Immunogenicity of Biosimilars for Rheumatic Diseases, Plaque Psoriasis, and Inflammatory Bowel Disease: A Review from Clinical Trials and Regulatory Documents

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Table 1. Characteristics of ADAb and nAb assays

Biosimilar / Manufacturer	Study	ADAb Assay	nAb Assay	Immunogenicity blood sample collection	Differentiation between IgG subtypes?
Reference product: Adalimumab					
Healthy volunteers					
Cyltezo (BI 695501) Boehringer Ingelheim	VOLTAIRE-PK (NCT02045979) [19]	Homogeneous ECL bridging assay (single assay, 3-tiered approach) with acid dissociation step	Inhibition of an in vitro functional activity in a cell-based format (TNFα-dependent ADCC)	Baseline (predose) and Days 1-9, 14, 21, 28, 35, 44, 56, and 71	n/a
Imraldi (SB5) Samsung Bioepis	SB5-G11-NHV (NCT02144714) [20]	ECL bridging assay (biotin and ruthenium), two-tiered approach	Competitive ligand-binding assay	Days 1 (predose), 15 (Week 2), and 71 (Week 10)	n/a
Solymbic (ABP 501, adalimumab-atto) Amgen	EudraCT 2012-000785-37 [21]	ECL bridging assay that detects all antibody classes [93]	A cell-based assay using TNFα-induced phosphorylation of NFκB	Days 1 (predose), 16, 29, and 63 (Weeks 2, 4, and 9)	No Both ADAb and nAb assays were expected to detect all antibody classes that inhibit biologic activity of the drug, including monovalent IgG4
Hulio (FKB327) Fujifilm Kyowa Kirin Biologics, Mylan	FKB327-001, EudraCT 2012-005140-23 [22, 33]	ECL assay (insufficient drug tolerance limit; many inconclusive samples)	ECL competitive assay (insufficient drug tolerance limit; many inconclusive samples)	Baseline and Days 15 (Week 2), 29 (Week 4), and 64 (Week 9)	n/a
Hyrimoz (GP2017, adalimumab-adaz) Hexal/Sandoz	GP17-101 (EudraCT 2012-004205-27), GP17-104 (EudraCT 2015-000579-28) [23]	multi-tiered ECL bridging assay	Competitive ligand-binding assay	Days 1-10, 16, 23, 30, 44, 58, and 72	n/a

Biosimilar / Manufacturer	Study	ADAb Assay	nAb Assay	Immunogenicity blood sample collection	Differentiation between IgG subtypes?
MSB11022 Merck	EMR200588-001 (NCT03014947) [24]	single ECL assay with acid dissociation	n/a	Day 1 (predose) and Days 15 (Week 2), 29 (Week 4), 43 (Week 6), and 71 (Week 10)	n/a
Rheumatic diseases					
Cyltezo (BI 695501) Boehringer Ingelheim	VOLTAIRE-RA (NCT02137226) [30]	Homogeneous ECL bridging assay (single assay approach)	Inhibition of an in vitro functional activity in a cell-based format (TNFα-dependent ADCC)	Baseline (predose) and Weeks 1, 2, 4, 12, 24, 40, 48, and 58	n/a
Imraldi (SB5) Samsung Bioepis	SB5-G31-RA (NCT02167139) [31, 70]	Bridging ligand-binding ECL assay	Inhibition of TNFα binding to immobilized SB5 by circulating ADAbs	**Baseline-Week 24**: Baseline, Weeks 4, 8, 16, and 24	n/a
Solymbic (ABP 501, adalimumab-atto) Amgen	20120262 (NCT01970475) [32]	ECL bridging assay	Ligand-binding bioassay	Baseline and Weeks 4, 12, and 26	No The nAb assay was expected to detect all antibody classes that inhibit biologic activity of the drug, including monovalent IgG4.
Hulio (FKB327) Fujifilm Kyowa Kirin Biologics, Mylan	FKB327-002, ARABESC (NCT02260791) and FKB327-003, ARABESC-OLE (NCT02405780) [33]	n/a	n/a	FBK327-002: Baseline and Weeks 2, 4, 12, 24; FKB327-003: Weeks 36, 48, 54, 78, and 100	n/a
PF-06410293 Pfizer	REFLECTIONS B538-02 (NCT02480153) [34]	ECL assay	Cell-based assay	Baseline and weeks 2, 6, 12, and 26	n/a

Biosimilar / Manufacturer	Study	ADAb Assay	nAb Assay	Immunogenicity blood sample collection	Differentiation between IgG subtypes?
Exemptia (ZRC-3197) Cadila Healthcare	[NOT REGISTERED AT ClinicalTrials.gov or EudraCT] [35]	n/a	n/a	Baseline and weeks 4 and 12	n/a
Plaque psoriasis					
Solymbic (ABP 501, adalimumab-atto) Amgen	20120263 (NCT01970488) [54, 69]	2-tiered ECL bridging assay	n/a	Baseline, Weeks 4, 16, 20, 32, and 52	n/a
Hyrimoz (GP2017) Hexal/Sandoz	GP17-301 (NCT02016105) [23, 55]	multi-tiered ECL bridging assay	Competitive ligand-binding assay	Baseline and Weeks 3, 7, 11, 17, 23, 29, 35, 41, 47, and 51	n/a
Reference product: Etanercept					
Healthy volunteers					
Benepali (SB4) Samsung Bioepis	SB4-G11-NHV (NCT01865552) [25]	ECL bridging assay	Cell-based assay	Predose in period 1 (Day 1) and predose in period 2 (Day 29)	n/a
Erelzi (GP2015, etanercept-szzs) Hexal/Sandoz	Studies GP15-101, GP15-102, and GP15-104 [26]	Bridging ECL assay (screening, followed by confirmatory assay), including acid dissociation steps (acid dissociation inferred based on EGALITY trial [56])	Competitive ligand-binding assay	n/a	n/a
LBEC0101 LG Chem	LG-ECCL003 (NCT01725620) [27]	Affinity capture elution assay, with acid dissociation step	n/a	Before the first dose and at 36 days after both the first and the second dose	n/a
Rheumatic diseases					

Biosimilar / Manufacturer	Study	ADAb Assay	nAb Assay	Immunogenicity blood sample collection	Differentiation between IgG subtypes?
Benepali (SB4)	SB4-G31-RA (NCT01895309) [36, 79, 80]	ECL (single assay with SB4 tag), with acid dissociation step	Competitive ligand-binding assay	Weeks 0, 2, 4, 8, 12, 16, 24, and 52	n/a
CHS-0214 Coherus BioSciences	CHS-0214-02, Part 1 and Part 2 (NCT02115750) [37]	n/a	n/a	n/a	n/a
LBEC0101 LG Chem	LG-ECCL002 (NCT02357069) [38]	ECL, using biotinylated ETN-RP and SULFO-TAG labelled ETN-RP	ECL, using biotinylated ETN-RP and SULFO-TAG labelled TNF-α	Baseline and Weeks 12, 24, and 52	n/a
Plaque psoriasis					
Erelzi (GP2015, etanercept-szzs) Hexal/Sandoz	EGALITY, Study GP15- 302 (NCT01891864) [56, 81]	Bridging ECL assay (screening, followed by confirmatory assay), including acid dissociation steps	Competitive ligand-binding assay	n/a	n/a
Reference product: Infliximab					
Healthy volunteers					
Flixabi/ Renflexis (SB2, infliximab-abda) Samsung Bioepis	SB2-G11-NHV, NCT01922336 [28]	ECL	Cell-based assay	Days 1 (predose), 29 (Week 4), and 71 (Week 10)	n/a
Inflectra (CT-P13, infliximab-dyyb)	CT-P13 1.4 (EudraCT 2013-003173-10) [29, 67]	ECL; reanalysis using ELISA	Flow-through immunoassay (Gyros immunoassay platform)	Day 1, Week 8	n/a

Biosimilar / Manufacturer	Study	ADAb Assay	nAb Assay	Immunogenicity blood sample collection	Differentiation between IgG subtypes?
Celltrion					
Rheumatic diseases					
Flixabi/ Renflexis (SB2, infliximab-abda) Samsung Bioepis	SB2-G31-RA (NCT01936181) [39, 77, 78]	ECL	Competitive ligand-binding assay	Baseline and Weeks 2, 6, 14, 22, 30, 38, 46, 54, 62, 70, and 78 (all predose)	n/a
Inflectra (CT-P13, infliximab-dyyb) Celltrion	PLANETRA (CT-P13 3.1, NCT01217086) [44, 94] and PLANETRA OLEX (NCT01571219) [45]	ECL	Flow-through immunoassay (Gyros immunoassay platform)	Screening, and Weeks 14, 30, 54, 78, and 102	n/a
Inflectra, Remsima (CT-P13, infliximab-dyyb) Nippon Kayaku Co. Ltd. Celltrion	JAPIC Clinical Trials Information Center study JapicCTI-111620 [42]	ECL	Flow-through immunoassay (Gyros immunoassay platform)	Weeks 14, 30, and 54	n/a
Inflectra (CT-P13, infliximab-dyyb) Celltrion	PLANETAS (CT-P13 1.1, NCT01220518) [40, 74] and PLANETAS OLEX (NCT01571206) [41]	ECL	Flow-through immunoassay (Gyros immunoassay platform)	Screening, and Weeks 14, 30, 54, 78, and 102	n/a

