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An update on the adalimumab biosimilar landscape following the approval of the first high-concentration biosimilar

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Biosimilars can reduce healthcare costs and expand patient access to biologic therapies. Currently, eight adalimumab biosimilars have received regulatory approval from the European Medicines Agency and/or the US FDA. Following recent European Medicines Agency approval of the first high-concentration adalimumab biosimilar, CT-P17, this review provides a contemporary update on adalimumab biosimilars currently licensed in Europe and the US. The totality of evidence from each clinical development program is summarized, and characteristics of each formulation and/or device that potentially affect the convenience of treatment for patients are discussed. Future perspectives are considered, including the potential impact of the US FDA's first interchangeability designation for an adalimumab biosimilar, ahead of their entry into the US marketplace in 2023.

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Reference adalimumab (Humira®; AbbVie Inc., IL, US) is a fully humanised IgG1 monoclonal antibody that binds to soluble and transmembrane TNF- α with high affinity [1,2]. This precludes TNF- α from binding to cell surface receptors, reducing TNF- α receptor-mediated signalling processes involved in inflammatory responses [1,2]. Fc-mediated apoptosis may also contribute to adalimumab efficacy [2].

Following etanercept and infliximab, adalimumab was the third TNF- α inhibitor to receive regulatory approval in Europe and the US [1,3]. Adalimumab was licensed for the treatment of rheumatoid arthritis (RA) in 2002 in the US [4] and 2003 in Europe [5,6]. Subsequently, adalimumab has been granted regulatory approval for use in the widest range of indications of any TNF- α inhibitor [1], including juvenile idiopathic arthritis, ankylosing spondylitis, psoriatic arthritis, plaque psoriasis (PsO), hidradenitis suppurativa, Crohn's disease (CD), pediatric CD, ulcerative colitis (UC), pediatric UC, uveitis (UV) and pediatric UV [7,8]. The European Medicines Agency (EMA) has additionally approved adalimumab for the treatment of enthesitis-related arthritis, nonradiographic axial spondyloarthritis and pediatric PsO [7]. The original adalimumab formulation is available at a concentration of 50 mg/ml (in volumes of 10 mg/0.2 ml, 20 mg/0.4 ml and 40 mg/0.8 ml), in a citrate buffer [8]. However, in 2018, a high-concentration (100 mg/ml), citrate-free formulation of the reference product became available, which offers smaller injection volumes (10 mg/0.1 ml, 20 mg/0.2 ml, 40 mg/0.4 ml and 80 mg/0.8 ml) [8]. This formulation was shown to result in less injection-site pain and has significantly improved adherence and persistence [9,10].

Adalimumab is widely used; however, high prices and long-term costs of therapy with the reference product pose limitations [3], directing attention toward biosimilars. Biosimilars are biologics that are highly similar to an already

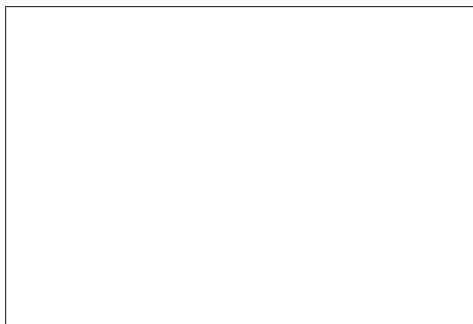


Figure 1. Adalimumab biosimilars licensed by the EMA and/or FDA [2,7,8,15,18,20–22,24–26,28–33,34–48]. Ticks indicate that products have the property listed, and crosses indicate that they do not. Dashes indicate that information could not be identified.

*Information is shown for the original formulation; †Licensed by the EMA; ‡Licensed by the FDA; §Withdrawn at the request of the marketing authorization holder; ¶Information shown is for the FDA followed by the EMA.

AS: Ankylosing spondylitis; CD: Crohn's disease; EMA: European Medicines Agency; ERA: Enthesitis-related arthritis; EU: European Union; G: Gauge; HS: Hidradenitis suppurativa; JIA: Juvenile idiopathic arthritis; N/A: Not applicable; nr-axSpA: Nonradiographic axial spondyloarthritis; PFP: Prefilled pen; PFS: Prefilled syringe; PsA: Psoriatic arthritis; PsO: Plaque psoriasis; RA: Rheumatoid arthritis; UC: Ulcerative colitis.

approved reference product with no clinically meaningful differences in biological activity, efficacy, safety, purity and potency, assessed through stepwise development programs [11,12]. A previous analysis of adalimumab biosimilars demonstrated that some variation in physicochemical characteristics exists between biosimilars and reference adalimumab; these differences did not preclude regulatory approval [2]. In general, the adalimumab biosimilars tested showed similar trends in characteristics like glycoform composition and charge variants, compared with the reference product [2]. Biosimilars can be cost-effective alternatives to reference products and can facilitate expansion of patient access to biologic therapies [13]. Indeed, impending reference product patent expiry has prompted interest in biosimilar development [3], with adalimumab biosimilars able to enter European markets from October 2018 and US markets from 2023 [2,14].

Currently, eight adalimumab biosimilars have received regulatory approval from the EMA and/or the US FDA, all of which have demonstrated similar pharmacokinetics (PK), safety and efficacy to reference adalimumab in non-clinical and clinical studies. However, the products vary noticeably in formulation, delivery device characteristics, and clinical programs. CT-P17 (Yuflyma™; Celltrion, Incheon, Republic of Korea) is the most recently licensed product, having received regulatory approval from the EMA in February 2021 [15]. While other products have demonstrated biosimilarity (i.e., being highly similar in terms of structure, biological activity, efficacy, safety and immunogenicity [16]) to the original low-concentration (50 mg/ml) reference adalimumab formulation, CT-P17 is the first adalimumab biosimilar prepared at a high concentration (100 mg/ml, in a volume of 40 mg/0.4 ml), reflecting the newer formulation of the reference product [17,18]. CT-P17 was launched in the second quarter of 2021 and is expected to become available in additional European countries [19].

This review analyses adalimumab biosimilars currently licensed in Europe and the US with regards to differences in their characteristics and clinical development programs. The article provides a timely update, given the recent approval of the first high-concentration adalimumab biosimilar.

Adalimumab biosimilars licensed by the EMA &/or FDA

The eight adalimumab biosimilars that are currently licensed in Europe and/or the US are ABP 501 (Amgevita™/Amjevita™; Amgen, CA, USA) [20–22], SB5 (Imraldi®/Hadlima®; Biogen, MA, USA/Samsung Bioepis, Incheon, Republic of Korea) [21–25], BI 695501 (Cyltezo®; Boehringer Ingelheim, Ingelheim am Rhein, Germany) [22,23], GP2017 (Hefiya®/Hyrimoz®; Sandoz, Holzkirchen, Germany) [24–30], FKB327 (Hulio®; Mylan, PA, USA) [25–33], MSB11022 (Idacio®; Fresenius Kabi, Bad Homburg, Germany) [26,27], PF-06410293 (Amsparity™/Abrilada™; Pfizer, NY, USA) [28–38] and CT-P17 [15]. As with reference adalimumab [7,8], all of the approved biosimilars are administered by subcutaneous (SC) injection.

Figure 1 presents the approved indications and dates of EMA and/or FDA approval for each biosimilar. ABP 501 was the first adalimumab biosimilar to be approved by the FDA in September 2016 and the EMA in March

2017. Some products are licensed in both the US and Europe, while others are licensed in only one of the countries/regions.

