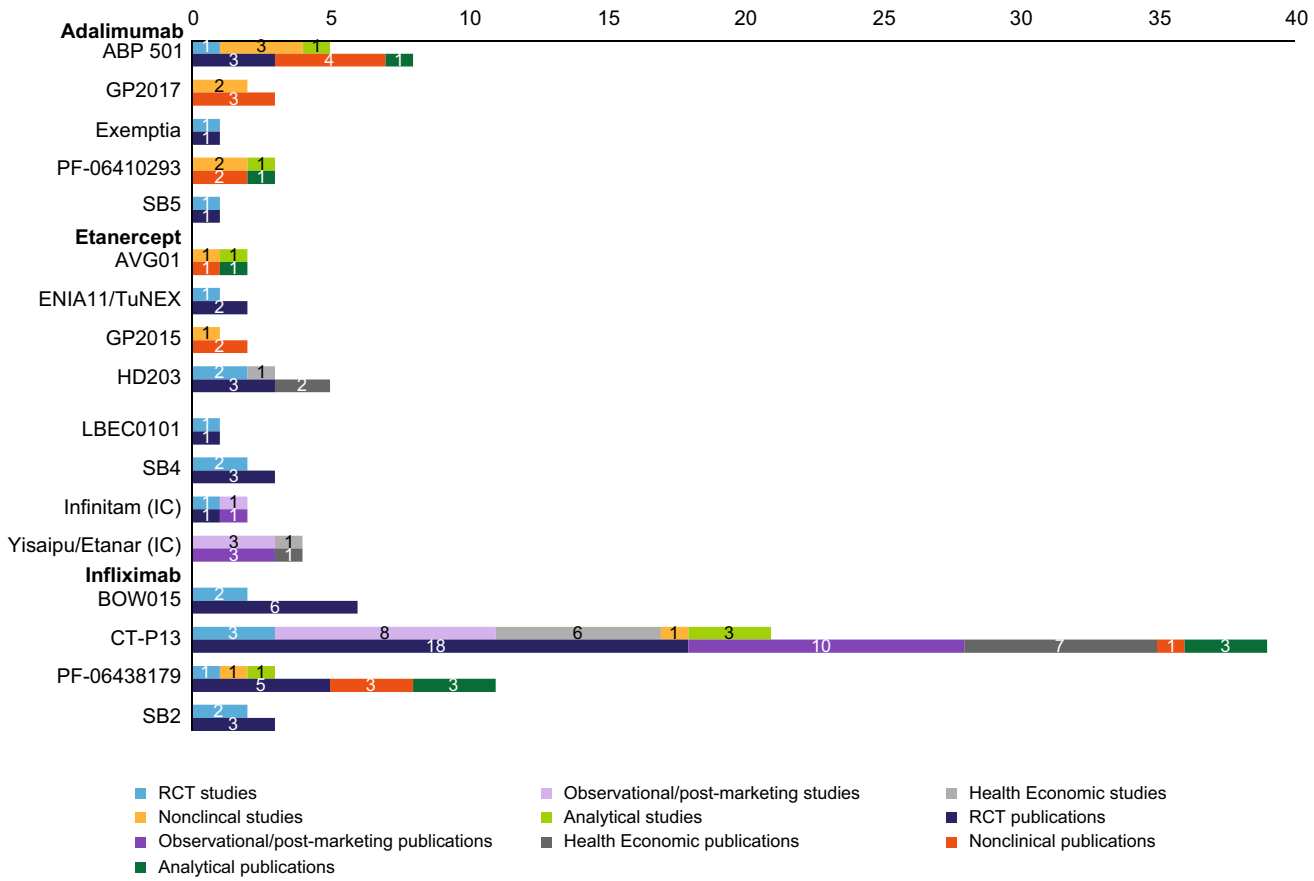

Fig. 5 Frequency of reported named biosimilars and intended copies in chronic inflammatory diseases. *IC* intended copy, *RCT* randomized controlled trial

3.4 Empirical Publications in Chronic Inflammatory Diseases

The reference counts for empirical studies and publications for identified originators in chronic inflammatory disease, along with corresponding biosimilars, are shown in Fig. 5. Of the biosimilars indicated for chronic inflammatory conditions (namely biosimilars of adalimumab, etanercept, and infliximab), Celltrion's CT-P13 was the most commonly reported, across all stages of development.

A total of 18 RCT publications (reporting three unique RCT studies) and ten observational/post-marketing publications (eight studies) were identified for CT-P13. During the study period, CT-P13 was evaluated in one nonclinical study, three analytical studies, and in six health economic studies. Several proposed biosimilars for chronic inflammatory diseases (namely SB5, ENIA11, and LBEC101 (LG Life Sciences, South Korea); etanercept) had entered into clinical development stages with published PK/safety data in healthy subjects, without published data from preclinical (analytical, functional, or nonclinical) studies. Furthermore, ZRC-3197, HD203, SB4, BOW015, and SB2 all had published data from PK/safety studies and/or comparative safety/efficacy trials (in RA), without underlying published data or evidence to suggest that they demonstrate similar structural or functional resemblance to that of their originators.

3.5 Empirical Publications on Biosimilars of Rituximab for Both Oncology and Inflammatory Diseases

PF-05280586 was the highest reported molecule, in five RCT publications (one study), six nonclinical publications (two studies applicable to the oncology indication and three studies applicable to inflammatory disease), and five analytical publications (two studies applicable in both therapy areas) (Table 1). BCD-020, RTXM83, and SAIT101 have all been evaluated in RCTs for oncology only, with published data available for just one RCT each to date. For RCTs in chronic inflammatory disease, CT-P10 and PF-05280586 have both been evaluated in a single study. Of the seven identified rituximab biosimilars, only four (namely, 1B8, GP2013, PF-05280586, and RTXM83) had undergone head-to-head analytical and nonclinical assessments with originator rituximab. The comprehensive

analytical data, upon meeting the scientific rigors of similarity assessment outlined by the EMA and FDA, can be used to extrapolate to either oncology or chronic inflammatory disease indications.

3.6 Empirical Publications in Other Disease Areas

Only three proposed biosimilars were identified in this category: clotinab, a biosimilar of abciximab (for cardiovascular disorders); CMAB007, a biosimilar of omalizumab (for respiratory conditions); and PF582, a ranibizumab biosimilar for ophthalmologic conditions (Table 2).

Generally, published empirical studies for biosimilars in other disease areas are scarce. To date, very little RCT or preclinical data have been published to support the use of these proposed biosimilars for these indications. Two empirical studies (both clinical PK/safety investigations), were identified for CMAB007 and clotinab.

3.7 Published or Ongoing Comparative Clinical Studies

Since demonstration of biosimilarity for FDA or EMA approval requires rigorous comparison with the originator molecule, the majority of the identified empirical studies compared some aspect of a biosimilar with its originator molecule—a finding that was apparent across all study types and in all therapy areas. A number of studies have also compared the biosimilar of interest with the originator from both US and EU sources across oncology and chronic inflammatory disease areas. To facilitate comparisons across molecules and to highlight gaps in the evidence base, Table 3 presents a summary of all of the comparative, PK/safety, safety/efficacy, and post-marketing/observational studies identified for each molecule.

Within oncology, all of the identified proposed biosimilars with the exception of RPH-001 (Alphamab/R-Pharm) were either undergoing or had completed comparative PK/safety studies or comparative efficacy/safety trials versus bevacizumab at the time of analysis.