Biosimilar / Manufacturer	Study	ADAb Assay	nAb Assay	Immunogenicity blood sample collection	Differentiation between IgG subtypes?
Inflectra (CT-P13, infliximab-dyyb) Celltrion	BIO-SWITCH, Dutch Trial Register identifier NTR5297 [43]	RIA [95]	n/a	Baseline and Month 6	n/a
Ixifi (PF-06438179/ GP1111, infliximab-qbtx) Pfizer	REFLECTIONS B537-02 (NCT02222493) [46]	ECL	Cell-based assay	Baseline and Weeks 2, 6, 14, and 30	n/a
IBD					
Inflectra (CT-P13, infliximab-dyyb) Celltrion	NOR-SWITCH (NCT02148640) [63]	n/a (only nAb assay was performed)	In-house inhibition assay	n/a	n/a
Inflectra (CT-P13, infliximab-dyyb) Celltrion	Gecse et al [61], Gonczi et al [71, 72]	Bridging ELISA	Not performed	n/a	n/a
Inflectra (CT-P13, infliximab-dyyb) Celltrion	Farkas et al [60]	ELISA	Not performed	Week 14	n/a
Inflectra (CT-P13, infliximab-dyyb) Celltrion	Farkas et al [59]	ELISA	Not performed	Week 8	n/a
Inflectra	Jahnsen et al [62]	Automated assay (AutoDELFIA platform)	Not performed	Week 14	n/a

Biosimilar / Manufacturer	Study	ADAb Assay	nAb Assay	Immunogenicity blood sample collection	Differentiation between IgG subtypes?
(CT-P13, infliximab-dyyb) Celltrion					
Inflectra (CT-P13, infliximab-dyyb) Celltrion	Buer et al [58] and Høivik et al [73]	Automated assay (AutoDELFIA platform)	Not performed	At each infusion	n/a
Inflectra, Remsima (CT-P13, infliximab-dyyb) Celltrion	Smits et al [66, 75, 76]	RIA	Not performed	Baseline and Weeks 16, 52, and 104	n/a
Inflectra/Remsima (CT-P13, infliximab-dyyb) Celltrion	Ben-Horin et al [57]	Anti-human λ chain ELISA	Competitive ligand-binding assay	Baseline only (cross-sectional case-control study)	No
Inflectra/Remsima (CT-P13, infliximab-dyyb) Celltrion	Kolar et al [64]	ELISA	n/a	IFN to CT-P13 switch cohort (prospective): Weeks 0 and 56 TNFi-naïve CT-P13 cohort (retrospective): Weeks 14 and 46	n/a
Inflectra (CT-P13, infliximab-dyyb) Celltrion	Razanskaite et al [65]	ELISA	n/a	Before switch and after 3-5 doses of CT-P13	n/a
Reference product: Rituximab					
Rheumatic diseases					

Biosimilar / Manufacturer	Study	ADAb Assay	nAb Assay	Immunogenicity blood sample collection	Differentiation between IgG subtypes?
Truxima (CT-P10) Celltrion	CT-P10 1.1 (NCT01534884) [49, 82] and the extension CT-P10 1.3 (NCT01873443) [48]	ECL bridging assay with CT-P10 tags (sulfo-tag [ruthenium] and biotin) Screening assay: labelled CT-P10 Confirmation assay: labelled + non-labeled CT-P10	CDC assay: binding of RTX or CT-P10 to CD20 of B-cells activates the complement system – nAbs inhibit this effect	Weeks 0, 24, and 48	n/a
Truxima (CT-P10) Celltrion	CT-P10 3.2 (NCT02149121) [47, 68]	Based on info for trial CT-P10 1.1 (see the row above): ECL bridging assay with CT-P10 tags (sulfo-tag [ruthenium] and biotin) Screening assay: labelled CT-P10 Confirmation assay: labelled + non-labelled CT-P-10	Based on info for trial CT-P10 1.1 (see the row above): CDC assay: binding of RTX or CT-P10 to CD20 of B-cells activates the complement system – nAbs inhibit this effect	Weeks 0, 24, and 48	n/a
Rixathon (GP2013) Hexal/Sandoz	GP13-201 (NCT01274182) [50]	Affinity capture elution ELISA	CDC assay	Randomization and weeks 4, 16, 24, 38, and 52	n/a
Hexal/Sandoz	GP13-302 (NCT02514772) [51]	Affinity capture elution ELISA (multi-tiered)	Cell-based assay	Each study visit and when any AE was considered immune system-related	n/a
PF-05280586 Pfizer	REFLECTIONS B328-01 (NCT01526057) [52]	ECL assays (assay for dosed product followed by cross-reactivity assay)	CDC assay	Baseline and weeks 2, 4, 8, 12, and 24	n/a

Biosimilar / Manufacturer	Study	ADAb Assay	nAb Assay	Immunogenicity blood sample collection	Differentiation between IgG subtypes?
PF-05280586 Pfizer	REFLECTIONS B328-04 (NCT01643928) [53]	ECL assays (assay for dosed product followed by cross-reactivity assay)	Cell-based assay	Predose on Days 1, 15 (Week 2), 85 (Week 12), and 169 (Week 24) during each of Courses 1, 2, and 3	n/a

ADAb, anti-drug antibody; ADA, adalimumab; ADCC, antibody-dependent cell-mediated cytotoxicity; AS, ankylosing spondylitis; BL, baseline; CDC, complement-dependent cytotoxicity; ECL, electrochemiluminescence; ELISA, enzyme-linked immunosorbent assay; ETN, etanercept; INF, infliximab; MTX, methotrexate; n/a, data not available; nAb, neutralizing antibody; RIA, radioimmunoassay; RP, reference product; RTX, rituximab; RA, rheumatoid arthritis.

Table 2. Incidence of ADAb and nAb and the Effects of ADAb Formation on PK, PD, Efficacy, and Safety

Biosimilar / Manufacturer	Participants	cDMARD or Previous Therapy	Trial Registration and Design	Patients with ADAbs (% of total patients per treatment group, [n_1/N]x100)		Patients with nAbs (% of ADAb-positive patients per treatment group, [n_2/n1]x100)		PK by ADAb Status	Effect of ADAbs on PD, efficacy, and safety parameters
				Reference product	Biosimilar	Reference product	Biosimilar		
Reference product: Adalimumab									
Healthy volunteers									
Cyltezo (BI 695501) Boehriner Ingelheim	Healthy volunteers	n/a	VOLTAIRE-PK (NCT02045979) [19] N=327 Single-dose, randomized (1:1:1) trial of BI 695501, US-ADL, and EU-ADL with 10-week follow-up	**Baseline** ADA-EU: 3.7% (4/108) ADA-US: 2.8% (3/108) **Week 4** ADA-EU: 37.4% (40/107) ADA-US: 56.1% (60/107) **Week 10** ADA-EU: 84.3% (91/108) ADA-US: 88.0% (95/108) denominator N calculated	**Baseline** 3.7% (4/108) **Week 4** 46.7% (50/107) **Week 10** 92.5% (99/107) denominator N calculated based on n and % values	**Baseline** ADA-EU: 50.0% (2/4) ADA-US: 33.3% (1/3) **Week 4** ADA-EU: 22.5% (9/40) ADA-US: 31.7% (19/60) **Week 10** ADA-EU: 69.2% (63/91) ADA-US: 72.6% (69/95)	**Baseline** 75.0% (3/4) **Week 4** 24.0% (12/50) **Week 10** 64.6% (64/99)	A decrease in $AUC_{0\text{-inf, pred}}$ was observed for patients with high titer values for ADAbs	n/a (healthy volunteers)

Biosimilar / Manufacturer	**Participants**	**cDMARD or Previous Therapy**	**Trial Registration and Design**	**Patients with ADAbs (% of total patients per treatment group, [n_1/N]x100)**		**Patients with nAbs (% of ADAb-positive patients per treatment group, [n_2/n1]x100)**		**PK by ADAb Status**	**Effect of ADAbs on PD, efficacy, and safety parameters**
				Reference product	**Biosimilar**	**Reference product**	**Biosimilar**		
				based on n and % values					
Imraldi (SB5) Samsung Bioepis	Healthy volunteers	n/a	SB5-G11-NHV (NCT02144714) [20] Randomized (1:1:1), single-blind, single-dose, 3-arm trial of ADA-EU, ADA-US, and SB5 N=189 ADAb tests were performed at days 1 (predose), 15 (Week 2), and 71 (Week 10)	**Overall:** ADA-EU: 95.2% (60/63) ADA-US: 100% (63/63)	**Overall:** 98.4% (62/63)	**Overall:** ADA-EU: 80.0% (48/60) ADA-US: 82.5% (52/63)	**Overall:** 79.0% (49/62)	98% of participants were ADAb-positive; higher ADAb titre was associated with lower AUC_{inf} and AUC_{last}, but also with higher drug clearance, in a way that was comparable between SB5 and the reference products	n/a (healthy volunteers)
Solymbic (ABP 501, adalimumab-atto) Amgen	Healthy volunteers	-	EudraCT 2012-000785-37 [21] Randomized (1:1:1), single-blind, single-dose, 3-arm, parallel-group trial of ADA-US, ADA-EU, or ABP 501 N=203	**Overall:** ADA-EU: 67.2% (45/67) ADA-US: 55.1% (38/69)	**Overall:** 53.7% (36/67)	**Overall:** ADA-EU: 31.1% (14/45) ADA-US: 39.5% (15/38)	**Overall:** 33.3% (12/36)	AUC_{inf} 20-30% lower in ADAb-positive than ADAb-negative patients $t_{1/2}$ 50% shorter in ADAb-	n/a (healthy volunteers)