Abbreviated regulatory pathways for biosimilars focus on demonstrating that there are no clinically meaningful differences between the candidate biosimilar and the reference product. Once biosimilarity has been established in at least one indication, the totality of evidence can be extrapolated to other indications held by the reference product, meaning clinical trials in each approved indication are not required [1]. For each adalimumab biosimilar, pivotal clinical trials for therapeutic equivalence versus reference adalimumab were conducted in patients with RA or PsO (see later section on Phase III clinical trials) as these are considered the most sensitive patient populations in which clinically meaningful differences may be detected [35]. Extrapolation from randomized controlled trials in RA and PsO supports the use of adalimumab biosimilars in other indications approved for the reference product. In Europe, all biosimilars are approved for the same indications as the reference product; however, those licensed in the US are not approved for pediatric CD, pediatric UC, UV (in adults or children) or hidradenitis suppurativa (Figure 1).

Recently, the FDA and EMA approved reference adalimumab for the treatment of moderately to severely active UC in pediatric patients aged ≥ 5 years (FDA) or ≥ 6 years (EMA) [7,8,36,37]. With the addition of the pediatric ulcerative colitis (pUC) indication to those licensed for reference adalimumab, the approved indications for adalimumab biosimilars are expected to expand. Notably, six biosimilars, CT-P17, ABP 501, SB5, GP2017, FKB327 and PF-06410293, already include treatment of pediatric ulcerative colitis in their EU product information [15,20,21,24,25,28].

Formulation & device characteristics for approved adalimumab biosimilars

There are noticeable differences between approved adalimumab biosimilars in terms of their formulations, delivery parameters, and stability (Figure 1). Formulation is an important determinant of injection-site pain. Studies with reference adalimumab have demonstrated that patients injected with the high-concentration (40 mg/0.4 ml) formulation experienced lower injection-site pain than those injected with the low-concentration (40 mg/0.8 ml) formulation [10]. The selection of buffer can also influence injection-site pain [38]. SB5, GP2017 and MSB11022 are all formulated in citrate-containing buffers [21,24,26,30,34], which are recognized as being associated with SC injection pain [10,38]. While other biosimilars are citrate-free [15,20,22,25,28,29,32,33], compared with high-concentration reference adalimumab, they may have a lower-gauge (wider diameter) needle (e.g., BI 695501) or have needle caps that contain latex (e.g., ABP 501, BI 695501) [2,20,22], a known irritant that can cause allergic reactions [39]. The formulation and delivery of FKB327 is citrate- and latex-free, with a 29-gauge (29G) needle; however, it has a lower drug concentration (50 mg/ml) than reference adalimumab (100 mg/ml) and, thus, requires a larger volume to be injected [2,8,25], potentially influencing pain [40]. CT-P17 is currently the only high-concentration, low-volume and citrate- and latex-free adalimumab biosimilar approved by the EMA [2,15]; no adalimumab biosimilar with these characteristics is currently approved by the FDA. It is likely that these properties, combined with the thinner (29G) needle, might benefit patients by reducing pain during self-injection [2,15]. Additionally, the high-concentration formulation of CT-P17 (and reference adalimumab) offers the potential to administer high-dose induction treatment (80 mg/0.8 ml) with a reduced number of injections for patients with inflammatory bowel disease.

The stability of biologics is also an important consideration, as medications are stored and administered at home by the patient and some patients can find it difficult to store their biologics correctly [41,42]. While most of the biosimilars have the same 14-day room temperature stability as the reference product, three have longer stability (SB5, PF-06410293 and CT-P17) (Figure 1). The 30-day duration of room temperature stability of CT-P17 is as long as that of any adalimumab biosimilar marketed in Europe and/or the US and twice as long as that of reference adalimumab. Comprehensive comparative stability testing has demonstrated that CT-P17 is stable when stored at 25°C with up to 60% relative humidity for up to 28 days, regardless of the administration device (autoinjector [AI] or prefilled syringe [PFS]), tested protein concentration (50 or 100 mg/ml), or manufacturing date [43]. Stability assessments were also conducted for high- and low-concentration formulations of CT-P17 and reference adalimumab: the high-concentration formulations showed no significant fluctuations in protein concentration, pH, osmolality or turbidity during the study period [43].

Clinical development programs for adalimumab biosimilars

A recent study by Gherghescu and Delgado-Charro [35] searched the EMA repository to identify centrally authorized adalimumab biosimilars, and examined corresponding European public assessment reports (EPARs) for the typical clinical data from Phase I comparative PK and Phase III efficacy studies required to assess biosimilarity. Following

this approach, we examined EPARs to determine how adalimumab biosimilars were evaluated for biosimilarity to the reference product through Phase I and III clinical trials (Table 1). For biosimilars only licensed by the FDA (BI 695501), US regulatory documents were evaluated. Additional details relating to trial design were sourced from published primary trial reports.

Clinical development program designs were analogous for the products, in that PK similarity to the reference product was evaluated in Phase I studies, followed by Phase III trials to determine efficacy and confirm clinical comparability [35]. However, evaluation of the biosimilars differed in terms of study populations (Table 1) [23,27,44–50]. The regulatory package for FKB327 was the only one to include a Phase I PK study in a Japanese male population [48]. ABP 501 was the only biosimilar to submit Phase III study data in both RA and PsO [44]. The other biosimilars were evaluated in Phase III studies in either RA or PsO prior to seeking regulatory approval. Phase III clinical trials of GP2017 and MSB11022 were conducted in patients with RA [51,52] in addition to the trials conducted in patients with PsO; however, data from the RA trials did not feature in the regulatory assessments [27,47]. The regulatory documents for some biosimilars also included data from further clinical trials to evaluate usability. In some cases, PK parameters were also assessed for different device types (AI, PFS or prefilled pen [PFP]), or for biosimilars produced at different manufacturing sites (Table 1). For some biosimilars, results from additional Phase I trials that assessed PK of AI and PFS devices but did not contribute to regulatory submissions have been published (SB5 [53] and BI 6995501 [54,55]).

The complexity of biologic molecules means that even slight changes to the manufacturing process have the potential to affect biological activity. For this reason, companies conduct the aforementioned bridging studies to prove that bioavailability is not compromised by a new drug–device combination or across different manufacturing sites [56]. Additionally, it can be argued that reference product manufactured in different regions is specific to that jurisdiction and many regulatory authorities require comparison data between local and foreign versions of the reference product [57]. Therefore, clinical trials were also conducted to demonstrate biosimilarity with reference adalimumab derived from different sources, including European Union-approved reference adalimumab (EU-adalimumab) and United States-licensed reference adalimumab (US-adalimumab) (Table 1).

Phase I clinical trials

The designs of Phase I clinical trials contributing to regulatory submissions for adalimumab biosimilars are summarized in Table 2. All studies evaluated PK after a single injection of the candidate biosimilar/reference adalimumab, and most studies assessed PK equivalence with low-concentration (50 mg/ml) reference adalimumab [23,27,44–50,58–70].

For each of ABP 501, SB5, BI-695501, FKB327 and MSB11022, a single three-way, Phase I PK similarity study was conducted to assess PK equivalence versus EU-adalimumab and US-adalimumab. Each study enrolled healthy volunteers [27,44,45,48]; healthy adult males were enrolled in the study for BI 695501 [59]. In all cases, equivalence between the biosimilar, EU-adalimumab and US-adalimumab was demonstrated for the primary PK end point(s) (specified in Table 2), as 90% CIs for geometric mean ratios of test and reference products were maintained within predefined 80–125% equivalence margins (Table 2) [27,44,45,48,59]. For all of the biosimilars, Phase I trials also demonstrated similarity between mean serum concentration–time profiles of the biosimilar, EU-adalimumab and US-adalimumab over the study period [27,44,45,48,59].