For the proposed trastuzumab biosimilars (BCD-022, CT-P6, FTMB/ABP 980, PF-05280014, and SB3 [Samsung Bioepis]), a number of comparative PK/safety or safety/efficacy trials were either ongoing or complete with published data versus trastuzumab at the time of analysis.

For the rituximab biosimilars being investigated within oncology, published comparative data from PK/safety or safety/efficacy trials versus rituximab were reported for RTXM83, SAIT101, and BCD-020, respectively. At the time of review, ongoing comparative safety/efficacy trials were reportedly also underway for BCD-020, CT-P10, GP2013, PF-05280586, and RTXM83.

In chronic inflammatory diseases, a number of comparative safety/efficacy trials for the rituximab biosimilars BCD-020, BI 69550 (Boehringer Ingelheim), and CT-P10 were reported as ongoing (but without published data at the time of analysis). Published comparative PK/safety trials in patients with RA were published for CT-P10 and PF-05280586.

Among the adalimumab, etanercept, and infliximab biosimilars, efficacy/safety data in RA versus the originator were published for ZRC-3197, HD203, SB4, BOW015, CT-P13, and SB2.

Comparative safety/efficacy trials were reportedly ongoing (with no publications to date) for a number of adalimumab biosimilars in chronic inflammatory diseases (Table 3). Comparative PK/safety evaluations were also reportedly underway for adalimumab biosimilars BCD-057 (Biocad), LBAL (LG Life Sciences), PF-06410293, and SB5 at the time of analysis.

Table 2 Originator monoclonal antibodies and corresponding named biosimilar agents in other disease areas classified by empirical study type

Biologic originator[a]	Biosimilar (name[b], company)	Reference counts for empirical publications (and studies)[c]					
		RCT	Observational/post-marketing	Nonclinical	Analytical	Health economics	Other
Abciximab	Clotinab (ISU ABXIS) [88]	1 (1)	–	–	–	–	–
Omalizumab	CMAB007 (National Engineering Research Center of Antibody Medicine, China) [89]	1 (1)	–	–	–	–	–
Ranibizumab	PF582 (Pfenex, USA/Hospira, USA)	–	–	–	–	–	–

mAbs monoclonal antibodies, *RCT* randomized controlled trial

[a] Abciximab is indicated for cardiovascular disorders, omalizumab is indicated for respiratory (allergic) conditions, ranibizumab is indicated for eye conditions (ophthalmology)

[b] Alternative names for biosimilars are provided where applicable

[c] Reference counts correspond to the number of identified publications. The number of unique empirical studies identified is indicated in parentheses

Table 3 Comparative studies of biosimilars by study type

Biologic originator generic name	Biosimilar or IC (alternative name[a], company)	Comparator studies				
		Analytical studies (comparator)	Nonclinical studies (comparator)	PK/safety trials in healthy subjects or patients (sample size, comparator)[b]	Comparative safety/efficacy studies (sample size, comparator)	Post-marketing/ observational studies (sample size, comparator)
Oncology mAbs						
Bevacizumab	ABP 215 (Amgen, USA) [45, 135–137]	1 (BEV)	2 (BEV)	1 (BEV)	1 (BEV)[c] [138]	–
	BCD-021 (Biocad, Russia) [40, 47]	–	–	1 (BEV)	1 (BEV) 1 (BEV)[c] [139] 1 (BEV/RAN)[c,d] [140]	–
	BEVZ92 (mAbxience, Switzerland)/Laboratorio Elea S.A.C.I.F. y A., Argentina)/LIBBS, Brazil)	–	–	1 (BEV)[c] [141]	–	–
	PF-06439535 (Pfizer, USA) [142, 143]	2 (BEV)	2 (BEV)	1 (BEV)[c] [144]	1 (BEV)[c] [145]	–
	RPH-001 (Alphamab, China/R-Pharm, Russia) [146]	–	1 (BEV)	–	–	–
	SB8 (Samsung Bioepis Co Ltd)	–	–	1 (BEV)[c] [147]	–	–
Trastuzumab	BCD-022 (Biocad, Russia) [48]	–	–	–	1 (TRA) 1 (TRA)[c] [148]	–
	CT-P6 (Celltrion, South Korea)/Hospira, USA) [42, 43]	–	–	1 (TRA)	1 (TRA) 2 (TRA)[c] [149, 150]	–
	FTMB (ABP 980; Allergan, USA /Amgen, USA/ Synthon, the Netherlands) [34, 151]	–	–	1 (TRA)	1 (TRA)[c] [152]	–
	PF-05280014 (Pfizer, USA) [35, 50, 153–161]	2 (TRA)	2 (TRA)	1 (TRA) 1 (TRA)[c] [162]	2 (TRA)[e]	–
	SB3 (Samsung Bioepis Co Ltd)	–	–	1 (TRA)[c] [163]	1 (TRA)[c] [164]	–

Table 3 continued

Biologic originator generic name	Biosimilar or IC (alternative name[a], company)	Comparator studies				
		Analytical studies (comparator)	Nonclinical studies (comparator)	PK/safety trials in healthy subjects or patients (sample size, comparator)[b]	Comparative safety/efficacy studies (sample size, comparator)	Post-marketing/ observational studies (sample size, comparator)
Oncology/Inflammatory disease mAbs						
Rituximab$^{\pm}$	1B8 (Center of Molecular Immunology, Cuba) Onc: [113]	Onc: 1 (RTX)	Onc: 1 (RTX)	–	–	–
	BCD-020 (AcellBia^{TM}; Biocad, Russia) Onc: [38, 114, 115]	–	–	–	Onc: 1 (RTX) Onc: 1 (RTX)[c] [165] Inflamm: 1 (RTX)[c] [166]	–
	BI 695500 (Boehringer Ingelheim, Germany)	–	–	–	Inflamm: 1 (RTX)[c] [167]	–
	CT-P10 (Celltrion, South Korea)/Hospira, USA) Inflamm: [83, 116]	–	–	Inflamm:1 (RTX)	Onc: 2 (RTX)[c] [168, 169] Inflamm: 2 (RTX)[c] [170, 171]	–
	GP2013 (Sandoz, Switzerland) Onc: [49, 117–119] Inflamm: [49, 117, 119]	Onc/Inflamm: 2 (RTX)	Onc/Inflamm: 2 (RTX)	Inflamm: 1 (RTX)[c] [172]	Onc: 1 (RTX)[c] [173] Inflamm: 1 (RTX)[c] [174]	–
	PF-05280586 (Pfizer, USA) Onc: [51, 120–122] Inflamm: [51, 67, 120–127]	Onc: 2 (RTX) Inflamm: 3 (RTX)	Onc: 2 (RTX) Inflamm: 3 (RTX)	Inflamm: 1 (RTX)	Onc: 1 (RTX)[c] [175]	–
	RTXM83 (mAbxience, Switzerland) Onc: [41, 128] Inflamm: [128]	Onc/Inflamm: 1 (RTX)	Onc/Inflamm: 1 (RTX)	Onc: 1 (RTX)	Onc: 1 (RTX)[c] [176]	–
	SAIT101 (Samsung, South Korea) Onc: [44]	–	–	Onc: 1 (RTX)	–	–
	IC of rituximab					
	Kikuzubam® (IC) (Probiomed, Mexico) Onc: [90] Inflamm: [66, 90]	Inflamm: 1 (RTX, Reditux^{TM})	Inflamm: (RTX, Reditux^{TM})	–	–	Inflamm: 1 (Infinitam®, Yisaipu®)
	Reditux^{TM} (IC) (Dr Reddy's Laboratories, India) Onc: [36, 37, 39, 46, 90, 129–133] Inflamm: [39, 62, 65, 90, 129–131, 134]	Onc/Inflamm: 3 (RTX, Kikuzubam®)	Onc/Inflamm: 2 (RTX, Kikuzumbam)	–	–	Onc: 2 (RTX, RTX literature])