Biosimilar / Manufacturer	Participants	cDMARD or Previous Therapy	Trial Registration and Design	Patients with ADAbs (% of total patients per treatment group, [n_1/N]x100)		Patients with nAbs (% of ADAb-positive patients per treatment group, [n_2/n1]x100)		PK by ADAb Status	Effect of ADAbs on PD, efficacy, and safety parameters
				Reference product	Biosimilar	Reference product	Biosimilar		
			ADAb tests were performed at day 1 (predose), and at Weeks 2, 4, and 9					positive than ADAb-negative patients	
Hulio (FKB327) Fujifilm Kyowa Kirin Biologics, Mylan	Healthy volunteers	-	FKB327-001, EudraCT 2012-005140-23 [22, 33] N=180 Randomized (1:1:1), double-blind, single-dose trial of ADA-EU, ADA-US, and FKB327 with a follow-up of 9 weeks	**Baseline:** ADA-EU 5.0% (3/60) ADA-US 5.0% (3/60) **Week 2:** ADA-EU 31.7% (19/60) ADA-US 25.0% (15/60) **Week 4:** ADA-EU 31.7% (19/60) ADA-US 30.0% (18/60) **Week 9:** ADA-EU	**Baseline:** 5.0% (3/60) **Week 2:** 35.0% (21/60) **Week 4:** 33.9% (20/60) **Week 9:** 69.5% (41/59)	**Baseline:** ADA-EU 0 ADA-US 0 **Week 2:** ADA-EU 0 ADA-US 0 **Week 4:** ADA-EU 52.6% (10/19) ADA-US 55.6% (10/18) **Week 9:** ADA-EU 81.8% (36/44) ADA-US 81.0% (34/42)	**Baseline:** 0 **Week 2:** 0 **Week 4:** 10.0% (2/20) **Week 9:** 85.4% (35/41)	In all groups, higher ADAb titre was associated with lower $AUC_{0-\infty}$ and shorter $t_{1/2}$ There was no clear relationship between ADAb titre and C_{max}	n/a (healthy volunteers)

Biosimilar / Manufacturer	Participants	cDMARD or Previous Therapy	Trial Registration and Design	Patients with ADAbs (% of total patients per treatment group, [n_1/N]x100)		Patients with nAbs (% of ADAb-positive patients per treatment group, [n_2/n1]x100)		PK by ADAb Status	Effect of ADAbs on PD, efficacy, and safety parameters
				Reference product	Biosimilar	Reference product	Biosimilar		
				73.3% (44/60) ADA-US 70.0% (42/60) (insufficient drug tolerance limit; many inconclusive samples)	(insufficient drug tolerance limit; many inconclusive samples)	(insufficient drug tolerance limit; many inconclusive samples)	(insufficient drug tolerance limit; many inconclusive samples)		
Hyrimoz (GP2017, adalimumab-adaz) Hexal/Sandoz	Healthy volunteers	n/a	GP17-101, GP17-104 [23] Double-blind, parallel-group studies in healthy men (GP17-104) or men and women (GP17-101) randomized to receive GP2017, ADA-US, or ADA-EU for 72 days	**n/a**	**n/a**	**n/a**	**n/a**	Smaller $AUC_{0\text{-}last}$ and $AUC_{0\text{-}inf}$ in patients in ADAb-positive vs ADAb-negative participants	n/a (healthy volunteers)
MSB11022 Merck	Healthy volunteers	-	EMR200588-001 (NCT03014947) [24] N=237	**Week 10:** ADA-EU: 83.5% (66/79)	**Week 10:** 82.1% (64/78)	n/a	n/a	ADAb-positive patients had 34-45% lower $AUC_{0\text{-}inf}$, 13-25% lower	n/a (healthy volunteers)

Biosimilar / Manufacturer	Participants	cDMARD or Previous Therapy	Trial Registration and Design	Patients with ADAbs (% of total patients per treatment group, [n_1/N]x100)		Patients with nAbs (% of ADAb-positive patients per treatment group, [n_2/n1]x100)		PK by ADAb Status	Effect of ADAbs on PD, efficacy, and safety parameters
				Reference product	**Biosimilar**	**Reference product**	**Biosimilar**		
			Randomized (1:1:1), double-blind, single-dose trial of ADA-EU, ADA-US, and MSB11022 with a follow-up of 10 weeks	ADA-US: 81.3% (65/80)				C_{max}, and 44-57% shorter $t_{1/2}$	
Rheumatic diseases									
Cyltezo (BI 695501) Boehriner Ingelheim	RA	MTX	VOLTAIRE-RA (NCT02137226) [30] N=645 Randomized (1:1) double-blind treatment with BI 695501 or ADA At Week 24, ADA-treated patients were re-randomized (1:1) for an additional 24 weeks of treatment with BI 695501 or ADA (follow-up to week 58)	**Baseline:** 6.5% (21/321) **Week 24:** 47.8% (144/301) **Week 48**: ADA/ADA 49.6% (69/139) **Week 58:** ADA/ADA 58.3% (21/36)	**Baseline:** 3.4% (11/324) **Week 24:** 43.2% (127/294) **Week 48:** 695501/ 695501 41.8% (118/282) ADL/ 695501 36.2% (50/138) **Week 58:** 695501/ 695501 44.7% (21/47) ADA/	**Baseline:** 76.2% (16/21) **Week 24:** 42.4% (61/144) **Week 48**: ADA/ADA 43.5% (30/69) **Week 58:** ADA/ADA 66.7% (14/21)	**Baseline:** 81.8% (9/11) **Week 24:** 37.8% (48/127) **Week 48:** 695501/ 695501 45.8% (54/118) ADA/ 695501 42.0% (21/50) **Week 58:** 695501/ 695501 76.2% (16/21)	ADAb-positive patients had lower drug plasma concentration than ADAb-negative ones	At Week 24, ADAb-positive patients had a lower ACR20 response rate than ADAb-negative ones: BI 695501: 69.3% vs 78.4% ADA: 64.6% vs 71.3% In both treatment groups, ACR20 response rate decreased with the higher ADAb titre

Biosimilar / Manufacturer	Participants	cDMARD or Previous Therapy	Trial Registration and Design	Patients with ADAbs (% of total patients per treatment group, [n_1/N]x100)		Patients with nAbs (% of ADAb-positive patients per treatment group, [n_2/n1]x100)		PK by ADAb Status	Effect of ADAbs on PD, efficacy, and safety parameters
				Reference product	Biosimilar	Reference product	Biosimilar		
					695501 41.2% (14/34)		ADA/ 695501 71.4% (10/14)		
Imraldi (SB5) Samsung Bioepis	RA	MTX	SB5-G31-RA (NCT02167139) [31, 70] N=544 Randomized (1:1) double-blind treatment with SB5 or ADA At Week 24, ADA-treated patients were re-randomized 1:1 for an additional 28 weeks of treatment with SB5 or ADA	**Weeks 1-24 (emergent):** 31.4% (82/261) **Weeks 1-24 (boosted):** 50.0% (4/8) **Weeks 25-52 (emergent):** ADA/ADA 12.6% (11/87) **Weeks 25-52 (boosted):** ADA/ADA 30.8% (12/39)	**Weeks 1-24 (emergent)**: 32.4% (80/247) **Weeks 1-24 (boosted):** 42.1% (8/19) **Weeks 25-52 (emergent)**: SB5/SB5 5.6% (9/160) ADLADA/SB5 6.3% (5/80) **Weeks 25-52 (emergent)**: SB5/SB5 33.0% (31/94) ADA/SB5 35.6% (16/45)	**Weeks 1-24 (overall):** ~50% **Weeks 1-24 (emergent):** 14.6% **Weeks 25-52**: n/a	**Weeks 1-24 (overall)**: ~50% **Weeks 1-24 (emergent):** 13.6% **Weeks 25-52**: n/a	Lower C_{trough} in ADAb-positive than ADAb-negative patients, regardless of treatment assignment	**Weeks 1-24:** Comparable ACR20 responses between ADAb-positive and –negative patients, according to Weinblatt et al [31], but there was a significant difference in Week 24 ACR20 according to SB5 EPAR (ADA, 71%; SB5, 58%). There was no significant difference in ACR20 responses in patients with nAbs (EPAR).

Biosimilar / Manufacturer	Participants	cDMARD or Previous Therapy	Trial Registration and Design	Patients with ADAbs (% of total patients per treatment group, [n_1/N]x100)		Patients with nAbs (% of ADAb-positive patients per treatment group, [n_2/n1]x100)		PK by ADAb Status	Effect of ADAbs on PD, efficacy, and safety parameters
				Reference product	Biosimilar	Reference product	Biosimilar		
									Switching phase (Weeks 25-52): ACR response rate (ACR20, ACR50, and ACR70), EULAR response rate (good and moderate), and proportions of patients with LDA or remission (DAS28, SDAI, or CDAI) had a trend toward decreased efficacy in ADAb-positive patients, versus ADAb-negative patients Post-switch (weeks 24-52), mean DAS28, SDAI, and CDAI values tended to improve in