Two PK similarity studies were performed for each of GP2017 and PF-06410293. The pivotal Phase I study, GP17–101, evaluated PK parameters in healthy males and females following a single 40-mg SC dose (50 mg/ml) of GP2017, EU-adalimumab or US-adalimumab. The study failed to demonstrate PK bioequivalence between GP2017 and EU-adalimumab, and between EU-adalimumab and US-adalimumab, as the upper limits of the 90% CIs for the ratios of geometric means for area under the concentration–time curve from time zero to infinity (AUC_{0-inf}) and area under the concentration–time curve from time zero to the last measured concentration (AUC_{0-last} or AUC_{0-t}) exceeded the predefined 1.25 threshold [47]. A second three-way PK similarity study (GP17–104) was conducted in a larger population of healthy males; primary end points were restricted to maximum serum concentration (C_{max}) and AUC_{0-inf} , and bioequivalence was demonstrated between all three treatments [47]. The results of the latter study were considered to support PK similarity of GP-2017 and EU-adalimumab, and established a PK bridge between EU- and US-adalimumab [47]. Two Phase I studies were also conducted for PF-06410293. Each study was carried out in healthy adult volunteers and compared the PK parameters of PF-06410293, EU-adalimumab and US-adalimumab. Study B5381001 demonstrated biosimilarity for the study end points C_{max} and area under the concentration–time curve from time zero to 2 weeks ($AUC_{0-2\text{ wk}}$), but the biosimilarity criteria

Table 1. Clinical development programs for adalimumab biosimilars approved by the European Medicines Agency and/or FDA.

Product	Study ID Clinical trial identifier [†]	Type of study	Phase	Study population [‡]	Study objectives	Duration of treatment arm	Ref. [§]
ABP 501	20110217	PK	I	HV	To demonstrate PK similarity, safety, tolerability, immunogenicity and bridging between ABP 501, US-ADL and EU-ADL	Up to day 63	[44]
	20120262 NCT01970475 2013-000525-31	Efficacy/safety	III	RA	To compare the efficacy, safety, immunogenicity and PK of ABP 501 with US-ADL	24 weeks	
	20120263 NCT01970488 2013-000537-12	Efficacy/safety	III	PsO	To compare the efficacy, safety, immunogenicity and PK of ABP 501 with EU-ADL	52 weeks	
SB5	SB5-G11-NHV NCT02144714	PK	I	HV	To compare the PK, safety, tolerability and immunogenicity of SB5 with EU-ADL and US-ADL	10 weeks	[45]
	SB5-G31-RA NCT02167139 2013-005013-13	Efficacy/safety	III	RA	To demonstrate the equivalence of SB5 to EU-ADL in terms of ACR20 at Week 24, and to compare the efficacy, safety, tolerability, immunogenicity and PK	60 weeks	
BI 695501	1297.8 NCT02045979	PK (pivotal PK study)	I	HV	To compare the PK, safety, tolerability and immunogenicity of BI 695501 with US-ADL and EU-ADL	Up to day 71	[23]
	1297.1 NCT01505491	PK (trial formulation)	I	HV	To compare the safety of BI 695501 with US-ADL and EU-ADL	NA	
	1297.2 NCT02137226 2012-002945-40	Efficacy/safety	III	RA	To compare the efficacy, safety, immunogenicity and PK of BI 695501 and US-ADL	48 weeks	
GP2017	GP17-104	PK (pivotal PK study)	I	HV (males)	To demonstrate PK bioequivalence for GP2017 and EU-ADL and PK bioequivalence for EU-ADL and US-ADL	Up to 14 weeks	[46,47]
	GP17-101	PK (supportive PK study)	I	HV	To demonstrate PK bioequivalence of GP2017, EU-ADL and US-ADL	Up to 14 weeks	
	GP17-102	PK (device)	I	HV (males)	To describe PK of GP2017 administered by AI or a PFS as a single SC injection of 40 mg	Up to 14 weeks	
	GP17-103	PK (manufacturing site)	I	HV	To demonstrate PK bioequivalence of GP2017-Cook and GP2017-Schaftenau	Up to 14 weeks	
	GP17-301 NCT02016105 2013-000747-11	Efficacy/safety	III	PsO	To demonstrate equivalent efficacy of GP2017 and reference adalimumab with respect to PASI75 response rate at Week 16, and similar safety and immunogenicity	51 weeks [¶]	
FKB327	FKB327-001	PK	I	HV	To compare the safety and PK of FKB327, EU-ADL and US-ADL, and to assess immunogenicity and tolerability of FKB327, EU-ADL and US-ADL	Up to day 65	[48]

[†] Registered ClinicalTrials and/or EudraCT study identifiers;

[‡] Healthy volunteers are male or female subjects unless otherwise stated;

[§] Clinical trials contributing to regulatory assessments are included; information is based on EPARs and published primary reports where the biosimilar is approved by the EMA; for biosimilars licensed by the FDA only, US regulatory documents and published primary reports were used;

[¶] Excludes screening period.

ACR20: 20% improvement in American College of Rheumatology criteria; AI: Autoinjector; EMA: European Medicines Agency; EPAR: European public assessment report; EU-ADL: European Union-approved reference adalimumab; HV: Healthy volunteers; PASI75: 75% reduction in Psoriasis Area and Severity Index score; PD: Pharmacodynamics; PFP: Prefilled pen; PFS: Prefilled syringe; PK: Pharmacokinetic(s); PsO: Psoriasis; RA: Rheumatoid arthritis; SC: Subcutaneous(ly); US-ADL: United States-licensed reference adalimumab.

Table 1. Clinical development programs for adalimumab biosimilars approved by the European Medicines Agency and/or FDA (cont.).

Product	Study ID Clinical trial identifier [†]	Type of study	Phase	Study population [‡]	Study objectives	Duration of treatment arm	Ref. [§]
	FKB327-005	PK (device)	I	HV	To assess relative bioavailability and safety of FKB327 delivered by vial/syringe, PFS and AI, and to describe the effect of body weight and injection site on single-dose PK of FKB327	Up to day 65	
	FKB327-004	PK (Japanese population)	I	HV (males)	To compare the PK and safety of FKB327 and reference adalimumab, and to assess immunogenicity and local tolerability of FKB327	Up to day 65	
	FKB327-002 NCT02260791 2014-000109-11	Efficacy/safety	III	RA	To compare the efficacy and safety of FKB327 and reference adalimumab when in combination with methotrexate; to compare steady-state PK of FKB327 and reference adalimumab administered by multiple dosing	Up to week 22	
	FKB327-003 NCT02405780 2014-000110-61	Efficacy/safety (long-term extension follow-up study)	III	RA	To compare the safety, efficacy, immunogenicity and PK of long-term treatment with FKB327 and reference adalimumab	Up to week 76	
MSB11022	EMR200588-001 NCT03014947	PK	I	HV	To compare the PK, safety, immunogenicity and tolerability of MSB11022 with US-ADL and EU-ADL	70 days	[27]
	EMR200588-002 NCT02660580 2015-003287-37	Efficacy/safety	III	PsO	To demonstrate equivalence in efficacy and similarity in PK, efficacy, safety and immunogenicity of MSB11022 and EU-ADL	52 weeks	
PF-06410293	B5381001 NCT01870986	PK	I	HV	To compare the PK of PF-06410293 to EU-ADL and US-ADL and evaluate immunogenicity and single-dose safety and tolerability	6 weeks	[49]
	B5381005 NCT02572245	PK (device)	I	HV	To compare the single-dose PK of PF-06410293 administered SC with a PFP or PFS, and to evaluate safety, tolerability and immunogenicity	6 weeks	
	B5381007 NCT02237729	PK	I	HV	To compare the PK of PF-06410293 with those of EU-ADL and US-ADL, and evaluate immunogenicity and single-dose safety and tolerability	7 weeks	
	B5381002 NCT02480153 2014-000352-29	Efficacy/safety	III	RA	To compare efficacy between PF-06410293 and EU-ADL, and evaluate safety, tolerability, immunogenicity, PK and PD	92 weeks	

[†] Registered ClinicalTrials and/or EudraCT study identifiers;

[‡] Healthy volunteers are male or female subjects unless otherwise stated;

[§] Clinical trials contributing to regulatory assessments are included; information is based on EPARs and published primary reports where the biosimilar is approved by the EMA; for biosimilars licensed by the FDA only, US regulatory documents and published primary reports were used;

[¶] Excludes screening period.