Table 3 continued

Biologic originator generic name	Biosimilar or IC (alternative name[a], company)	Comparator studies				
		Analytical studies (comparator)	Nonclinical studies (comparator)	PK/safety trials in healthy subjects or patients (sample size, comparator)[b]	Comparative safety/efficacy studies (sample size, comparator)	Post-marketing/ observational studies (sample size, comparator)
Chronic inflammatory disease mAbs						
Adalimumab	ABP 501 (Amgen, USA) [71, 177–182]	1 (ADA)	3 (ADA)	1 (ADA)	3 (ADA)[c] [183–185]	–
	BCD-057 (Biocad)	–	–	1 (ADA)[c] [186]	–	–
	BI 695501 (Boehringer Ingelheim, Germany)	–	–	–	1 (ADA)[c] [187]	–
	CHS-1420 (Coherus Biosciences, Inc., USA)	–	–	–	1 (ADA)[c] [188]	–
	Exemptia™ (Cadila Healthcare, India) [55]	–	–	–	1 (ADA)	–
	GP2017 (Sandoz, Switzerland) [189–191]	–	2 (ADA)	–	1 (ADA)[c] [192]	–
	LBAL (LG Life Sciences, South Korea)	–	–	1 (ADA)[c] [193]	–	–
	PF-06410293 (Pfizer, USA) [194, 195]	1 (ADA)	2 (ADA)	3 (ADA)[c] [196–198]	1 (ADA)[c] [199]	–
	SB5 (Samsung Bioepis, South Korea) [80]	–	–	1 (ADA) 1 (ADA)[c] [200]	1 (ADA)[c] [201]	–
Infliximab	BCD-055 (Biocad, Russia)	–	–	1 (INF)[c] [202]	–	–
	BOW015 (Ranbaxy Laboratories, India /Epirus Biopharmaceuticals, USA) [72, 203–207]	–	–	1 (INF)	1 (INF)	–
	CT-P13 (Remsima™; Inflectra™; Celltrion, South Korea /Hospira, USA) [56, 58–61, 68–70, 73, 76, 77, 82, 85, 86, 208–230]	2 (INF)	1 (INF)	1 (INF)	2 (INF) 1 (INF)[c] [231]	1 (ADA, ETN, INF, RTX) 2 (INF)[c] [232, 233]
	PF-06438179 (Pfizer, USA) [81, 234–239]	1 (INF)	2 (INF)	1 (INF)	1 (INF)[c] [240]	–
	SB2 (Flixabi®; Samsung Bioepis, South Korea) [52, 78, 241]	–	–	1 (INF)	1 (INF)	–

Table 3 continued

Biologic originator generic name	Biosimilar or IC (alternative name[a], company)	Comparator studies				
		Analytical studies (comparator)	Nonclinical studies (comparator)	PK/safety trials in healthy subjects or patients (sample size, comparator)[b]	Comparative safety/efficacy studies (sample size, comparator)	Post-marketing/ observational studies (sample size, comparator)
Inflammatory disease fusion proteins						
Etanercept	AVG01 (Avent™; Avesthagen, India) [84]	1 (ETN)	1 (ETN)	–	–	–
	CHS-0214 (Coherus Biosciences, Inc., USA/Daiicho Sankyo, Japan | Baxalta, USA)	–	–	–	3 (ETN)[c] [242–244]	–
	ENIA11 (TuNEX®; Mycenax Biotech/TSH Biopharm Corp, Taiwan) [54, 245]	–	–	1 (ETN)	1 (DMARDs)[c] [246]	–
	GP2015 (Sandoz, Switzerland) [247, 248]	–	1 (ETN)	–	1 (ETN)[c] [249]	–
	HD203 (Hanwha Chemical, South Korea/ Merck, USA) [57, 64, 250]	–	–	1 (ETN) 2 (ETN)[c] [251, 252]	1 (ETN)	–
	LBEC0101 (LG Life Sciences, South Korea) [69]	–	–	1 (ETN) 1 (ETN)[c] [253]	1 (ETN)[c] [254]	–
	SB4 (Benepali®; Samsung Bioepis, South Korea) [53, 63, 74]	–	–	1 (ETN)	1 (ETN)	–
	IC of etanercept					
	Infinitam® (IC) (Probiomed, Mexico) [66, 75]	–	–	1 (ETN)	–	1 (Yisaipu®, Kikuzubam®)
	Yisaipu® (IC) (Etanar®; Shanghai CP Guojian Pharmaceutical, China) [63, 66, 79, 87]	–	–	–	–	3 (Kikuzubam®, Infinitam®, ADA, INF, ETN, TCZ)
Other disease area mAbs						
Abciximab	Clotinab (ISU ABXIS) [88]			1 (ABX)		
Omalizumab	CMAB007 (National Engineering Research Center of Antibody Medicine, China) [89]			1 (OMA)		

Corresponding indications for study counts for rituximab are labelled with 'Onc' for oncology and 'Inflamm' for chronic inflammatory disease

ABX abciximab, *ADA* adalimumab, *BEV* bevacizumab, *DMARDs* disease-modifying antirheumatic drugs, *ETN* etanercept, *IC* intended copy, *INF* infliximab, *mAbs* monoclonal antibodies, *OMA* omalizumab, *PK* pharmacokinetic, *RAN* ranibizumab, *RTX* rituximab, *TCZ* tocilizumab, *TRA* trastuzumab

[a] Alternative names for biosimilars are provided where applicable

[b] Refers to PK/safety studies in either healthy subjects or patients where PK/safety was listed as the primary outcome measure. Efficacy endpoints were also reported in some studies as secondary outcome measures

[c] Refers to unpublished studies identified from ClinicalTrials.gov search

[d] Comparative safety/efficacy study of BCD-021 vs. lucentis (ranibizumab)/bevacizumab for age-related macular degeneration

[e] Published protocols for comparative safety/efficacy studies on PF-05280014 (trastuzumab) have been reported in the literature

The etanercept biosimilars ENIA11, HD203, LBEC0101, and SB4 all had published comparative PK/safety data. Comparative efficacy/safety studies were reported as still active or completed for CHS-0214 (Coherus Biosciences/Daiicho Sankyo/Baxalta), ENIA11 (vs. disease-modifying anti-rheumatic diseases [DMARDs]), GP2015, and LBEC0101.

Among infliximab biosimilars, comparative efficacy/safety trials were reported as ongoing for CT-P13 and PF-06438179. A comparative PK/safety trial of BCD-055 (Biocad) in ankylosing spondylitis was also identified in the search of ClinicalTrials.gov. At the time of the review, no published data had been retrieved for BCD-055.

Unsurprisingly, at the analysis cut-off, approved biosimilar CT-P13 had the greatest number of published studies (one clinical PK/safety, two clinical safety/efficacy), with a further study (clinical safety/efficacy) listed in ClinicalTrials.gov but not published at the time of review.