Biosimilar / Manufacturer	Participants	cDMARD or Previous Therapy	Trial Registration and Design	Patients with ADAbs (% of total patients per treatment group, [n_1/N]x100)		Patients with nAbs (% of ADAb-positive patients per treatment group, [n_2/n1]x100)		PK by ADAb Status	Effect of ADAbs on PD, efficacy, and safety parameters
				Reference product	Biosimilar	Reference product	Biosimilar		
									ADAb-negative patients and worsen in ADAb-positive patients
Solymbic (ABP 501, adalimumab-atto) Amgen	RA	MTX	20120262 (NCT01970475) [32] N=526 Randomized (1:1) double-blind treatment with ABP 501 or ADA for 24 weeks, with follow-up until Week 26	**Baseline:** 2.3% (6/262) **Week 4:** 17.2% (45/262) **Week 12:** 23.7% (62/262) **Week 26:** 35.1% (92/262) **Overall**: 38.2% (100/262)	**Baseline:** 1.9 (5/264) **Week 4:** 18.9% (50/264) **Week 12:** 23.5% (62/264) **Week 26:** 31.8% (84/264) **Overall**: 38.3% (101/264)	**Baseline:** 0 **Week 4:** 8.9% (4/45) **Week 12:** 16.1% (10/62) **Week 26:** 28.3% (26/92) **Overall**: 29.0% (29/100)	**Baseline:** 0 **Week 4:** 10.0% (5/50) **Week 12:** 12.9% (8/62) **Week 26:** 22.6% (19/84) **Overall**: 23.8% (24/101)	n/a	In both treatment groups, similar proportions of ADAb-positive and –negative patients achieved ACR20 response
Hulio (FKB327) Fujifilm Kyowa Kirin Biologics, Mylan	RA, inadequate response to MTX	MTX	FKB327-002, ARABESC (NCT02260791) [33] N=728	**Baseline:** 5.3% (17/321) **Week 2:** 12.1% (39/321)	**Baseline:** 3.7% (12/324) **Week 2:** 9.9% (32/324) **Week 4:**	**Baseline:** 82.4% (14/17) **Week 2:** 76.9% (30/39) **Week 4:**	**Baseline:** 66.7% (8/12) **Week 2:** 84.4% (27/32) **Week 4:**	n/a	For both ADA and FKB327, there was a decrease in efficacy associated with an increase in

Biosimilar / Manufacturer	Participants	cDMARD or Previous Therapy	Trial Registration and Design	Patients with ADAbs (% of total patients per treatment group, [n_1/N]x100)		Patients with nAbs (% of ADAb-positive patients per treatment group, [n_2/n1]x100)		PK by ADAb Status	Effect of ADAbs on PD, efficacy, and safety parameters
				Reference product	Biosimilar	Reference product	Biosimilar		
			Randomized (1:1), double-blind, 24-week trial of ADA-US and FKB327	**Week 4:** 35.6% (114/320) **Week 12:** 52.5% (168/320) **Week 24:** 59.4% (190/320)	38.8% (125/322) **Week 12:** 57.2% (183/320) **Week 24:** 62.0% (201/324)	93.0% (106/114) **Week 12:** 98.2% (165/168) **Week 24:** 99.5% (189/190)	93.6% (117/125) **Week 12:** 98.9% (181/183) **Week 24:** 98.5% (198/201)		ADAb/nAb incidence For both ADA and FKB327, presence of ADAbs/nAbs was associated with a slight increase in treatment-emergent hypersensitivity adverse events (with very low overall incidence)
Hulio (FKB327) Fujifilm Kyowa Kirin Biologics, Mylan	RA, inadequate response to MTX	MTX	FKB327-003, ARABESC-OLE (NCT02405780) [33] N=645 Open-label extension of FKB327-002; in Period 1, patients in each treatment group were re-randomized (2:1) to continue or switch treatments; in Period 2, all	**Period 1** **Week 36:** 50.5% (102/202) **Week 48:**	**Period 1** **Week 36:** FKB327/ FKB327 54.0% (109/202) FKB327/ADA 58.3% (60/103) ADA/FKB327 52.4% (54/103) **Week 48:** FKB327/ FKB327	**Period 1** **Week 36:** 100% (102/102) **Week 48:**	**Period 1** **Week 36:** FKB327/ FKB327 99.1% (108/109) FKB327/ADA 100% (60/60) ADA/FKB327 98.1% (53/54) **Week 48:** FKB327/	n/a	Presence of ADAbs/nAbs was associated with a slight increase in treatment-emergent hypersensitivity adverse events (with very low overall incidence)

Biosimilar / Manufacturer	Participants	cDMARD or Previous Therapy	Trial Registration and Design	Patients with ADAbs (% of total patients per treatment group, [n_1/N]x100)		Patients with nAbs (% of ADAb-positive patients per treatment group, [n_2/n1]x100)		PK by ADAb Status	Effect of ADAbs on PD, efficacy, and safety parameters
				Reference product	Biosimilar	Reference product	Biosimilar		
			patients received FKB327 for an additional 48 weeks	50.8% (101/199)	50.8% (100/197) FKB327/ADA 58.0% (58/100) ADA/FKB327 49.0% (47/96) **Period 2** (includes sequences FKB327/ FKB327/ FKB327, FKB327/ADA/ FKB327, ADA/ FKB327/ FKB327, and ADA/ADA/FKB 327) **Week 54:** 52.5% (299/569) **Week 78:** 49.8% (271/544) **Week 100:** 48.4% (252/521)	98.0% (99/101)	FKB327 100% (100/100) FKB327/ADA 98.3% (57/58) ADA/FKB327 100% (47/47) **Period 2** (includes sequences FKB327/ FKB327/ FKB327, FKB327/ADA / FKB327, ADA/ FKB327/ FKB327, and ADA/ADA/F KB327) **Week 54:** 99.0% (296/299)		

Biosimilar / Manufacturer	Participants	cDMARD or Previous Therapy	Trial Registration and Design	Patients with ADAbs (% of total patients per treatment group, [n_1/N]x100)		Patients with nAbs (% of ADAb-positive patients per treatment group, [n_2/n1]x100)		PK by ADAb Status	Effect of ADAbs on PD, efficacy, and safety parameters
				Reference product	Biosimilar	Reference product	Biosimilar		
							Week 78: 98.2% (266/271) **Week 100:** 99.2% (250/252)		
PF-06410293 Pfizer	RA, inadequate response to MTX	MTX	REFLECTIONS B538-02 (NCT02480153) [34] N=597 Period 1 (Weeks 0-26): Randomized (1:1) double-blind treatment with ADA (EU) or PF-06410293 Period 2 (Weeks 27-52): Patients treated with PF-06410293 in Period 1 continue treatment; patients initially randomized to ADA-EU are re-randomized (1:1) to PF-06410293 or ADA-EU Period 3 (Weeks 53-78): All patients	**Week 26:** 43.5% (130/299) **Overall:** 50.5% (151/299)	**Week 26:** 37.7% (112/297) **Overall:** 44.4% (132/297)	**Week 26:** 23.1% (30/130) **Overall:** 27.8% (42/151)	**Week 26:** 25.9% (29/112) **Overall:** 31.1% (41/132)	For both ADA-EU and PF-06410293, ADAb-positive patients had approx. 60% lower serum drug concentration than ADAb-negative patients	n/a

Biosimilar / Manufacturer	Participants	cDMARD or Previous Therapy	Trial Registration and Design	Patients with ADAbs (% of total patients per treatment group, [n_1/N]x100)		Patients with nAbs (% of ADAb-positive patients per treatment group, [n_2/n1]x100)		PK by ADAb Status	Effect of ADAbs on PD, efficacy, and safety parameters
				Reference product	Biosimilar	Reference product	Biosimilar		
			receive PF-06410293 Follow-up period: Weeks 79-92						
Exemptia (ZRC-3197) Cadila Healthcare	Moderate to severe RA	MTX	[NOT REGISTERED AT ClinicalTrials.gov or EudraCT] [35] N=120 Randomized (1:1) double-blind study patients treated with ADA (US) or ZRC-3197 for 12 weeks	**Week 12:** 1.6% (1/60)	**Week 12:** 3.3% (2/60)	n/a	n/a	n/a	n/a
Plaque psoriasis									
Solymbic (ABP 501, adalimumab-atto) Amgen	Moderate to severe plaque psoriasis	Non-biologic: 75% Biologic: 18%	20120263 (NCT01970488) N=350 [54, 69] Randomized (1:1) double-blind treatment with ABP 501 or ADL for 16 weeks After Week 16, patients with ≥50% improvement in PASI were eligible	**Week 16:** 63.6% (110/173) **Week 20:** ADL/ADL 59.5% (47/79)	**Week 16:** 55.2% (96/174) **Week 20:** ABP 501/ ABP 501 54.6% (83/152) ADL/ ABP 501 64.9% (50/77) **Week 52:** ABP 501/	**Week 16:** 21.8% (24/110) **Week 20:** ADL/ADL 19.1% (9/47) **Week 52:**	**Week 16:** 17.7% (17/96) **Week 20:** ABP 501/ ABP 501 13.3% (11/83) ADL/ ABP 501 20.0% (10/50) **Week 52:** ABP 501/	n/a	n/a

Biosimilar / Manufacturer	Participants	cDMARD or Previous Therapy	Trial Registration and Design	Patients with ADAbs (% of total patients per treatment group, [n_1/N]x100)		Patients with nAbs (% of ADAb-positive patients per treatment group, [n_2/n1]x100)		PK by ADAb Status	Effect of ADAbs on PD, efficacy, and safety parameters
				Reference product	**Biosimilar**	**Reference product**	**Biosimilar**		
			to continue treatment until week 48 - those initially randomized ABP 501 continued their regimen and those randomized to ADL were re-randomized (1:1) to ADL or ABP 501; follow-up was to Week 52	**Week 52:** ADL/ADL 74.7% (59/79) **Week 17-52 (emergent):** ADL/ADL 35.5% (11/31)	ABP 501 68.4% (104/152) ADL/ ABP 501 72.7% (56/77) **Week 17-52 (emergent):** ABP 501/ ABP 501 35.6% (26/73) ADL/ ABP 501 28.6% (8/28)	ADL/ADL 27.1% (16/59) **Week 17-52 (emergent):** ADL/ADL 0	ABP 501 20.2% (21/104) ADL/ ABP 501 33.9% (19/56) **Week 17-52 (emergent):** ABP 501/ ABP 501 0 ADL/ ABP 501 0		
Hyrimoz (GP2017, adalimumab-adaz) Hexal/Sandoz	Moderate to severe plaque psoriasis	Topical: 76% Biologic: 21%	GP17-301 (NCT02016105) [23, 55] N=465 Treatment Period 1 (Weeks 1-16): Randomized (1:1) double-blind treatment with GP2017 or ADL for 15 weeks (Period 1)	**Weeks 1-17:** 34.1% (75/220) **Weeks 17-51:** ADL/ADL 45.1% (55/122)	**Weeks 1-17**: 36.8% (81/220) **Weeks 17-51:** ADL/GP2017 39.3% (24/61) GP2017/GP2017 35.8% (44/123) GP2017/ADL 46.7% (28/60)	**Weeks 1-17:** 80.0% (60/75) **Weeks 17-51:** ADL/ADL 85.4% (47/55)	**Weeks 1-17:** 80.2% (65/81) **Weeks 17-51:** ADL/GP2017 100% (24/24) GP2017/GP2017 86.4% (38/44) GP2017/ADL 75.0% (21/28)	n/a	PASI75 response at Week 16: **ADL** ADAb-positive: 39% ADAb-negative: 72% **GP2017** ADAb-positive: 43%