ACR20: 20% improvement in American College of Rheumatology criteria; AI: Autoinjector; EMA: European Medicines Agency; EPAR: European public assessment report; EU-ADL: European Union-approved reference adalimumab; HV: Healthy volunteers; PASI75: 75% reduction in Psoriasis Area and Severity Index score; PD: Pharmacodynamics; PFP: Prefilled pen; PFS: Prefilled syringe; PK: Pharmacokinetic(s); PsO: Psoriasis; RA: Rheumatoid arthritis; SC: Subcutaneous(y); US-ADL: United States-licensed reference adalimumab.

Table 1. Clinical development programs for adalimumab biosimilars approved by the European Medicines Agency and/or FDA (cont.).

Product	Study ID Clinical trial identifier [†]	Type of study	Phase	Study population [‡]	Study objectives	Duration of treatment arm	Ref. [§]
	B5381002b (sub-study of B5381002)	Device	III	RA	To evaluate the success of PF-06410293 administration by the subject with RA or their nonhealthcare professional caregiver using the PFP device, and to describe its safety	10 weeks	
CT-P17	CT-P17 1.1 NCT03970824	PK	I	HV	To demonstrate PK similarity to EU-ADL and US-ADL, and to evaluate safety and immunogenicity	10 weeks	[50]
	CT-P17 1.2	Safety (pilot)	I	HV (males)	To assess safety in terms of treatment-emergent adverse events, and evaluate PK and immunogenicity	17 weeks	
	CT-P17 1.3 NCT04295356	PK (device)	I	HV	To demonstrate PK similarity of CT-P17 administered by AI or PFS, and evaluate safety and immunogenicity	10 weeks	
	CT-P17 3.1 NCT03789292 2018-001690-25	Efficacy/safety	III	RA	To demonstrate similarity of efficacy in terms of ACR20 at Week 24, and to evaluate PK, PD, usability, safety and immunogenicity	52 weeks	
	CT-P17 3.2 NCT04171414 2019-000660-25	Usability	III	RA	To determine usability of AI administration of CT-P17, as assessed by PRE- and POST-Self-Injection Assessment Questionnaire scores at Week 4	28 weeks	

[†] Registered ClinicalTrials and/or EudraCT study identifiers;

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for the end points AUC_{0-t} and AUC_{inf} were not formally met [49]. In response to a request from the Committee for Medicinal Products for Human Use, a second single-dose PK study (B5381007) was performed in healthy volunteers. In this pivotal study, the criteria for biosimilarity in PK were formally met for the comparison between PF-06410293 and EU-adalimumab and between PF-06410293 and US-adalimumab [49]. Mean concentrations were slightly higher with PF-06410293 than with EU-adalimumab in both studies.

CT-P17 is the only adalimumab biosimilar with a high-concentration (100 mg/ml) formulation approved following submission of data demonstrating PK equivalence with high-concentration reference adalimumab [17]. In the CT-P17 1.1 study, mean peak and total systemic exposure (assessed by AUC_{0-inf} , AUC_{0-last} , and C_{max}) were equivalent among CT-P17, US-adalimumab and EU-adalimumab, following a single SC administration of each study drug. The 90% CIs for the ratios of geometric least squares (LS) means were within the predefined 80–125% equivalence margin for each pairwise treatment comparison [17]. Safety of CT-P17 and EU-adalimumab was evaluated in the CT-P17 1.2 study. Proportions of participants with treatment-emergent adverse events considered to be study drug-related by the investigator were comparable between treatment groups [50].

Additional Phase I device studies were conducted for GP2017, FKB327, PF-06410293, and CT-P17 to compare the PK parameters of each biosimilar following administration by AI, PFP and/or PFS. Study GP17–102 compared PK parameters in healthy male volunteers following a single 40-mg SC injection of GP2017 administered by AI or PFS [47]. The 90% CIs for the ratios of geometric means (PFS vs AI) were contained within the predefined 80–125% acceptance limits for the co-primary end points C_{max} and area under the concentration–time curve from time zero to 360 h (AUC_{0-360h}), although the study was not powered for formal equivalence testing [47]. A clinical device

Table 2. Characteristics of Phase I studies for adalimumab biosimilars approved by the European Medicines Agency and/or FDA.

Product	Study ID	Type of study	n	Treatment arms Dose and route of administration	Primary end point(s)	Equivalence margin	Ref.†
ABP 501	20110217	PK	203	ABP 501 (n = 67) EU-ADL (n = 67) US-ADL (n = 69) 40 mg SC (40 mg/0.8 ml) PFS	C_{max} , AUC_{inf}	80–125%	[44,58]
SB5	SB5-G11-NHV	PK	189	SB5 (n = 63) EU-ADL (n = 63) US-ADL (n = 63) 40 mg SC (40 mg/0.8 ml) PFS	For EMA: AUC_{inf} , C_{max} For FDA: AUC_{inf} , AUC_{last} , C_{max}	80–125%	[45]
BI 695501	1297.8	PK	324	BI 695501 (n = 108) EU-ADL (n = 108) US-ADL (n = 108) 40 mg SC (40 mg/0.8 ml) PFS	$AUC_{0-inf, pred}$, AUC_{0-last} , C_{max}	80–125%	[23,59]
GP2017	GP17-104	PK	318	GP2017 (n = 107) EU-ADL (n = 106) US-ADL (n = 105) 40 mg SC (40 mg/0.8 ml) PFS	C_{max} , AUC_{0-inf}	80–125%	[46,47]
	GP17-101	PK	219	GP2017 (n = 73) EU-ADL (n = 73) US-ADL (n = 73) 40 mg SC (40 mg/0.8 ml) PFS	C_{max} , AUC_{0-inf} , AUC_{0-last}	80–125%	
	GP17-102	PK (device)	108	GP2017-AI (n = 54) GP2017-PFS (n = 54) 40 mg SC (40 mg/0.8 ml) AI or PFS	$AUC_{0-360 h}$, C_{max}	80–125%	
	GP17-103	PK (manufacturing site)	178	GP2017-Cook (n = 88) GP2017-Schaftenau (n = 90) 40 mg SC (40 mg/0.8 ml) PFS	C_{max} , AUC_{0-inf} , AUC_{0-last}	80–125%	
FKB327	FKB327-005	PK (device)	195	FKB327 vial/syringe (n = 66) FKB327 PFS (n = 63) FKB327 AI (n = 66) 40 mg SC (40 mg/0.8 ml) AI or PFS	AUC_{0-t} , AUC_{0-inf} , C_{max}	80–125%	[48,60,61]
	FKB327-001	PK	180	FKB327 (n = 60) EU-ADL (n = 60) US-ADL (n = 60) 40 mg SC (40 mg/0.8 ml)‡	AUC_{0-inf} , AUC_{0-t} , C_{max}	80–125%	
	FKB327-004	PK (Japanese)	131	FKB327 (n = 66) US-ADL (n = 65) 40 mg SC (40 mg/0.8 ml)‡	$AUC_{0-360 h}$, AUC_{0-t} , C_{max}	80–125%	
MSB11022	EMR200588-001	PK	237	MSB11022 (n = 79) EU-ADL (n = 79) US-ADL (n = 79) 40 mg SC (40 mg/0.8 ml) PFS	AUC_{0-inf} , C_{max} , AUC_{0-last}	80–125%	[27]
PF-06410293	B5381001	PK	210	PF-06410293 (n = 69) EU-ADL (n = 70) US-ADL (n = 71) 40 mg SC (40 mg/0.8 ml) PFS	C_{max} , AUC_t , AUC_{inf}	80–125%	[49]