The findings additionally demonstrate a significant body of past or ongoing clinical trial activity for biosimilars in development across both oncology and chronic inflammatory disease areas, particularly for trastuzumab biosimilars CT-P6 and PF-05280014 and for adalimumab biosimilars ABP 501 and PF-06410293, respectively.

A detailed evaluation of the findings across all of these studies will be presented as part of a separate analysis of biosimilars for the treatment of chronic inflammatory diseases and cancer (Jacobs et al. 2016b [submitted]; Jacobs et al. 2016c [manuscript in preparation]).

3.8 Intended Copies

Empirical data on marketed intended copies of etanercept (Yisaipu® [Etanar®; Shanghai CP Guojian Pharmaceutical], Infinitam® [Probiomed]) and rituximab (Kikuzubam® [Probiomed], Reditux™ [Dr. Reddy's Laboratories]) were identified in the published literature (Table 1; Fig. 5; ESM Table S3).

Yisaipu® was reported in four studies described in four empirical publications (Fig. 5; ESM Table S3). Infinitam® was investigated in two studies reported in two publications (Fig. 5; ESM Table S3).

Kikuzubam® was reported in a single study in oncology (one publication) and in two independent studies (two publications) in chronic inflammatory disease (Table 1; ESM Table S3). Reditux™ was referenced in eight oncology studies (in ten publications) and seven inflammatory disease studies (in eight publications) (Table 1; ESM Table S3).

In summary, most comparative studies reported for intended copies were either analytical/nonclinical or observational in nature, with only a single RCT identified for Infinitam® (Table 3). Suffice to say, significant evidence gaps remain with respect to the efficacy and safety of intended copies for the treatment of cancer and chronic inflammatory diseases based on the published information currently available.

3.9 Risk of Bias Assessments for Empirical Studies

3.9.1 Oncology Studies

Two RCTs [34, 35] were evaluated using the NICE STA template and Jadad scoring tool (ESM Fig. S1). Both studies were considered excellent quality. Two observational studies [36, 37] were assessed using the Downs and Black scoring tool (ESM Fig. S2). Both were considered good quality. Since abstracts generally provide limited information on study methodologies and outcomes, the Downs and Black instrument was adapted to assess the quality of the 11 identified abstracts for original studies [38–48]. The total score was fair quality (3–4) for one study [39], good quality (5–8) for two studies [41, 46], and excellent quality (9–12) for eight studies [38, 40, 42–45, 47, 48] (ESM Fig. S3). The majority of studies published as conference abstracts were of good or excellent quality (90.9%). Three animal studies were assessed using SYRCLE's risk of bias tool [49–51] (ESM Fig. S4) and found to be of moderate quality. Nonclinical abstract publications and cell-based or analytical studies were not assessed for risk of bias, as validated risk of bias assessment tools for these types of studies and publications were unavailable at the time of analysis.

3.9.2 Chronic Inflammatory Disease Studies

Seven RCTs were assessed using the NICE STA manufacturer's template and Jadad scoring tool [52–58], and all were considered excellent quality (ESM Fig. S1). Four observational studies were assessed using the Downs and Black scoring tool [59–62] and considered to be of fair quality (ESM Fig. S2). The modified Downs and Black instrument was used to assess the quality of the 22 identified abstracts for original studies [39, 63–83], with scores of fair quality (3–4) for four studies [39, 66, 70, 76], good quality (5–8) for seven studies [63, 65, 67, 68, 73, 77, 79], and excellent quality (9–12) for 11 studies [64, 69, 71, 72, 74, 75, 78, 80–83] (ESM Fig. S3). The majority of studies published as conference abstracts were of good or excellent quality (81.8%). Three animal studies were assessed using SYRCLE's risk of bias tools [49, 51, 84] and found to be of moderate quality (ESM Fig. S4). Three health economic studies were assessed using Drummond's checklist for assessing economic evaluations [85–87] and considered good quality (ESM

Fig. S5). As with studies identified for oncology, nonclinical abstract publications and cell-based or analytical studies were not assessed for risk of bias.

3.9.3 Other Disease Area Studies

Two RCTs were assessed using the NICE STA manufacturer's template and Jadad scoring tool [88, 89]; both were considered good quality (ESM Fig. S1).

3.10 Weight and Breadth of Evidence for Biosimilarity

Regulatory authorities (e.g., FDA) base their final determination of biosimilarity between the proposed biosimilar and the originator on the totality of the data submitted by the biosimilar manufacturer for consideration. The authors of this review did not attempt to assess the agents against the criteria used by regulatory authorities, but instead based their analysis on the totality of evidence in the public domain with biosimilarity determined on the basis of investigators' conclusions.

In this analysis, the total number of studied variables (from identified analytical/nonclinical studies) and total reported patient numbers (from clinical studies) were extracted and then mapped (Fig. 6a, b) against the 'degree of similarity' (as observed by the study investigator). This was to demonstrate the depth of the research programs and the relative weight of supporting evidence available for each agent. The number of studied variables and the number of patients enrolled was not a factor in the determination of biosimilarity.

Molecules were mapped on a grid to illustrate relative positioning. For the x-axis, the degree of similarity was ranked using the investigator assessment of individual clinical (Fig. 6a), analytical and nonclinical variables (Fig. 6b). As an example, for PF-05280014, a proposed biosimilar for trastuzumab, analytical and nonclinical data were reported by investigators to be either similar or identical (i.e., superimposable) across all variables assessed. The positioning of PF-05280014 on the grid reflects this. In contrast, Flores-Ortiz et al. [90], noted the mass spectrometry and cation exchange data were heterogeneous for the intended copy Kikuzubam® in comparison with its rituximab originator, while other variables (differential scanning calorimetry analysis, peptide mapping, glycan quantification, etc.) were reported to be the same. Thus, the positioning of Kikuzubam® was determined to be both dissimilar and identical across selected variables. Kikuzubam® is the only molecule in this review that exhibited such heterogeneity.

Based on clinical reports (Fig. 6a), development candidates FTMB, RTXM83, and HD203 were reported to be similar to their originators. Intended copy Yisaipu® was also considered by investigators to be similar. On the basis of clinical studies, investigators found all other development candidates and intended copies to be highly similar.

Investigators deemed a few molecules not to have met biosimilarity criteria, at the time of reporting. Based on preclinical reports (Fig. 6b), development candidate ABP 501 was determined to be dissimilar with respect to carbohydrate structure. Intended copies Reditux™ and Kikuzubam® (refer to Fig. 6 footnote) were also reported to be dissimilar on the basis of a number of analytical and nonclinical variables.

The body of evidence for biosimilar use in human subjects from clinical studies is growing, with a high proportion reporting patient samples of more than 100. Seven proposed biosimilars have published clinical data on fewer than 100 human subjects (namely BCD-020, BCD-022, LBEC0101, SAIT101, ENIA11, RTXM83, and clotinab), while CT-P13 and PF-05280014 have published studies involving more than 1000 human subjects (which for PF-05280014, includes patients from two published study protocols, with an estimated pooled enrollment of $N = 910$) (Fig. 6a).

When considering the breadth of data available for preclinical studies for named biosimilars (based on number of variables reported from structural, functional, and nonclinical studies), the amount of reported information available across studies was inconsistent (Fig. 6b). More investigated variables for analytical and nonclinical biosimilarity (ranging from 29 to 54) were published for PF-05280586, PF-05280014, and GP2013. The remaining agents published an average of only five variables across their preclinical programs, as reported in the literature. Although the investigators concluded that the majority of molecules exhibited biosimilarity to their originator, it is worth noting that comparative data were not provided for all attributes studied.