Biosimilar / Manufacturer	Participants	cDMARD or Previous Therapy	Trial Registration and Design	Patients with ADAbs (% of total patients per treatment group, [n_1/N]x100)		Patients with nAbs (% of ADAb-positive patients per treatment group, [n_2/n1]x100)		PK by ADAb Status	Effect of ADAbs on PD, efficacy, and safety parameters
				Reference product	Biosimilar	Reference product	Biosimilar		
			Treatment Period 2 (Weeks 17-35): At Week 17, patients with ≥50% improvement in PASI were eligible to continue treatment until week 35, after re-randomization (2:1) to continued treatment with GP2017 or ADL or to 3 alternating 6-week periods (ADL-GP2017-ADL or GP2017-ADL-GP2017, respectively) Extension period (Weeks 36-52): All patients received treatment assigned in Period 1						ADAb-negative: 74% PASI score change, Baseline to Week 16: **ADL** ADAb-positive: -47 ADAb-negative: -65 **GP2017** ADAb-positive: -51 ADAb-negative: -63
Reference product: Etanercept									
Healthy volunteers									

Biosimilar / Manufacturer	**Participants**	**cDMARD or Previous Therapy**	**Trial Registration and Design**	**Patients with ADAbs (% of total patients per treatment group, [n_1/N]x100)**		**Patients with nAbs (% of ADAb-positive patients per treatment group, [n_2/n1]x100)**		**PK by ADAb Status**	**Effect of ADAbs on PD, efficacy, and safety parameters**
				Reference product	**Biosimilar**	**Reference product**	**Biosimilar**		
Benepali (SB4) Samsung Bioepis	Healthy volunteers	-	SB4-G11-NHV (NCT01865552) [25] N=138 Randomized, 3-part, 2-period (21 days each), cross-over study of ETN-EU, ETN-US, and SB4	ETN-EU **(Parts A, C)**: 15.6% (7/45) ETN-US **(Parts B, C)**: 22.7% (10/44) Numbers of available samples for ETN-EU and ETN-US were calculated based on the percentages and the numbers patients with ADAbs	**Parts (A, B)**: 0	ETN-EU **(Parts A, C)**: 14.3% (1/7) ETN-US **(Parts B, C)**: 0	**Parts (A, B)**: 0	n/a	n/a
Erelzi (GP2015, etanercept-szzs) Hexal/Sandoz	Healthy volunteers	n/a	Studies GP15-101, GP15-102, and GP15-104 [26] Randomized, 12-week, double-blind, 2-way cross-over studies of GP2015 and ETN-EU (G15-101, and GP15-104) or	**n/a**	**n/a**	**n/a**	**n/a**	Not assessed, because of only 3 patients with ADAbs across all three studies (Study GP15-104, EU-ETN arm); all were near the detection limit and none	n/a

Biosimilar / Manufacturer	Participants	cDMARD or Previous Therapy	Trial Registration and Design	Patients with ADAbs (% of total patients per treatment group, [n_1/N]x100)		Patients with nAbs (% of ADAb-positive patients per treatment group, [n_2/n1]x100)		PK by ADAb Status	Effect of ADAbs on PD, efficacy, and safety parameters
				Reference product	Biosimilar	Reference product	Biosimilar		
			ETN-US (GP15-102)					were neutralizing.	
LBEC0101 LG Chem	Healthy volunteers	-	LG-ECCL003 (NCT01725620) [27] N=48 Randomized, double-blind, single-dose, 2-period, 2-sequence (LBEC0101-ETN and ETN-LBEC0101), cross-over study of ETN or LBEC0101	Anti-ETN antibodies **Week 5, After 1st dose in ETN-LBEC0101 sequence:** 16.7% (4/24)	Anti-ETN antibodies **Week 5, After 1st dose in LBEC0101-ETN sequence:** 4.5% (1/22)	n/a	n/a	C_{max} and AUC_{inf} after ETN or LBEC0101 administration did not differ significantly between ADAb-positive and ADAb-negative participants	n/a (healthy volunteers)
Rheumatic diseases									
Benepali (SB4) Samsung Bioepis	RA	MTX	SB4-G31-RA (NCT01895309) [36, 79, 80, 96] N=596 Randomized (1:1) double-blind treatment with SB4 or ETN for 52 weeks OL treatment with SB4 in patients who completed the	**Week 0:** 0 **Week 4:** 11.0% (32/291)[a] **Week 8**: 2.1% (6/288)[a] **Week 52**: 0.7% (2/296)	**Week 0:** 0 **Week 4:** 0.3% (1/299) **Week 8**: 0.3% (1/298)[a] **Week 52**: 0.3% (1/299) **Weeks 53-100:**	**Week 0:** 0 **Week 4:** 0 **Week 8**: 2.6% (1/38) **Week 52**: 0	**Week 0:** 0 **Week 4:** 0 **Week 8**: 0 **Week 52**: 0 **Weeks 53-100:**	No data	At Week 24, ADAb-positive patients had lower ACR20 rate than ADAb-negative patients in the ETN group (72.4% vs 81.5%), but not in the SB4 group (100% vs 78.0%) [there were only 2

Biosimilar / Manufacturer	Participants	cDMARD or Previous Therapy	Trial Registration and Design	Patients with ADAbs (% of total patients per treatment group, [n_1/N]x100)		Patients with nAbs (% of ADAb-positive patients per treatment group, [n_2/n1]x100)		PK by ADAb Status	Effect of ADAbs on PD, efficacy, and safety parameters
				Reference product	Biosimilar	Reference product	Biosimilar		
			double-blind phase for additional 48 weeks		SB4/SB4: 0.8% (1/126) ETN/SB4: 0.9% (1/117)		SB4/SB4: 0 ETN/SB4: 0		patients with ADAbs in the SB4 group]
CHS-0214 Coherus BioSciences	RA	MTX	CHS-0214-02, Part 1 and Part 2 (NCT02115750) [37] N=512 Part 1: Randomized (1:1) double-blind treatment with CHS-0214 or ETN for 24 weeks Part 2: ACR20 achievers in both groups received CHS-0214 for an additional 24 weeks	**Week 1-24:** 4.7%	**Week 1-24:** 1.3% **Week 25-52**: CHS-0214/ CHS-0214 1.4% **Week 25-52**: ETN/ CHS-0214 0.7%	n/a	n/a	n/a	n/a
LBEC0101 LG Chem	RA	MTX	LG-ECCL002 (NCT02357069) [38] N=374 Randomized (1:1) treatment with LBEC0101 or ETN	**Week 12:** 4.3% (8/187) **Week 24**: 2.1% (4/187) **Week 52**: 3.7% (7/187)	**Week 12:** 0.5% (1/187) **Week 24**: 0.5% (1/187) **Week 52**: 0.5% (1/187)	**Week 12:** 0 **Week 24**: 0 **Week 52**: 0	**Week 12:** 0 **Week 24**: 0 **Week 52**: 0	Not determined, because of the low number of ADAb-positive patients in the	Not determined, because of the now number of ADAb-positive patients in the LBEC0101 group

Biosimilar / Manufacturer	Participants	cDMARD or Previous Therapy	Trial Registration and Design	Patients with ADAbs (% of total patients per treatment group, [n_1/N]x100)		Patients with nAbs (% of ADAb-positive patients per treatment group, [n_2/n1]x100)		PK by ADAb Status	Effect of ADAbs on PD, efficacy, and safety parameters
				Reference product	Biosimilar	Reference product	Biosimilar		
			for 52 weeks (Period 1, weeks 1-24 [primary assessment]; Period 2, weeks 25-52 [secondary assessment]), with follow-up to week 54	**Overall**: 9.6% (18/187)	**Overall**: 1.6% (3/187)	**Overall**: 0	**Overall**: 0	LBEC0101 group	
Plaque psoriasis									
Erelzi (GP2015, etanercept-szzs) Hexal/Sandoz	Chronic plaque-type psoriasis	None: 68.9% Any: 30.1% TNFi (not ETN): 0.9%	EGALITY, Study 302 (NCT01891864) [56, 81] N=531 Treatment period 1 (Weeks 1-12): Randomized (1:1), double-blind treatment with GP2015 or ETN for 12 weeks Treatment period 2 (Weeks 13-30): Patients with ≥PASI 50 at week 12 were re-randomized 1:1 to continue existing	**Week 12**: 1.9% (5/267) **Weeks 13-30**: ETN/ETN 0 GP2015/ETN 0	**Week 12**: 0 **Weeks 13-30**: GP2015/GP2015 0 ETN/GP2015 0	**Week 12**: 0 **Weeks 13-30**: ETN/ETN 0 GP2015/ETN 0	**Week 12**: 0 **Weeks 13-30**: GP2015/GP2015 0 ETN/GP2015 0	n/a	Not assessed, because of only 3 patients with ADAbs