†Clinical trials contributing to regulatory assessments are included; information is based on EPARs and published primary reports where the biosimilar is approved by the EMA; for biosimilars licensed by the FDA only, US regulatory documents and published primary reports were used;

‡Information about SC administration device could not be identified.

AI: Autoinjector; $AUC_{0-2 wk}$: Area under the concentration–time curve from time zero to 2 weeks; $AUC_{0-360 h}$: Area under the concentration–time curve from time zero to 360 h; AUC_{0-inf} : Area under the concentration–time curve from time zero to infinity; $AUC_{0-inf, pred}$: Area under the concentration–time curve from time zero to predicted infinity; AUC_{0-last} or AUC_{0-t} : Area under the concentration–time curve from time zero to the last measured concentration; C_{max} : Maximum serum concentration; EMA: European Medicines Agency; EPAR: European public assessment report; EU-ADL: European Union-approved reference adalimumab; N/A: Not applicable; PFP: Prefilled pen; PFS: Prefilled syringe; PK: Pharmacokinetic; SC: Subcutaneously; TEAE: Treatment-emergent adverse event; US-ADL: United States-licensed reference adalimumab.

Table 2. Characteristics of Phase I studies for adalimumab biosimilars approved by the European Medicines Agency and/or FDA (cont.).

Product	Study ID	Type of study	n	Treatment arms Dose and route of administration	Primary end point(s)	Equivalence margin	Ref.†
	B5381005	PK (device)	164	PF-06410293 PFS (n = 81) PF-06410293 PFP (n = 83) 40 mg SC (40 mg/0.8 ml) PFS or PFP	C_{max} , $AUC_{0-2\text{ wk}}$	80–125%	
	B5381007	PK	362	PF-06410293 (n = 121) EU-ADL (n = 119) US-ADL (n = 122) 40 mg SC (40 mg/0.8 ml) PFS	C_{max} , $AUC_{0-2\text{ wk}}$, AUC_{tr} , AUC_{inf}	80–125%	
CT-P17	CT-P17 1.1	PK	312	CT-P17 (n = 103) EU-ADL (n = 106) US-ADL (n = 103) 40 mg SC (40 mg/0.4 ml) PFS	AUC_{0-inf} , AUC_{0-last} , C_{max}	80–125%	[50]
	CT-P17 1.2	Safety (pilot)	30	CT-P17 (n = 15) EU-ADL (n = 15) 40 mg SC (40 mg/0.4 ml) PFS	TEAEs	N/A	
	CT-P17 1.3	PK (device)	193	CT-P17 PFS (n = 95) CT-P17 AI (n = 98) 40 mg SC (40 mg/0.4 ml) AI or PFS	AUC_{0-inf} , AUC_{0-last} , C_{max}	80–125%	

† Clinical trials contributing to regulatory assessments are included; information is based on EPARs and published primary reports where the biosimilar is approved by the EMA; for biosimilars licensed by the FDA only, US regulatory documents and published primary reports were used;

‡ Information about SC administration device could not be identified.

AI: Autoinjector; $AUC_{0-2\text{ wk}}$: Area under the concentration–time curve from time zero to 2 weeks; $AUC_{0-360\text{ h}}$: Area under the concentration–time curve from time zero to 360 h; AUC_{0-inf} : Area under the concentration–time curve from time zero to infinity; $AUC_{0-inf, pred}$: Area under the concentration–time curve from time zero to predicted infinity; AUC_{0-last} or AUC_{0-t} : Area under the concentration–time curve from time zero to the last measured concentration; C_{max} : Maximum serum concentration; EMA: European Medicines Agency; EPAR: European public assessment report; EU-ADL: European Union-approved reference adalimumab; N/A: Not applicable; PFP: Prefilled pen; PFS: Prefilled syringe; PK: Pharmacokinetic; SC: Subcutaneously; TEAE: Treatment-emergent adverse event; US-ADL: United States-licensed reference adalimumab.

comparison (PFP vs PFS) was also conducted in healthy volunteers for PF-06410293 (study B5381005); primary PK end points were C_{max} and $AUC_{0-2\text{ wk}}$. The study demonstrated PK similarity between the PFP and PFS following administration of a single 40-mg SC dose of the drug [49]. Study FKB327-005 compared the relative bioavailability of FKB327 in healthy volunteers following administration of a single 40-mg SC dose (50 mg/ml) using a PFS, AI, or vial with a disposable syringe. The PFS was bioequivalent to the vial for the primary study end points AUC_{0-inf} , AUC_{0-last} and C_{max} . For the AI versus vial and AI versus PFS comparisons, the bioequivalence criteria were met for the end points AUC_{0-inf} and C_{max} ; however, the upper 90% CIs of the geometric LS mean ratios for AUC_{0-last} were slightly outside the predefined limits for bioequivalence. The latter finding was not considered a concern by the Committee for Medicinal Products for Human Use, who deemed that the results do not preclude switching between the three delivery methods [48]. The CT-P17 1.3 study (NCT04295356) evaluated the PK equivalence of CT-P17 administered by AI or PFS in healthy volunteers. PK equivalence of the AI and PFS was demonstrated, with 90% CIs within the 80–125% equivalence margin for the primary end points AUC_{0-inf} , AUC_{0-last} and C_{max} [18]. Overall safety and immunogenicity were also comparable between the two delivery devices [18].

Phase III clinical trials

Phase III clinical trials for the approved adalimumab biosimilars were conducted in patients with RA or PsO (Table 3).

The pivotal Phase III studies in RA populations were randomized, controlled, double-blind, parallel-group trials with durations ranging from 22 to 92 weeks [22,27,44,45,47–50,63–74,67,69,70]. Study populations were generally consistent across the trials, which each enrolled adult patients aged ≥ 18 years with moderate-to-severe RA despite treatment with methotrexate for ≥ 12 weeks prior to study start [22,27,44,45,47–50,63,64,67,69,70]. While all of the trials assessed the proportion of patients achieving a 20% improvement by American College of Rheumatology criteria (ACR20) as the primary study outcome, the timepoint for assessment and the predefined limits for bioequivalence varied slightly across trials (Table 3). Most of the trials included a period where patients receiving reference adalimumab were switched to receive either reference adalimumab or adalimumab biosimilar from Weeks 24–26 (CT-P17, BI-695501, SB5) [50,64,65]. One study included two opportunities for patients receiving reference adalimumab to switch to PF-06410293 (patients receiving reference adalimumab were rerandomized to receive

Table 3. Characteristics of Phase III studies for adalimumab biosimilars approved by the European Medicines Agency and/or FDA.