3.11 Non-Empirical Publication Classifications for Originators or Named Biosimilars

A significant number of non-empirical biosimilar publications on topics concerning 'development and production', 'market analysis and uptake', 'regulation and safety', or general 'overview' review articles referenced originators without citing named biosimilars (Table 4). The majority of non-empirical publications cited originators for chronic inflammatory diseases without reference to named biosimilars (Table 4).

Publications focusing on development and production were mainly concerned with biosimilar development, manufacturing or supply processes, or quality and analytical methods. Publications categorized under 'market

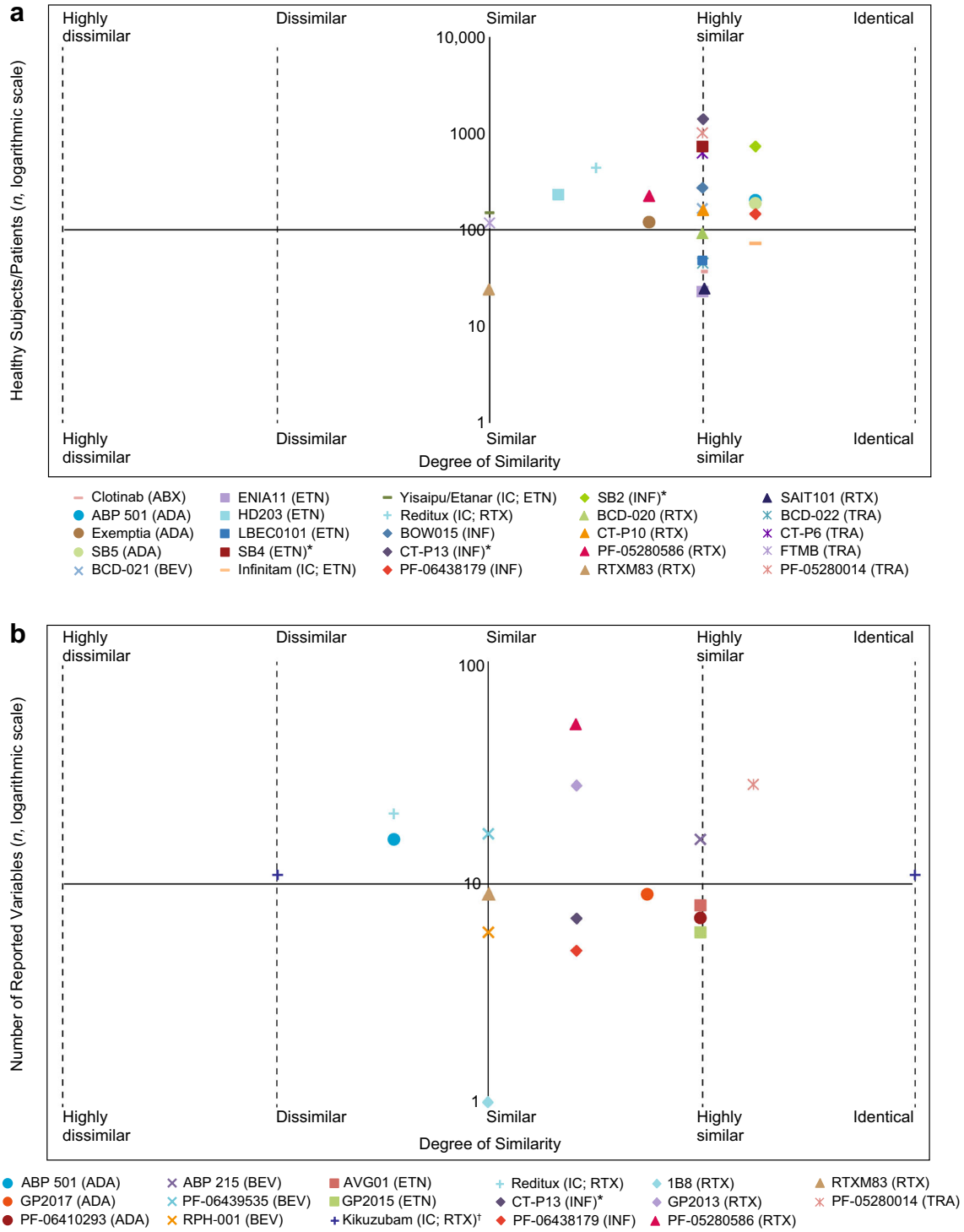

Fig. 6 Biosimilarity and **a** total treated patients for named biosimilars in clinical trials, **b** breadth of data for named biosimilars in analytical and nonclinical studies. 'Degree of similarity' for biosimilars and intended copies is inferred from the totality of evidence provided from all available 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 not uniformly reported. *Agents that have already met the European Medicines Agency and/or US FDA requirements and have been approved as biosimilars. †Based on author interpretation of study data, Kikuzubam® purportedly exhibits some highly dissimilar and some identical physicochemical characteristics compared with the originator. PF-05280014 had two published study protocols at the time of analysis with a combined enrollment of $N = 910$ and a published study in 105 healthy subjects. *ABX* abciximab, *ADA* adalimumab, *BEV* bevacizumab, *ETN* etanercept, *IC* intended copy, *INF* infliximab, *RTX* rituximab, *TRA* trastuzumab

Table 4 Originator monoclonal antibodies or fusion proteins and corresponding named biosimilar agents classified by non-empirical publication type[a]

Biologic originator	Biosimilar or IC (name[b], company)	Reference counts for non-empirical publications[c]				
		Development and production	Market analysis and uptake	Overview	Regulation and safety	Other topics
Oncology mAbs						
Bevacizumab	Biosimilars without unique identifiers	2 (biosimilar development [255]; manufacturing or supply [256])	–	1 therapy area overview [257]	–	–
	No non-empirical publications were identified for bevacizumab biosimilars ABP 215, BCD-021, PF-06439535, or RPH-001					
Cetuximab	Biosimilars without unique identifiers	2 (quality or analysis [258]; manufacturing or supply [259])	–	–	–	–
Trastuzumab	Biosimilars without unique identifiers	4 (biosimilar development [260]; 2 manufacturing or supply [256, 259]; quality or analytical methods [258])	1 economics or pricing [261]	2 (therapy area overview [257]; general [262])	1 regulatory or policy [263]	–
	No non-empirical publications were identified for trastuzumab biosimilars BCD-022, CT-PC, FTMB/ABP 980, or PF-05280014					
Oncology/inflammatory disease mAbs						
Rituximab	*GP2013* (Sandoz, Switzerland)	–	–	1 systematic review in inflamm [264]	–	–
	Biosimilars without unique identifiers	3 (biosimilar development [265]; 2 manufacturing or supply [256, 259])	3 (2 guidelines [266, 267]; 1 terminology or naming [268])	9 (7 therapy area overview [257, 264, 269–273]; 2 general [262, 274])	2 regulatory or policy [275, 276]	–
	No non-empirical publications were identified for rituximab biosimilars CT-P10, PF-05280586, RTXM83, or SAIT101, or for ICs Kikuzubam® or Reditux™					
Chronic inflammatory disease mAbs						
Abciximab	Biosimilars without unique identifiers	–	–	–	–	–
Adalimumab	Biosimilars without unique identifiers	3 (2 quality or analytical methods [277, 278]; manufacturing or supply [279])	4 (3 guidelines [266, 267, 280]; 1 terminology/naming [268])	4 (2 systematic review [272, 281]; 2 therapy area overview [282, 283])	2 (regulatory or policy [284]; safety or pharmacovigilance [285])	–
	No non-empirical publications were identified for adalimumab biosimilars ABP 501, GP2017, PF-06410293, or SB5					
Certolizumab pegol	Biosimilars without unique identifiers	1 quality or analysis methods [278]	3 (2 guidelines [266, 267]; 1 terminology or naming [268])	3 (systematic review [272]; 2 therapy area overview [282, 283])	–	–
Clazakizumab	Biosimilars without unique identifiers	–	1 terminology or naming [268]	–	–	–
Golimumab	Biosimilars without unique identifiers	1 quality or analysis methods [278]	3 (2 guidelines [266, 267]; 1 terminology or naming [268])	3 (systematic review [272]; 2 therapy area overview [282, 283])	–	–