Biosimilar / Manufacturer	Participants	cDMARD or Previous Therapy	Trial Registration and Design	Patients with ADAbs (% of total patients per treatment group, [n_1/N]x100)		Patients with nAbs (% of ADAb-positive patients per treatment group, [n_2/n1]x100)		PK by ADAb Status	Effect of ADAbs on PD, efficacy, and safety parameters
				Reference product	Biosimilar	Reference product	Biosimilar		
			treatment for 18 weeks or undergo three 6-week switches Extension Period (Weeks 31-52): Patients continued treatment from the end of period 2 for an additional 22 weeks						
Reference product: Infliximab									
Healthy volunteers									
Flixabi/ Renflexis (SB2, infliximab-abda) Samsung Bioepis	Healthy volunteers	n/a	SB2-G11-NHV, NCT01922336 [28] N=159 Randomized (1:1:1), single-blind, single-dose study of INF (US), INF (EU), and SB2 with a follow-up of 10 weeks	**Predose:** INF-EU: 0 INF-US: 0 **Week 4:** INF-EU: 0 INF-US: 1.9% (1/53) **Week 10:** INF-EU:	**Predose:** 0 **Week 4:** 3.8% (2/53) **Week 10:** 47.2% (25/53)	**Predose:** INF-EU: 0 INF-US: 0 **Week 4:** INF-EU: 0 INF-US: 0 **Week 10:** INF-EU: 70.0% (14/20)	**Predose:** 0 **Week 4:** 50.0% (1/2) **Week 10:** 56.0% (14/25)	Compared with ADAb-negative individuals, ADAb-positive ones had approx. 30% lower AUC_{inf}, 35-40% higher clearance, 40-50% lower $t_{1/2}$, and similar C_{max}	n/a (healthy volunteers)

Biosimilar / Manufacturer	Participants	cDMARD or Previous Therapy	Trial Registration and Design	Patients with ADAbs (% of total patients per treatment group, [n_1/N]x100)		Patients with nAbs (% of ADAb-positive patients per treatment group, [n_2/n1]x100)		PK by ADAb Status	Effect of ADAbs on PD, efficacy, and safety parameters
				Reference product	**Biosimilar**	**Reference product**	**Biosimilar**		
				37.7% (20/53) INF-US: 37.7% (20/53)		INF-US: 35.0% (7/20)			
Inflectra (CT-P13, infliximab-dyyb) Celltrion	Healthy volunteers	n/a	CT-P13 1.4 (EudraCT 2013-003173-10) [29, 67] N=213 Randomized (1:1:1) trial evaluating PK, PD, and immunogenicity of single-dose INF-EU, INF-US, and CT-P13 for 8 weeks	**Week 8** INF-EU 25.4% (18/71) INF-US 11.4% (8/70) (p-value for difference between INF-EU and INF-US: 0.15)	**Week 8** 27.1% (19/70)	**Week 8** INF-EU 100% (18/18) INF-US 100% (8/8)	**Week 8** 100% (19/19)	In ADAb-positive patients, AUC_{inf} was 15-23% lower than in ADAb-negative patients	n/a (healthy volunteers)
Rheumatic diseases									
Flixabi/ Renflexis (SB2, infliximab-abda) Samsung Bioepis	RA	MTX	SB2-G31-RA (NCT01936181) [39, 77, 78, 97] N=584 Randomized (1:1) double-blind treatment with SB2	**Week 0:** 2.4% (7/293) **Week 6:** 5.6% (16/286)	**Week 0:** 1.7% (5/290) **Week 6:** 7.4% (21/282)	**Week 0:** 0 **Week 6:** 43.8% (7/16)	**Week 0:** 0 **Week 6:** 52.4% (11/21)	n/a	In both treatment groups, there was a lower ACR20 response rate and higher rate of IRRs among

Biosimilar / Manufacturer	Participants	cDMARD or Previous Therapy	Trial Registration and Design	Patients with ADAbs (% of total patients per treatment group, [n_1/N]x100)		Patients with nAbs (% of ADAb-positive patients per treatment group, [n_2/n1]x100)		PK by ADAb Status	Effect of ADAbs on PD, efficacy, and safety parameters
				Reference product	Biosimilar	Reference product	Biosimilar		
			or INF for 54 weeks At week 54, INF-treated patients were re-randomized (1:1) to switch to SB2 or continue on INF until week 70 (assessment continued until week 78)	**Week 14:** 22.5% (63/280) **Week 30:** 43.9% (116/264) **Week 54**: 40.1% (89/222)[b] **Weeks 54-78**: INF/INF[c] 14.9% (7/47)	**Week 14:** 26.6% (73/274) **Week 30:** 53.0% (133/251) **Week 54**: 52.9% (118/223)[b] **Weeks 54-78**: INF/SB2[c] 14.6% (6/41) SB2/SB2[c] 14.1% (11/78)	**Week 14:** 95.2% (60/63) **Week 30:** 94.0% (109/116) **Week 54**: 87.6% (78/89)[b] **Weeks 54-78**: INF/INF[c] 100% (7/7)	**Week 14:** 95.9% (70/73) **Week 30:** 97.0% (129/133) **Week 54**: 83.9% (99/118)[b] **Weeks 54-78**: INF/SB2[c] 100% (36/6) SB2/SB2[c] 100% (11/11)		ADAb-positive vs ADAb-negative patients **ACR20** **Week 30:** INF: 58.7% vs 73.6% SB2: 56.7% vs 73.1% **Week 54:** INF: 68.1% vs 70.8% SB2: 58.7% vs 76.3% IRR INF: 6.5% vs 3.2% SB2: 8.4% vs 1.9%
Inflectra, Remsima (CT-P13, infliximab-dyyb) Celltrion	RA	MTX	PLANETRA (CT-P13 3.1, NCT01217086) [44, 94] N=606 Randomized (1:1) double-blind	**Week 14:** 25.8% (70/271) **Week 30:** 48.2% (122/253) **Week 54**:	**Week 14:** 25.4% (69/272) **Week 30:** 48.4% (122/252) **Week 54**:	**Week 54**: ~100%	**Week 54**: ~100%	In ADAb-positive patients, C_{max} was 12-16% lower and C_{min} was 67-68% lower than in ADAb-	Efficacy responses were generally lower in ADAb-positive than ADAb-negative patients

Biosimilar / Manufacturer	Participants	cDMARD or Previous Therapy	Trial Registration and Design	Patients with ADAbs (% of total patients per treatment group, [n_1/N]x100)		Patients with nAbs (% of ADAb-positive patients per treatment group, [n_2/n1]x100)		PK by ADAb Status	Effect of ADAbs on PD, efficacy, and safety parameters
				Reference product	Biosimilar	Reference product	Biosimilar		
			treatment with CT-P13 or IFN for 54 weeks	36.0% (108/300) denominator N calculated based on n and % values	41.1% (124/302) denominator N calculated based on n and % values	n/N data not available	n/N data not available	negative patients	ADAb-positive vs ADAb-negative: **ACR20** INF: 64.5% vs 75.2% CT-P13: 64.8% vs 81.7% **ACR50** INF: 33.9% vs 47.3% CT-P13: 29.5% vs 54.8% **ACR70** INF: 13.2% vs 22.5% CT-P13: 7.4% vs 32.5% **EULAR-CRP (mod-good)** INF: 82.5% vs 91.4% CT-P13: 79.5% vs 91.9% **EULAR-ESR (mod-good)** INF: 75.0% vs 89.1%

Biosimilar / Manufacturer	Participants	cDMARD or Previous Therapy	Trial Registration and Design	Patients with ADAbs (% of total patients per treatment group, [n_1/N]x100)		Patients with nAbs (% of ADAb-positive patients per treatment group, [n_2/n1]x100)		PK by ADAb Status	Effect of ADAbs on PD, efficacy, and safety parameters
				Reference product	Biosimilar	Reference product	Biosimilar		
									CT-P13: 77.1% vs 91.9%
Inflectra, Remsima (CT-P13, infliximab-dyyb) Celltrion	RA	MTX	PLANETRA OLEX (NCT01571219) [45] N=302 Single-arm, OL treatment with CT-P13 in patients who completed PLANETRA	**Week 102**: INF/CT-P13 44.8% (64/143)	**Week 102**: CT-P13/CT-P13 40.3% (64/159)	**Week 102**: INF/CT-P13 100% (64/64)	**Week 102**: CT-P13/CT-P13 100% (64/64)	n/a	At weeks 54 and 102, in both maintenance and switch groups, there was a comparable change from baseline in CRP and ESR between ADAb-positive and ADAb-negative patients The proportions of ADAb-positive and –negative patients achieving ACR20 at weeks 54 and 102 were also similar
Inflectra, Remsima	RA	MTX	JAPIC Clinical Trials Information	**Week 14:** 15.1%	**Week 14:** 19.6%			AUC_τ and C_{max} were	n/a