Product	Study ID	Type of study	Study population	Test product(s) Dosage regimen and route of administration	Subjects, N (n)	Primary end point	Equivalence margin	Ref.†
ABP 501	20120263 NCT01970488	Efficacy/safety	PsO	ABP 501 vs EU-ADL 80 mg SC on Day 1, then 40 mg SC Q2W from Week 2 onwards	350 (175, 175)	PASI improvement (%) from BL to Week 16	-15%; 15%	[44,62]
	20120262 NCT01970475	Efficacy/safety	RA	ABP 501 vs US-ADL 40 mg SC Q2W	526 (264, 262)	Risk ratio of ACR20 at Week 24	0.738; 1/0.738	[44,63]
SB5	SB5-G31-RA	Efficacy/safety	RA	SB5 vs EU-ADL 40 mg SC Q2W	544 (271, 273)	ACR20 at Week 24	-15%; 15%	[45,64]
BI 695501	1297.2 NCT02137226	Efficacy/safety	RA	BI-695501 vs US-ADL 40 mg SC Q2W	645 (324, 321)	ACR20 at Weeks 12 and 24	Week 12: -12%; 15% Week 24: -15%; 15%	[23,65]
GP2017	GP17-301 NCT02016105	Efficacy/safety	PsO	GP2017 vs EU-ADL, US-ADL D1: 80 mg SC (loading dose) Week 1 to Week 49: 40 mg SC Q2W (40 mg/0.8 mL PFS)	465 (231, 234 [EU-ADL 44, US-ADL 190])	Proportion of patients achieving PASI75 at Week 16	-18%; 18%	[47,66]
FKB327	FKB327-002 NCT02260791	Efficacy/safety	RA	FKB327 vs US-ADL 40 mg SC Q2W	730 (367, 363)	ACR20 at Week 24	EU: -13%; 13% US: -12%; 15%	[48,67]
	FKB327-003 NCT02405780	Efficacy/safety (long-term extension follow-up study)	RA	Period I: FKB327 vs US-ADL 40 mg SC Q2W Period II: FKB327 40 mg SC Q2W	645 (324, 321)			
MSB11022	EMR200588-002 NCT02660580	Efficacy/safety	PsO	MSB11022 vs EU-ADL Week 1: 80 mg SC Week 2 to Week 16: 40 mg SC Q2W	443 (222, 221)	Proportion of patients achieving PASI75 at Week 16	-18%; 18%	[68]
PF-06410293	B5381002 NCT02480153	Efficacy/safety	RA	PF-06410293 vs EU-ADL 40 mg SC Q2W (40 mg/0.8 ml)	597 (297, 300)	ACR20 at Week 12	EU: -14%; 14% US: -12%, 15%	[49,69]
	B5381002b	Device	RA	PF-06410293 PFP 40 mg SC Q2W (40 mg/0.8 ml)	63	Delivery system success rate	N/A	
CT-P17	CT-P17 3.1 NCT03789292	Efficacy/safety	RA	CT-P17 vs EU-ADL 40 mg SC Q2W (40 mg/0.4 ml)	648 (324, 324)	ACR20 at Week 24	EU: -15%; 15% US: -12%; 15%	[50,70]
	CT-P17 3.2	Usability	RA	CT-P17 AI 40 mg SC Q2W (40 mg/0.4 ml)	62	PRE- and POST-Self-Injection Assessment Questionnaire at Week 4	N/A	

† Clinical trials contributing to regulatory assessments are included; information is based on EPARs and published primary reports where the biosimilar is approved by the EMA; for biosimilars licensed by the FDA only, and US regulatory documents and published primary reports were used.

ACR20: 20% improvement in American College of Rheumatology criteria; AI: Autoinjector; BL: Baseline; ΔDAS28-CRP: Change in Disease Activity Score-28 including high-sensitivity C-reactive protein; EMA: European Medicines Agency; EPAR: European public assessment report; EU-ADL: European Union-approved reference adalimumab; N/A: Not applicable; PASI75: 75% reduction in Psoriasis Area and Severity Index score; PFP: Prefilled pen; PsO: Psoriasis; Q2W: Every 2 weeks; RA: Rheumatoid arthritis; SC: Subcutaneously; US-ADL: United States-licensed reference adalimumab.

PF-06410293 or reference adalimumab at Week 26, and patients who remained on reference adalimumab were switched to PF-06410293 at Week 52) [69]. The phase III study of FKB-327 included the option for patients to enroll in an open-label extension study at Week 26 with rerandomization to ensure that two-thirds of participants remained on the same treatment, while a third were switched to receive either FKB327 or reference adalimumab up to Week 54 [67]. The Phase III study of ABP 501 did not include an option to switch [63]. With the exception of the CT-P17 Phase III study, all of the Phase III trials in patients with RA assessed bioequivalence versus the low-concentration formulation of reference adalimumab (Table 3). Since CT-P17 is the only high-concentration, citrate-free adalimumab biosimilar approved to date, this is the only biosimilar for which a Phase III pivotal trial was conducted to demonstrate similar efficacy (and safety) to that of the high-concentration formulation of reference adalimumab [50,70].

Table 4. Efficacy, safety, and immunogenicity results[†] of pivotal trials in patients with rheumatoid arthritis for adalimumab biosimilars approved by the European Medicines Agency and/or FDA.

	Adalimumab (Humira®)	ABP 501	SB5	FKB327	PF-06410293	BI695501	CT-P17	Ref.
N	268 [‡]	264 vs 262	269 vs 273	363 vs 358	297 vs 300	321 vs 318	324 vs 324	
Efficacy outcomes at Week 24								
ACR20, %	63.3–65.1	74.6 vs 72.4	72.4 vs 72.2	74.1 vs 75.7	68.4 vs 71.3 (Week 12)	69.0 vs 64.5	82.7 vs 82.7	
ACR50, %	39.1–52.4	49.2 vs 52.0	38.1 vs 39.7	49.0 vs 49.4	NR	NR	60.2 vs 63.6	
ACR70, %	20.8–23.8	26.0 vs 22.9	19.2 vs 20.3	21.3 vs 25.1	NR	NR	40.7 vs 44.4	
DAS28 (Δ from BL)	NR	-2.32 vs -2.32 [§]	-2.74 vs -2.68 [¶]	NR	-2.7 vs 2.8 [§]	-2.4 vs -2.4 [¶]	-2.7 vs -2.7 [§]	
DAS28 remission, %	42.9 (Week 52)	30.5 vs 35.5 [§]	NR	NR	29.3 vs 33.0 [§]	NR	48.8 vs 48.5 [§]	
Boolean remission, %	NR	NR	NR	NR	8.8 vs 9.0	1.9 vs 0.9	17.9 vs 21.0	
Good EULAR response, %	NR	NR	34.1 vs 34.6	NR	54.5 vs 49.0	21 vs 26	64.2 vs 64.2	
Safety outcomes, %								
Any TEAE	NR	50.0 vs 54.6	35.8 vs 40.7	62.2 vs 66.2	48.1 vs 47.8	59.6 vs 60.0	52.2 vs 56.8	
Serious TEAE	18.5/100 PY	3.8 vs 5.0	1.1 vs 2.9	5.3 vs 7.2	4.0 vs 4.3	5.6 vs 9.7	3.1 vs 4.9	
Serious infections	2.9/100 PY	NR	0.4 vs 0.7	NR	NR	0.6 vs 4.0	NR	
Injection-site reactions	NR	2.3 vs 5.0	3.0 vs 2.9	NR	1.7 vs 2.0	NR	4.9 vs 6.8	
ADAs	5.5	38.3 vs 38.2	33.1 vs 32.0	57.9 vs 55.5	44.4 vs 50.5	47.4 vs 53.0	28.7 vs 35.8	
nAbs	NR	9.1 vs 11.1	13.6 vs 14.6	57.7 vs 55.5	13.8 vs 14.0	NR	25.6 vs 31.8	

[†] Results are for biosimilar vs reference adalimumab;

[‡] Not applicable to ACR response data;

[§] DAS28 (CRP);

[¶] DAS28 (ESR).