Table 4 continued

Biologic originator	Biosimilar or IC (name[b], company)	Reference counts for non-empirical publications[c]				
		Development and production	Market analysis and uptake	Overview	Regulation and safety	Other topics
Infliximab	*CT-P13* (Remsima™; Inflectra™; Celltrion, South Korea / Hospira, USA)	2 biosimilar development [286, 287]	2 (substitution or interchangeability [288]; guidelines [289])	22 (2 systematic review [264, 271]; 17 therapy area overview [290–306]; 2 general [307, 308]; geographical [309])	12 (11 regulatory or policy [310–320]; safety or pharmacovigilance [321])	–
	Biosimilars without unique identifiers	4 (2 quality or analytical methods [277, 278]; 2 manufacturing or supply [279, 322])	6 (5 guidelines [266, 267, 280, 323, 324]; 1 terminology or naming [268])	11 (2 systematic review [272, 281]; 6 therapy area overview [282, 283, 325–328]; 2 general [262, 329]; geographical [330])	5 (3 regulatory or policy [263, 276, 331]; 2 safety or pharmacovigilance [285, 332])	–
	No non-empirical publications were identified for infliximab biosimilars BOW015, PF-06438179, or SB2 (Flixabi®)					
Ixekizumab	Biosimilars without unique identifiers	–	1 terminology or naming [268]	–	–	–
Sarilumab	Biosimilars without unique identifiers	–	1 terminology or naming [268]	–	–	–
Secukinumab	Biosimilars without unique identifiers	–	1 terminology or naming [268]	–	–	–
Sirukumab	Biosimilars without unique identifiers	–	1 terminology or naming [268]	–	–	–
Tocilizumab	Biosimilars without unique identifiers	–	3 (2 guidelines [266, 267]; 1 terminology or naming [268])	1 systematic review [272]	–	–
Ustekinumab	Biosimilars without unique identifiers	–	–	1 systematic review [281]	–	–
Chronic inflammatory disease fusion proteins/interleukin-1 receptor antagonists						
Abatacept	Biosimilars without unique identifiers	–	3 (2 guidelines [266, 267]; 1 terminology or naming [268])	2 (systematic review [272]; therapy area overview [269])	1 safety or pharmacovigilance [285]	–
Anakinra	Biosimilars without unique identifiers	–	1 terminology or naming [268]	1 systematic review [272]	1 safety or pharmacovigilance [285]	–

Table 4 continued

Biologic originator	Biosimilar or IC (name[b], company)	Reference counts for non-empirical publications[c]				
		Development and production	Market analysis and uptake	Overview	Regulation and safety	Other topics
Etanercept	*ENIA11* (TuNEX®; Mycenax Biotech/ TSH Biopharm Corp, Taiwan)	–	–	1 systematic review [264]	–	–
	HD203 (Hanwha Chemical, South Korea/Merck, USA)	–	–	1 systematic review [264]	–	–
	Yisaipu® (IC) (Etanar®; Shanghai CP Guojian Pharmaceutical, China)	–	–	1 therapy area overview [333]	–	–
	Biosimilars without unique identifiers	1 Quality or analysis methods [278]	3 (2 guidelines [266, 267]; 1 terminology or naming [268])	5 (2 systematic review [272, 281]; 2 therapy area overview [283, 334]; general [100])	3 (2 regulatory or policy [275, 284]; safety or pharmacovigilance [285])	–
	No non-empirical publications were identified for etanercept biosimilars AVG01, GP2015, LBEC0101, or SB4 (Benepali®), or for IC Infinitam®					
Other disease area mAbs						
Ranibizumab[d]	PF582 (Pfenex, USA/ Hospira, USA)	–	–	1 therapy area overview [335]	–	–

IC intended copy, *Inflamm* chronic inflammatory diseases, *mAbs* monoclonal antibodies

[a] Bold text indicates originators where named biosimilars have been identified. Italic formatting indicates biosimilars are included in at least one reference naming multiple biosimilars. Publications that did not disclose unique names of biosimilars were categorized as 'Biosimilars without unique identifiers'

[b] Alternative names for biosimilars are provided in parentheses where applicable

[c] Reference counts correspond to the number of identified publications

[d] Ranibizumab is indicated for eye conditions (ophthalmology)

analysis or uptake' were mostly guidelines or reviews on terminology and naming. The majority of non-empirical overview publications were therapy area review articles or systematic literature reviews. Publications on regulation and safety aspects (either regulatory/policy or safety/pharmacovigilance) were mostly identified for etanercept and infliximab without reference to any named biosimilars. The majority of non-empirical publications naming biosimilars referenced CT-P13, which also appeared most frequently in empirical publications. Other proposed biosimilars featuring in a single non-empirical publication included ENIA11, HD203, PF582, and GP2013.

3.12 Publishing Trends on Biosimilars

3.12.1 Journals

A total of 110 unique journal publications publishing relevant material on mAb and fusion protein biosimilars were identified between 2002 and September 2015. The journal *mAbs* published the most articles on biosimilars, with 19 different articles since 2008, five of which were published in 2015 (ESM Table S4). In September 2011, the journal *Biologicals* published seven articles in a special issue entitled 'Evaluation of Similar Biotherapeutic products: Scientific and Regulatory Challenges' [91], which focused on the key global health authorities in the evolving regulatory considerations and approval pathways for biosimilars. This issue accounted for nearly half of the sharp rise in publications in a single year, to a total of 19. The number of publications dropped slightly in 2012 ($n = 15$), before rising again to 17 and 18 publications in 2013 and 2014, respectively. In 2014, the most articles were published by the journals *mAbs* ($n = 4$), *Annals of Rheumatic Diseases* ($n = 3$), *Bioanalysis* ($n = 3$), and *BioDrugs* ($n = 3$). Between January and September 2015, nine publications relevant to the topic of mAb or fusion protein biosimilars were identified, the majority ($n = 5$) in *mAbs*.

3.12.2 Congresses

Proceedings from 17 conferences were searched and 192 congress abstracts publishing on biosimilar-relevant topics were identified between 2009 and August 2015.

The top three identified congresses (in order of most abstracts identified between 2009 and August 2015) were European League Against Rheumatism (EULAR) ($n = 48$), International Society for Pharmacoeconomics and Outcomes Research (ISPOR) ($n = 33$), and American Association of Pharmaceutical Scientists (AAPS) National Biotechnology Conference ($n = 24$) (ESM Table S5). These congresses reflect the diversity of venues at which biosimilars have been presented: disease specific (immunology), outcomes research and payer-focused, and manufacturing. Since 2012, the number of relevant abstract publications has steadily risen from 14 in 2012 to 73 in 2014. In 2015 (up to the analysis cut-off date), 59 abstracts were published on the topic of biosimilars, with the majority (22 abstracts) appearing at the annual EULAR congress and 11 at ECCO.