Biosimilar / Manufacturer	Participants	cDMARD or Previous Therapy	Trial Registration and Design	Patients with ADAbs (% of total patients per treatment group, [n_1/N]x100)		Patients with nAbs (% of ADAb-positive patients per treatment group, [n_2/n1]x100)		PK by ADAb Status	Effect of ADAbs on PD, efficacy, and safety parameters
				Reference product	Biosimilar	Reference product	Biosimilar		
(CT-P13, infliximab-dyyb) Nippon Kayaku Corp. Celltrion			Center study JapicCTI-111620 [42] N=101 Randomized (1:1) double-blind treatment with CT-P13 or IFN for 54 weeks	**Week 30:** 26.4% **Week 54**: 32.1% n/N data not available	**Week 30:** 25.5% **Week 54**: 25.5% n/N data not available	**Week 54**: 100% n/N data not available	**Week 54**: 100% n/N data not available	higher among ADAb-negative patients than in the entire study sample	
Inflectra, Remsima (CT-P13, infliximab-dyyb) Celltrion	AS	-	PLANETAS (CT-P13 1.1, NCT01220518) [40, 74] N=250 Randomized (1:1) double-blind treatment with CT-P13 or IFN for 54 weeks	**Week 14:** 10.7% (13/122) **Week 30:** 20.5% (25/122) **Week 54**: 23.0% (28/122)	**Week 14:** 8.6% (11/128) **Week 30:** 25.0% (32/128) **Week 54**: 19.5% (25/128)	**Week 14:** 100% (13/13) **Week 30:** 96.0% (24/25) **Week 54**: 100% (28/28)	**Week 14:** 90.9% (10/11) **Week 30:** 96.9% (31/32) **Week 54**: 100% (25/25)	At week 30, in both treatment groups, there was a trend toward lower $C_{max,ss}$ and AUC_τ with higher ADAb titre. In both treatment groups, ADAb-positive patients had 14% lower C_{max} than ADAb-negative patients	At week 30, efficacy responses were generally lower in ADAb-positive than ADAb-negative patients **ASAS20** IFN: 65.4% vs 74.4% CT-P13: 50.0% vs 77.4% **ASAS40** IFN: 38.5% vs 50.0% CT-P13: 42.9% vs 54.8%

Biosimilar / Manufacturer	**Participants**	**cDMARD or Previous Therapy**	**Trial Registration and Design**	**Patients with ADAbs (% of total patients per treatment group, [n_1/N]x100)**		**Patients with nAbs (% of ADAb-positive patients per treatment group, [n_2/n1]x100)**		**PK by ADAb Status**	**Effect of ADAbs on PD, efficacy, and safety parameters**
				Reference product	**Biosimilar**	**Reference product**	**Biosimilar**		
Inflectra, Remsima (CT-P13, infliximab-dyyb) Celltrion	AS	-	PLANETAS OLEX (NCT01571206) [41] N=174 Single-arm, open-label treatment with CT-P13 in patients who completed PLANETAS	**Week 102**: INF/CT-P13 27.4% (23/84)	**Week 102**: CT-P13/CT-P13 23.3% (21/90)	**Week 102**: INF/CT-P13 100% (23/23)	**Week 102**: CT-P13/CT-P13 100% (23/23)	n/a	At weeks 54 and 102, in both maintenance and switch groups, there was a greater decline baseline in CRP and ESR in ADAb-negative than ADAb-positive patients At weeks 54 and 102, in both maintenance and switch groups, there was a higher ASAS20 response rate in ADAb-negative than ADAb-positive patients: **Week 54** Maintenance: 75.7% vs 50.0% Switch: 79.0% vs 66.7%

Biosimilar / Manufacturer	Participants	cDMARD or Previous Therapy	Trial Registration and Design	Patients with ADAbs (% of total patients per treatment group, [n_1/N]x100)		Patients with nAbs (% of ADAb-positive patients per treatment group, [n_2/n1]x100)		PK by ADAb Status	Effect of ADAbs on PD, efficacy, and safety parameters
				Reference product	Biosimilar	Reference product	Biosimilar		
									Week 102 Maintenance: 83.9% vs 70.0% Switch: 84.6% vs 62.5% The proportions of ADAb-positive and –negative patients achieving ACR20 at weeks 54 and 102 were also similar
Inflectra, Remsima (CT-P13, infliximab-dyyb) Celltrion	AS, PsA, RA	csDMARDs, MTX	BIO-SWITCH, Dutch Trial Register identifier NTR5279 [43] N=192 Multicenter, prospective, cohort study of INF-treated patients who switched to CT-P13 for 6 months	n/a	Anti-INF antibodies **Baseline**: 10.3% (14/136) **Month 6**: 6.6% (9/136)	n/a	n/a	n/a	n/a

Biosimilar / Manufacturer	**Participants**	**cDMARD or Previous Therapy**	**Trial Registration and Design**	**Patients with ADAbs (% of total patients per treatment group, [n_1/N]x100)**		**Patients with nAbs (% of ADAb-positive patients per treatment group, [n_2/n1]x100)**		**PK by ADAb Status**	**Effect of ADAbs on PD, efficacy, and safety parameters**
				Reference product	**Biosimilar**	**Reference product**	**Biosimilar**		
Ixifi (PF-06438179/ GP1111, infliximab-qbtx) Pfizer	Moderate to severe RA	MTX	REFLECTIONS (B537-02, NCT02222493) [46] N=650 Randomized (1:1) DB treatment with IFN-EU or PF-06438179/ GP1111 for 30 weeks	**Baseline:** 2.8% (9/323) **Week 14:** 31.8% (100/314) **Week 30:** 49.5% (144/291) **Overall**: 51.4% (167/325)	**Baseline:** 2.8% (9/322) **Week 14:** 31.8% (96/302) **Week 30:** 48.2% (136/282) **Overall**: 49.1% (157/320)	**Baseline:** 11.1% (1/9) **Week 14:** 78.0% (78/100) **Week 30:** 83.3% (120/144) **Overall**: 85.6% (143/167)	**Baseline:** 11.1% (1/9) **Week 14:** 76.0% (73/96) **Week 30:** 77.2% (105/136) **Overall**: 79.0% (124/157)	In ADAb-positive patients, C_{max} was 10-18% lower than in ADAb-negative patients	At Week 14, a greater proportion of ADAb-negative than ADAb-positive patients achieved ACR20: PF-06438179/ GP1111: 69.1% vs 51.0% INF-EU: 71.2% vs 49.5%
IBD									
Inflectra, Remsima (CT-P13, infliximab-dyyb) Celltrion	IBD, 51.6% Rheumatic diseases, 41.2% Psoriasis, 7.3%	21.8%	NOR-SWITCH (NCT02148640) [63] N=481 In this double-blind trial, patients receiving stable INF for ≥6 months were randomized (1:1) to continue their INF treatment or be switched to CT-P13, for 52weeks	**Only nAbs were assessed**	**Only nAbs were assessed**	**Week 52 (all):** 10.8% (26/241) **Week 52 (emergent):** 7.1% (17/241) Due to study design, nAb incidence was presented as % of all patients,	**Week 52 (all):** 12.5% (30/240) **Week 52 (emergent):** 7.9% (19/240) Due to study design, nAb incidence was presented as % of all patients,	n/a	n/a

Biosimilar / Manufacturer	Participants	cDMARD or Previous Therapy	Trial Registration and Design	Patients with ADAbs (% of total patients per treatment group, [n_1/N]x100)		Patients with nAbs (% of ADAb-positive patients per treatment group, [n_2/n1]x100)		PK by ADAb Status	Effect of ADAbs on PD, efficacy, and safety parameters
				Reference product	Biosimilar	Reference product	Biosimilar		
						not those who were ADAb-positive	not those who were ADAb-positive		
Inflectra (CT-P13, infliximab-dyyb) Celltrion	CD, UC	21.8%	Gecse et al [61] N=210 (Week 14) Gonczi et al [71] N=353 (Weeks 14, 30, 54 – updated data set) Gonczi et al [72] N=291 (Week 54, predictor analysis) Prospective, nation-wide Hungarian trial of patients receiving CT-P13; those with clinical remission at Week 14 continued receiving treatment until Week 30 (follow-up until Week 54)	**n/a**	**<u>Baseline</u>** **All:** CD: 8.9% (15/169) UC: 11.3% (11/97) **TNFi-naive:** CD: 3.7% (5/134)[d] UC: 5.1% (4/79)[e] **TNFi-experienced:** CD: 28.6% (10/35)[d] UC: 38.9% (7/18)[e] **<u>Week 14</u>** **All:** CD: 16.8% (32/190) UC: 21.3% (26/122) **TNFi-naive:** CD: 11.5% (17/148)[d]	**n/a**	**n/a**	n/a	**UC** Compared with ADAb-negative patients, ADAb-positive patients at Week 14 did not have significantly lower rates of clinical remission at Week 14 (62.5% vs 66.1%, *P*=0.79) or Week 30 (41.7% vs 56.5%, *P*=0.36 **CD** Compared with ADAb-negative patients, ADAb-positive patients at Week 14 had significantly lower rates of clinical remission at

Biosimilar / Manufacturer	Participants	cDMARD or Previous Therapy	Trial Registration and Design	Patients with ADAbs (% of total patients per treatment group, [n_1/N]x100)		Patients with nAbs (% of ADAb-positive patients per treatment group, [n_2/n1]x100)		PK by ADAb Status	Effect of ADAbs on PD, efficacy, and safety parameters
				Reference product	Biosimilar	Reference product	Biosimilar		
					UC: 18.8% (13/101) **TNFi-experienced:** CD: 35.7% (15/42)[d] UC: 33.3% (7/21) **<u>Week 30</u>** **All:** CD: 22.9% (39/170) UC: 25.8% (31/120) **TNFi-naive:** CD: 19.1% (25/131)[d] UC: 23.2% (23/99) **TNFi-experienced:** CD: 35.9% (14/39)[d] UC: 38.1% (8/21) **<u>Week 54</u>** **All:**				Week 14 (48.5% vs 66.9%, *P*=0.04), but not at Week 30 (46.2% vs 64.2%, *P*=0.09) or Week 54 (45.5% vs 60.4%, *P*=0.24)