ACR: American College of Rheumatology; ACRX: The proportion of patients achieving an X% improvement by American College of Rheumatology criteria; ADA: Anti-drug antibody; BL: Baseline; CRP: C-reactive protein; DAS28: 28-point Disease Activity Score; EMA: European Medicines Agency; ESR: Erythrocyte sedimentation rate; EULAR: European League Against Rheumatism; nAb: Neutralising antibody; NR: Not reported; PY: Patient-years; RA: Rheumatoid arthritis; TEAE: Treatment-emergent adverse event.

Pivotal Phase III trials in patients with PsO were conducted for ABP 501 [62], GP2017 [66] and MSB11022 [68]. All were randomized, controlled, double-blind, parallel-group trials with treatment durations ranging from 51 to 52 weeks. The trials all enrolled adults with active, clinically stable, moderate-to-severe PsO and compared the biosimilar of interest with reference adalimumab. Across trials, all adalimumab products (biosimilar and reference) were administered subcutaneously at a dose of 80 mg during Week 1, then 40 mg every 2 weeks from Week 2 onwards. Primary study end points and prespecified limits for bioequivalence were percent improvement in Psoriasis Area and Severity Index (PASI) score from baseline to Week 16 (ABP 501; equivalence margin: -15–15%) or the proportion of patients achieving a 75% reduction in PASI at Week 16 (GP2017 and MSB11022; equivalence margin: -18–18%). All three studies included switches between treatments. In the ABP 501 study, patients who initially received reference adalimumab were rerandomized at Week 16 to either continue treatment or switch to ABP 501 [62]. In the GP2017 study, patients were initially randomized to receive GP2017 or reference adalimumab and all patients were rerandomized at Week 17 to either remain on the initial treatment or to switch to the other treatment; patients were switched again at Weeks 23, 29 and 35 [66]. In the MSB11022 study, patients who initially received reference adalimumab were rerandomized at Week 16 to either remain on reference adalimumab or switch to MSB11022 [68].

In the pivotal clinical trials for each product, no significant differences were identified between the biosimilar and reference product in terms of efficacy, safety and immunogenicity (Table 4 & Table 5).

In the Phase III studies, absolute values reported for the primary end point varied among studies (Figure 2), although this is likely to have been influenced by the different study settings and time points for evaluation of ACR20. Nevertheless, there was no clinically significant difference in the proportions of patients achieving ACR20 with reference adalimumab or biosimilars within each study, and all of the Phase III studies met their primary end points. In each case, the differences between biosimilar adalimumab and reference adalimumab were contained

Table 5. Efficacy, safety, and immunogenicity results[†] of pivotal trials in patients with plaque psoriasis for adalimumab biosimilars approved by the European Medicines Agency and/or FDA.

	Adalimumab (Humira®)	ABP 501	GP2017	MSB11022	Ref.
N	814	172 vs 173	234 vs 231 [‡]	222 vs 221 [‡]	[62,66,68]
Efficacy outcomes, %					
PASI75 at Week 16	71	74.4 vs 82.7	67.0 vs 64.8 [§]	89.7 vs 91.6 [¶]	
PASI90 at Week 16	37 (Week 12)	47.1 vs 47.4	NR	NR	
PASI100 at Week 16	14 (Week 12)	16.9 vs 19.7	NR	NR	
Mean PASI improvement from BL	76 (Week 12)	80.9 vs 83.1	NR	92.1 vs 93.0 [¶]	
PGA clear or minimal	60 (Week 12)	58.7 vs 65.3	NR	NR	
PGA clear	16 (Week 12)	NR	NR	NR	
Safety outcomes, %					
Any TEAE	62.2	67.2 vs 63.6	50.2 vs 52.6	51.6 vs 53.2	
Serious TEAE	1.8	3.4 vs 2.9	1.3 vs 4.3	3.6 vs 2.7	
Serious infections	0.6	1.1 vs 0.6	NR	NR	
Injection-site reaction	NR	1.7 vs 5.2	6.5 vs 3.4	11.8 vs 13.6	
ADAs	8.8	55.2 vs 63.6	36.8 vs 34.1	88.1 vs 88.4	
nAbs	NR	9.8 vs 13.9	29.5 vs 27.2	41.1 vs 42.3	

[†]Results are for biosimilar vs reference adalimumab;

[‡]Patients randomized;

[§]Per-protocol analysis (GP2017, n = 197; reference adalimumab, n = 196);

[¶]Per-protocol analysis (MSB11022, n = 203; reference adalimumab, n = 191).

ADA: Anti-drug antibody; BL: Baseline; EMA: European Medicines Agency; NR: Not reported; PASIX: Proportion of patients achieving an X% improvement in Psoriasis Area and Severity Index; PGA: Physician Global Assessment; PsO: Psoriasis; nAb: Neutralizing antibody; TEAE: Treatment-emergent adverse event.

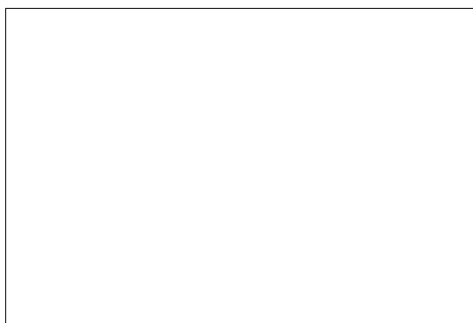


Figure 2. Forest plot for the primary end points of pivotal trials (proportions of patients achieving an ACR20 response) in patients with RA for adalimumab biosimilars approved by the EMA and/or FDA [63–74,67,69,70]. ACR20 was evaluated at Week 24 unless otherwise specified.

*95% CIs were calculated using a Mantel–Haenszel random-effects model; [†]ACR20 at Week 12; [‡]n is based on nonresponder imputation in the full analysis set.

ACR20: 20% improvement in American College of Rheumatology criteria; EMA: European Medicines Agency; RA: Rheumatoid arthritis.

within the prespecified limits for bioequivalence/biosimilarity (where applicable) (Tables 3 & 4) [63–74,67,69,70]. In addition, we analyzed the risk ratio for achieving ACR20 between patients treated with biosimilars and reference adalimumab: the results also support the lack of significant differences (Figure 2). Efficacy results for CT-P17 are noteworthy in that the proportion of patients achieving an ACR20 response (primary end point) or a good European League Against Rheumatism response at Week 24 were exactly the same for the CT-P17 and reference adalimumab groups [70].