4 Discussion

Although an increasing number and broader range of biosimilars are under development, and recently, the world's first mAb biosimilar was approved under the rigors of the approval process of both the EMA and the FDA, many clinicians still exercise caution over the use of biosimilar products [92, 93]. Findings from the 2015 Coalition of State Rheumatology Organizations (CSRO) survey suggested that, at the time, there were shared concerns over the biosimilar approval process and unaddressed critical issues, including the requirement for clearer guidance from the FDA on interchangeability and naming, which were considered important to address before new biosimilar products arrived onto the market [93]. In a US Alliance for Safe Biologic Medicines (ASBM) survey conducted in 2015 [94, 95], 79% of physicians considered that a definition of 'biosimilarity' was important/very important for label inclusion. Over 80% of respondents felt it was important to include analytical and clinical data to demonstrate biosimilarity to the reference product; 79% regarded the availability of post-marketing data in the biosimilar label as important. As yet, there is no international harmonized approach to the labeling of biosimilars. The FDA has released draft guidance on labeling of biosimilar products [84, 96]. The draft guidance includes the addition of a 'biosimilarity statement' that is intended to describe the biosimilar's relationship with the reference product [17, 96]. While biosimilar product-specific data are regarded as "necessary to inform safe and effective use of the product," the FDA's stance on inclusion of comparative data in the label is that this may cause confusion among healthcare providers and is not considered particularly "relevant to a health care provider's prescribing considerations" [17]. The draft guidance is currently issued for comment only, and the FDA will seek to incorporate feedback from the public and industry before releasing the finalized guidance. Under EMA guidelines, clinical and preclinical data of the biosimilar are included in the European Public Assessment Report (EPAR), with no requirement to include comparative data on the biosimilar product in the label. Furthermore, there is no citation of the EPAR data in the label. Physicians may, therefore, not be aware of how to access these data and incorrectly assume

that all information on the biosimilar product is included in the label [97]. Findings from a European survey in seven countries revealed that 90.5% of physicians use the label frequently or occasionally as an information source and 87.2% felt that a clear statement on the origin of the data would be helpful [98]. Efficacy and safety considerations notwithstanding, clinicians are becoming increasingly receptive to prescribing biosimilars [99]. Certainly, further clarity around biosimilar labeling will guide clinicians toward making more informed prescribing decisions, which may encourage the effective and appropriate use of these agents in daily clinical practice.

During the course of this research it became evident that a range of umbrella terms for biosimilarity has been adopted to describe different attributes of molecules under development, and in some cases applied to products that have not undergone rigorous similarity exercises, as required by the regulatory bodies (meaning they would be more correctly named 'intended copies', or 'non-comparable biologics') [1, 22, 23]. Thus, the published data available on these products are insufficient to provide robust evidence on their structural/functional similarity and clinical efficacy and safety compared with the originator product [24].

With this in mind, increased efforts should be made to educate healthcare providers and other key stakeholders responsible for the introduction and assimilation of biosimilars into healthcare practice on the major distinction not only between biosimilars of reference biologics and generics of small molecules but also between biosimilars and intended copies or biobetters. As an illustration, across several emerging markets (including Mexico, Columbia, and India), intended copies of biologics are marketed as 'biosimilars' without any published analytical similarity data or robust clinical trials or based on evidence from potentially flawed studies [1, 97, 100, 101]. Noteworthy adverse events (grade 3/4) following administration of intended copies of etanercept (Yisaipu® or Infinitam®) and rituximab (Kikuzubam®) have been reported in Mexico and Columbia [66] along with claims of therapeutic failure [1], which further serves to reinforce the importance of maintaining a clear differentiation between these products and biosimilars approved under the scientific and clinical rigors of similarity assessment, as outlined by regulatory agencies, to ensure the biosimilar drug efficacy and safety are equivalent to those of the originator. Approval of intended copies with limited or non-comparable data may not only jeopardize patient safety but also create potential confusion amongst healthcare stakeholders, especially as these products co-exist on the market with biosimilars while not conforming to the rigorous regulatory standards set by the World Health Organization (WHO) [97] and leading regulatory health agencies such as the EMA and FDA. A further distinction must be made between biosimilars and 'next-generation biologics' or 'biobetters', which seek to outperform the originator molecules. Since biobetters have been structurally engineered to improve their clinical performance (including improved potency, extended half-life, or reduced adverse events) [1], they are not biosimilars and they must be differentiated on account of structural differences and altered clinical behavior [1, 22, 102].

Although immunogenicity is a key safety concern for any biologic (i.e., for both originators and biosimilars), the potential for it to arise during biosimilar production as a result of small or undetectable differences between the originator product and the biosimilar [103] presents a unique challenge for biosimilar developers and regulatory agencies. This is of particular importance for mAb and fusion protein biosimilars because of their large molecular size, complex protein structure, and post-translational modifications [103].

At the time of marketing authorization or approval application, pharmacovigilance and risk-management activities for the post-authorization phase are recommended by the FDA, EMA, and in accordance with the WHO regulations to provide additional data on the safety and efficacy of the biosimilar [104–108]; however, only EMA guidelines specifically address immunogenicity during post-approval surveillance monitoring. Furthermore, as is the case for all medicines, side effects relating to use in daily clinical practice, including off-label use or drug interactions, will only be identified if biosimilar products are continually traced and monitored in post-marketing studies [109, 110]. During the course of our research into biosimilars and intended copies, the majority of clinical studies reported only limited data on immunogenicity versus the originator.

Extrapolation of indications is particularly important for mAb or fusion protein biosimilar products whose reference agents are licensed for multiple indications [97, 111]. Both the FDA and the EMA permit the extrapolation of biosimilars [97], based on the totality of evidence provided from clinical and nonclinical data, as well as taking into consideration the proposed mechanism of action of the product [111, 112]. Thus, biosimilar manufacturers need only supply a sufficient degree of evidence to demonstrate biosimilarity, without any requirement to provide clinical trial data for all indications [13, 97, 104]. Indication extrapolation remains an area of uncertainty, with regulatory decisions made on a case-by-case basis, and no 'one-size-fits-all' approach.

As identified in this review, rituximab has a large number of proposed biosimilars under development, both for chronic inflammatory disease and oncology indications. In oncology, biosimilars for trastuzumab, followed by

bevacizumab, are leading the way; in chronic inflammatory disease, etanercept and infliximab have the most biosimilars as well as the largest volume of published data, particularly for Celltrion's EMA- and FDA-approved biosimilar CT-P13. Almost without exception, studies we reviewed focused on mainly RA (for chronic inflammatory disease), non-squamous non-small-cell lung cancer, non-Hodgkin's lymphoma, and HER2-positive breast cancer (for oncology). At the time of review, no published data for biosimilars in chronic inflammatory diseases were available for psoriasis, psoriatic arthritis, juvenile idiopathic arthritis, Crohn's disease/ulcerative colitis (with the exception of CT-P13), or ankylosing spondylitis (excluding CT-P13). In oncology, among biosimilars of bevacizumab, no published data were available for colorectal cancer, cervical cancer, HER2-negative breast cancer, renal cell carcinoma, or recurrent glioblastoma multiforme. Within oncology indications for rituximab biosimilars, no published data were retrieved for chronic lymphocytic leukemia. Development in disease areas outside of oncology and chronic inflammatory disease was less active; only three biosimilars were identified with published data and only two molecules with published empirical data.

Until recently, information comparing biosimilars with their originator product has been limited outside of clinical trials required for biosimilar approval; even less information exists comparing biosimilars of the same reference molecule. In this review, the majority of studies compared biosimilars with their originators. However, due to the widespread use of biologic disease-modifying antirheumatic drug therapy (and availability of intended copies on the market), along with the development and approval of an increasing number of biosimilar agents for chronic inflammatory conditions, research efforts are now turning towards comparisons with products of a different biological class. Assuming all data are made public, this may be of direct benefit to healthcare stakeholders and patients to improve their understanding of how biosimilars compare not only to their reference molecule but also to biologic originators and approved or proposed biosimilars.

The growing number of marketed biosimilar agents available, and increased volume of published clinical data, presents future opportunities to develop post-marketing comparative observational analyses or indirect treatment comparisons, which may also be of benefit to regulatory and healthcare stakeholders to better inform decision making. Despite the existence of a relatively significant amount of analytical, nonclinical, and clinical data, as identified in this study, the majority are published as abstracts in conference proceedings. Further studies published in full text are required to reliably communicate biosimilarity between originators and biosimilars, and the completion of ongoing clinical trials in a variety of biosimilar candidates is expected soon.

This study has provided information on the range of mAb and fusion protein biosimilars available or in various stages of development and the available scientific data comparing them with their originator. CT-P13 and PF-05280014 had the greatest evidence of similarity to their originators on the basis of results from clinical studies involving larger numbers of patients compared with other named biosimilars for which the body of evidence is still growing.

Strong evidence of similarity provided from analytical, PK, and nonclinical studies is as essential as clinical evidence in establishing the safety and efficacy of a biosimilar and in meeting regulatory standards and requirements set by the EMA and FDA for approval [104, 108]. Irrespective of therapy area, this analysis also revealed that a significant number of candidate products had no published evidence (to date) of structural and functional comparability with their originators from preclinical studies. This is true among biosimilars of bevacizumab, trastuzumab, adalimumab, infliximab, rituximab, and etanercept. Not only are these assessments important from a regulatory standpoint for approval, but release of these data in the public domain is also necessary for gaining acceptance among prescribers, payers, and patients and to ensure sustainable market uptake.

Several limitations of the study should be noted. Although the search strategy was designed to capture a relevant set of records, the database searches may not have captured all terms related to therapy area or mAbs or fusion protein biosimilars. Another limitation was that only proceedings from 17 conferences were searched, and although consideration was given to identifying the most likely venues for dissemination of relevant biosimilar research, data may be available from other conference proceedings not considered in this analysis. Owing to a lack of differentiation in the published literature between biosimilars and intended copies or biobetters, molecules may have been labeled as biosimilars without rigorous data to support biosimilarity, which could not be verified from this analysis. Several publications were retrieved with published data on biosimilar molecules and referenced without a distinguishable name. However, only data from publications disclosing names of biosimilars were extracted. The final search result from each database was also limited to reference records published in the English language. The search for ongoing, planned, or complete clinical trials was conducted using the ClinicalTrials.gov results database; no other clinical trial registries were used in this analysis. Therefore, it is possible that some trials (particularly those being conducted outside of the USA) may not have been captured. The registration and dissemination of trial data

(including updates to protocols) on the ClinicalTrials.gov site is at the full discretion of the study investigator or sponsor and it is possible that some of the captured trial information may be either out of date or inaccurate.

In this analysis, all studies were included regardless of the risk of bias scores. For simplicity, conclusions on biosimilarity were collectively drawn from a variety of clinical study types (e.g., RCTs and observational [prospective or retrospective] studies), without accounting for any variation in the overall quality of evidence provided by each study type. The determination of biosimilarity was based on the specific term(s) chosen by the investigators in formulating their conclusions. Therefore the determination of, for example, 'similar' versus 'highly similar' was based on the scale of reference used by each investigator. Country of origin analyses were also not conducted on the retrieved clinical data. This may present some information bias, owing to varying standards between countries in reporting trial data. In addition, biosimilars may have been evaluated in different patient sub-populations (e.g., DMARD-naïve vs. DMARD-IR [inadequate response] patients); therefore, it may not be possible to draw adequate conclusions on biosimilarity. Note also that when this analysis was conducted, limited data were available for analytical studies, and overall there was an inconsistency in the data reported across studies of the same designated category, limiting the extent to which conclusions could be drawn. The determination of 'proposed biosimilar' versus 'intended copy' is limited in this analysis by uncertainty surrounding the intentions of manufacturers with development candidates. Therefore, the assumption that all development stage molecules are 'proposed biosimilars' may not be accurate. Lastly, as this review represents a cross-sectional analysis of available published evidence over a defined period of time, the authors acknowledge the molecules reviewed are at different stages of development, and thus cannot be compared like-for-like. Since completion of this review, several biosimilars have new published data across study types and several have transitioned into their next stages of development.

Furthermore, new biosimilars in development (which were not captured in this analysis) have since entered the arena. For example, for chronic inflammatory diseases, comparative safety/efficacy trials have since been listed in the ClinicalTrials.gov registry for M923 (adalimumab; Baxalta; psoriasis, RA) and MYL-1401A (adalimumab; Mylan; psoriasis, psoriatic arthritis). In oncology, comparative safety/efficacy trials were recently documented for ABP798 (rituximab; Amgen; non-Hodgkin's lymphoma) and for HLX01 (rituximab; Shanghai Henlius Biotech; CD20 + diffuse large B-cell lymphoma). In other disease areas, a comparative safety/efficacy trial was identified in the update search for FYB201 (ranibizumab; Bioeq GmbH; age-related macular degeneration). It is important therefore, to acknowledge that this systematic review provides only a cross-sectional analysis of biosimilar development activities at the time the analysis was undertaken. The authors may consider performing an update on this systematic review in the future.

5 Conclusions

The launch of biosimilars is expected to provide cost savings and offers the potential to expand patient access to important biologic medicines. At the time of writing, two mAb biosimilars and one fusion protein biosimilar were approved for use in the EU or USA and two further molecules had received recommendations for approval in the USA. However, recent surveys have revealed that some confusion remains surrounding regulatory requirements, labeling, and naming conventions for biosimilars. Additional knowledge gaps also exist for many clinicians and other stakeholders around indication extrapolation.

With this in mind, this systematic review collated and synthesized publically available information from the scientific literature and conference proceedings on biosimilars on the market and in development. The analysis highlighted progress on many fronts to harmonize and clarify regulations and demonstrated the growing evidence base available for biosimilar molecules. While the authors' findings in this regard are reassuring, the analysis also exposed significant differences in the extent of published evidence between molecules at preclinical, clinical, and post-marketing stages of development, something that is particularly true for intended copies.

Concerted efforts by manufacturers and investigators to disseminate available data and address gaps in the literature together with further education and awareness among all key stakeholders will be required to instill confidence and trust in the safety and efficacy of biosimilar medicines, thereby helping to support their use for the benefit of patients.

An update of this SLR in the future may serve to consolidate more recent data and further highlight remaining gaps in the published literature.

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Compliance with Ethical Standards

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