Safety and tolerability were comparable between biosimilar adalimumab and reference adalimumab in all of the RA trials and no new safety signals were identified. Furthermore, no clinically relevant differences in immunogenicity were noted between biosimilar and reference adalimumab groups in any of the RA trials [63–74,67,69,70]. Higher ADA levels were observed at Weeks 4, 12 or 26 postbaseline in the Phase III study of ABP 501, compared with

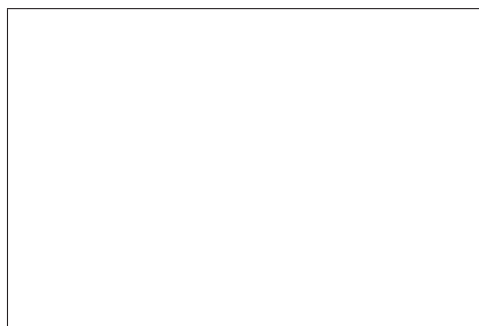


Figure 3. Forest plot for the proportions of patients achieving PASI75 at Week 16 in patients with PsO for adalimumab biosimilars approved by the EMA and/or FDA [62,66,68].

*95% CIs were calculated using a Mantel–Haenszel random-effects model; †n is based on nonresponder imputation in the full analysis set.

EMA: European Medicines Agency; PASI75: 75% reduction in Psoriasis Area and Severity Index; PsO: Psoriasis.

previously reported levels in historical pivotal trials, possibly due to the use of a more sensitive assay; however, the percentages of patients who tested positive for binding and neutralizing antibodies were similar between ABP 501 and reference adalimumab groups (anti-drug antibodies [ADAs]: 38.3 vs 38.2%; neutralizing antibodies: 9.1 vs 11.1%) [63].

Similarly to the Phase III studies in RA populations, all of the Phase III studies in PsO populations met their primary efficacy end points, with the differences between biosimilar adalimumab and reference adalimumab contained within the prespecified limits for bioequivalence (Tables 3 & 5) [62,66,68]. Absolute values reported for the proportion of patients achieving a 75% reduction in PASI score (PASI75) at Week 16 varied among studies, likely reflecting differences in the study designs; however, the risk ratios for PASI75 at Week 16 supported a lack of significant differences between the biosimilar and reference adalimumab in each case (Figure 3). No clinically relevant differences in the rates of treatment-emergent adverse events or immunogenicity were noted between biosimilar adalimumab and reference adalimumab in any of the PsO trials [62,66,68].

CT-P17 and PF-06410293 differ from the other approved biosimilars in that additional clinical trials were conducted to evaluate the ease of injection for patients (Table 3) [49,50]. An open-label, single-arm, ‘PFP sub-study’ was conducted in 50 patients with moderate-to-severe RA who were enrolled in the main Phase III study of PF-06410293 [49,69]. The delivery system success rate was assessed based on six consecutive PF-06410293 doses over a period of 10 weeks. The delivery system success rate was 100% and no medical device complaints were recorded [49]. For CT-P17, the usability of PFS and AI devices was evaluated in the CT-P17 3.1 and 3.2 studies (Table 3). The CT-P17 3.1 study showed that patients can self-inject CT-P17 safely and satisfactorily at a level similar to the reference drug [70] and the CT-P17 3.2 study supported the sufficiency of CT-P17 AI usability [50].

Conclusion

To date, eight adalimumab biosimilars have been approved by the EMA and/or FDA. All have proven biosimilarity to the reference drug, but there are differences in the characteristics of each formulation and device, which may affect the convenience of treatment for patients. As the first high-concentration biosimilar to receive EMA approval, the introduction of CT-P17 is expected to have a significant impact on the adalimumab treatment landscape with potential benefits including reduced pain during self-injection and the need for fewer injections. In addition, although the clinical trials underpinning regulatory approval for each biosimilar had similar designs, additional supportive studies were conducted for some biosimilars. Trials comparing PK parameters according to device type or usability studies, for example, may help to solidify the totality of evidence for the biosimilar. This review provides a contemporary update on adalimumab biosimilars, wherein device and formulation characteristics are compared for all currently available products, and clinical trials for each biosimilar are summarised.

Future perspective

Having been available in Europe since 2018, adalimumab biosimilars are set to enter the US market from 2023 [2]. With the current (Europe) and anticipated (US) availability of multiple adalimumab biosimilars, competition among

reference adalimumab and its biosimilars is expected to be fierce. Indeed, the international net revenue for reference adalimumab fell by 13.6% in 2020, following a 31.1% decrease in 2019 due to biosimilar competition [72,73].

There are several factors that affect the market share of the reference product and adalimumab biosimilars, with the characteristics of the products themselves being one important consideration [74]. Thus, it is and will continue to be important for healthcare providers and patients to understand the characteristics of each biosimilar product, as summarized in the present review, to determine the potential benefits and limitations of the various options. Licensed biosimilars have varied product characteristics, and in particular, this study focused on formulations and properties with the potential to influence injection-site pain. This reflects the importance of making subcutaneous injections as painless as possible for patients, as any discomfort could reduce patient adherence or lead to treatment discontinuation [40,75,76]. Studies comparing the original and newer formulations of reference adalimumab have demonstrated that the low-injection-volume, citrate-free version of adalimumab is associated with less injection-site pain [10] and improved adherence and persistence [9]. In addition, an analysis of the Italian national pharmacovigilance database found that the change in reference adalimumab formulation was followed by a decrease in reported injection-site reactions [77]. Taken together, the newer reference adalimumab formulation may alleviate injection-site pain experienced by patients and improve treatment adherence, potentially improving outcomes [76]. Thanks to these advantages, it seems that many patients have moved to the high-concentration formulation of reference adalimumab, which has captured over 60% of the EU market share and 70% of the US market share for adalimumab [78]. Therefore, it is anticipated that biosimilars may need to reflect the newer formulation of reference adalimumab, rather than the lower-concentration formulation, to be potentially competitive in the market [79].

In the US, an interchangeability designation for a biosimilar means that it can be substituted for the reference product without the intervention of the prescriber [80]. With the recent FDA approval of the first interchangeable adalimumab biosimilar, issues related to product concentration continue to be key topics of discussion. In October 2021, the FDA designated BI 695501 interchangeable with the reference product, following original approval of BI 695501 in 2017 [81]. Having filed a Citizen Petition in 2020, the developer is continuing to lobby the FDA to change how it determines the ‘strength’ for biosimilar approval, from requiring that both the total content and concentration of the drug are the same between the reference product and a candidate biosimilar (whether interchangeable or not), to only considering the total drug content (without regard to concentration) [82–94]. The FDA has not yet provided a clear answer, with an interim response indicating that further review is required [83]. The requested change would enable biosimilars reflecting the original reference adalimumab formulation to be deemed biosimilar to or interchangeable with the newer reference adalimumab formulation [84]. Given the large market share of the high-concentration reference product, it is expected that the FDA’s decision could have a significant impact on the adalimumab biosimilar market.

Executive summary

Adalimumab biosimilars licensed by the European Medicines Agency &/or FDA

- There are currently eight adalimumab biosimilars approved by the European Medicines Association and/or the US Food and Drug Administration.

Formulation & device characteristics for approved adalimumab biosimilars

- There are differences between the approved adalimumab biosimilars in terms of their formulations, delivery device parameters and stability, which may potentially affect the convenience of treatment for patients.

Clinical development programs for adalimumab biosimilars

- Although the clinical trials underpinning regulatory approval for each biosimilar had similar designs, each biosimilar differed slightly in terms of study populations evaluated and/or the additional supporting studies that were conducted.
- CT-P17 is currently the only biosimilar approved based on data comparing the biosimilar to the high-concentration reference product across all clinical trials.

Conclusion

- The present article provides a timely update on adalimumab biosimilars, given the recent approval of the first high-concentration adalimumab biosimilar.

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