Biosimilar / Manufacturer	Participants	cDMARD or Previous Therapy	Trial Registration and Design	Patients with ADAbs (% of total patients per treatment group, [n_1/N]x100)		Patients with nAbs (% of ADAb-positive patients per treatment group, [n_2/n1]x100)		PK by ADAb Status	Effect of ADAbs on PD, efficacy, and safety parameters
				Reference product	Biosimilar	Reference product	Biosimilar		
					CD: 30.6% (38/124) UC: 34.4% (33/96) **TNFi-naive:** CD: 25.5% (24/94)[d] UC: 32.1% (26/81) **TNFi-experienced:** CD: 46.7% (14/30)[d] UC: 46.7% (7/15)				
Inflectra (CT-P13, infliximab-dyyb) Celltrion	UC	7.9%	Farkas et al [60] N=63 14-week, prospective, multicenter, Hungarian and Czech trial of inpatients with acute relapse and outpatients with chronic, steroid-dependent and/or immunodulatory-refractory disease receiving CT-P13	**n/a**	**Week 14 (all TNFi-naïve):** 11.1% (7/63)	**n/a**	**n/a**	n/a	n/a

Biosimilar / Manufacturer	Participants	cDMARD or Previous Therapy	Trial Registration and Design	Patients with ADAbs (% of total patients per treatment group, [n_1/N]x100)		Patients with nAbs (% of ADAb-positive patients per treatment group, [n_2/n1]x100)		PK by ADAb Status	Effect of ADAbs on PD, efficacy, and safety parameters
				Reference product	Biosimilar	Reference product	Biosimilar		
Inflectra (CT-P13, infliximab-dyyb) Celltrion	CD, UC	10.3%	Farkas et al [59] N=39 8-week, prospective, single-center, Hungarian trial of patients receiving CT-P13	**n/a**	**Week 8:** 19.0% (4/21)	**n/a**	**n/a**	Mean serum IFX levels were significantly lower in ADAb-positive than ADAb-negative patients (1.7 mg/L vs 12.8 mg/L, *P*=0.005)	n/a
Inflectra (CT-P13, infliximab-dyyb) Celltrion	CD, UC	28.2%	Jahnsen et al [62] N=78 14-week, prospective, single-center Norwegian trial of patients receiving CT-P13	**n/a**	**Week 14:** n=8 (denominator value n/a)	**n/a**	**n/a**	All 8 patients with trough levels of CT-P13 of 0 mg/L had detectable ADAbs	n/a
Inflectra (CT-P13, infliximab-dyyb) Celltrion	CD, UC	n/a	Buer et al [58] and Høivik et al [73] N=143 In a single-center Norwegian trial, all patients with IBD treated with INF were switched to CT-P13 and	**n/a**	**Baseline:** 1.4% (2/143) **Month 6 (emergent):** 2.1% (3/143) **Month 18 (overall):** 5.6% (8/143)	**n/a**	**n/a**	n/a	n/a

Biosimilar / Manufacturer	Participants	cDMARD or Previous Therapy	Trial Registration and Design	Patients with ADAbs (% of total patients per treatment group, [n_1/N]x100)		Patients with nAbs (% of ADAb-positive patients per treatment group, [n_2/n1]x100)		PK by ADAb Status	Effect of ADAbs on PD, efficacy, and safety parameters
				Reference product	Biosimilar	Reference product	Biosimilar		
			followed up for 18 months						
Inflectra (CT-P13, infliximab-dyyb) Celltrion	CD, UC	TNFi: 62.7%	Smits et al [66, 75, 76] N=83 In a single-center Dutch trial, all patients with IBD treated with INF were switched to CT-P13 and followed up for 2 years	**n/a**	**Baseline:** 6.0% (5/83) **Weeks 1-52 (emergent):** 2.4% (2/83) **Weeks 53-104 (emergent):** 0	**n/a**	**n/a**	6 out of 7 patients with ADAb had CT-P13 trough levels of 0 mg/L	n/a
Inflectra (CT-P13, infliximab-dyyb) Celltrion	CD, UC	n/a	Kolar et al [64] Switch cohort: N=74 TNFi-naive cohort: N=119 Single-center Czech study, consisting of a switch cohort (patients switched from INF to CT-P13 and evaluated prospectively for 56 weeks) and a TNFi-naive cohort (patients initiated on CT-P13	**n/a**	**<u>Switch cohort</u>** **Week 0**: 9.5% **Week 56:** 6.0% **<u>TNFi-naïve cohort</u>** **Week 14**: 2.8% **Week 46:** 11.7%	**n/a**	**n/a**	n/a	n/a

Biosimilar / Manufacturer	Participants	cDMARD or Previous Therapy	Trial Registration and Design	Patients with ADAbs (% of total patients per treatment group, [n_1/N]x100)		Patients with nAbs (% of ADAb-positive patients per treatment group, [n_2/n1]x100)		PK by ADAb Status	Effect of ADAbs on PD, efficacy, and safety parameters
				Reference product	Biosimilar	Reference product	Biosimilar		
			treatment and evaluated retrospectively at Weeks 14 and 46).						
Inflectra (CT-P13, infliximab-dyyb) Celltrion	CD, UC, IBD unclassified	18.9%	Razanskaite et al [65] N=143 (switched patients) Prospective cohort from a UK managed-switch program (ADAb evaluations performed after 3-5 infusions in 70 patients)	**n/a**	**Before switch:** 40.0% (28/70) **After switch:** 40.0% (28/70)	**n/a**	**n/a**	n/a	n/a
Reference product: Rituximab									
Rheumatic diseases									
Truxima (CT-P10) Celltrion	RA, poor response to TNFi	MTX	CT-P10 1.1 (NCT01534884) [49, 82] N=154 Randomized (2:1) double-blind treatment with CT-P10 or RTX (course 1: i.v. infusions at weeks 0 and 2); based on	**Weeks 1-24 (1st course)**: 17.6% (9/51) **Weeks 25-48 (2nd course)**: 21.7% (5/23)	**Weeks 1-24 (1st course)**: 17.6% (18/102) **Weeks 25-48 (2nd course)**: 20.0% (12/60)	**Weeks 1-24 (1st course)**: 11.1% (1/9) **Weeks 25-48 (2nd course)**: 20.0% (1/5)	**Weeks 1-24 (1st course)**: 11.1% (2/18) **Weeks 25-48 (2nd course)**: 8.3% (1/12)	ADAb-positive patients had a 20-30% lower $AUC_{0\text{-last}}$ and 12-21% lower C_{max} (mg/L) than ADAb–negative patients	ADAb-positive vs ADAb-negative: Week 24 **ACR20** RTX: 62.5% vs 75.0% CT-P10: 61.1% vs 67.5%

Biosimilar / Manufacturer	Participants	cDMARD or Previous Therapy	Trial Registration and Design	Patients with ADAbs (% of total patients per treatment group, [n_1/N]x100)		Patients with nAbs (% of ADAb-positive patients per treatment group, [n_2/n1]x100)		PK by ADAb Status	Effect of ADAbs on PD, efficacy, and safety parameters
				Reference product	Biosimilar	Reference product	Biosimilar		
			disease activity, patients could receive a course 2, between weeks 24 and 48, with a max. follow-up until Week 72						
Truxima (CT-P10) Celltrion	RA, poor response to TNFi	MTX	Extension study CT-P10 1.3 (NCT01873443) [48] N=87 Patients from trial CT-P10 1.1 who had responded to treatment, but whose disease activity or B cell/IgM levels then worsened received 1 or 2 courses of CT-P10, with a follow-up of up to 56 weeks; ADAbs and nAbs were assessed at Week 24 (post-course 1 only)	n/a	**Week 24:** CT-P10/ CT-P10 13.2% (5/38) RTX/ CT-P10 15.0% (3/20)	n/a	**Week 24:** CT-P10/ CT-P10 20.0% (1/5) RTX/ CT-P10 0	n/a	n/a

Biosimilar / Manufacturer	Participants	cDMARD or Previous Therapy	Trial Registration and Design	Patients with ADAbs (% of total patients per treatment group, [n_1/N]x100)		Patients with nAbs (% of ADAb-positive patients per treatment group, [n_2/n1]x100)		PK by ADAb Status	Effect of ADAbs on PD, efficacy, and safety parameters
				Reference product	**Biosimilar**	**Reference product**	**Biosimilar**		
Truxima (CT-P10) Celltrion	RA, poor response to TNFi	MTX	CT-P10 3.2 (NCT02149121) [47, 68] N=372 Part 1 - PK evaluation (n=189): randomized (1:1:1) to US-RTX, EU-RTX, and CT-P10) Part 2 – efficacy, safety, PD, immunogenicity (n=372): 183 newly randomized patients (1:1 to CT-P10 and US-RTX) plus all patients from Part 1 for 24 weeks Extension period (n=295): patients initially randomized to receive CT-P10 continued with their treatment; those randomized to EU-RTX were switched to CT-P10 and those	**Baseline:** 9.5% (20/211) **Week 24:** 23.2% (49/211) 7 patients were ADAb-positive at both Baseline and Week 24 **Week 48:** 8.5% (18/211) **Week 72:** RTX/RTX 3.1% (2/64) 1 patient newly ADAb-positive	**Baseline:** 11.8% (19/161) **Week 24:** 14.9% (24/161) 7 patients were ADAb-positive at both Baseline and Week 24 **Week 48:** 4.3% (7/161) **Week 72:** CT-P10/CT-P10 4.1% (5/122) RTX/CT-P10 10.3% (11/107) 1 patient newly ADAb-positive	**Baseline:** 0 **Week 24:** 2.0% (1/49) **Week 48:** 5.5% (1/18) **Week 72:** RTX/RTX 0	**Baseline:** 5.3% (1/19) **Week 24:** 0 **Week 48:** 14.3% (1/7) **Week 72:** CT-P10/CT-P10 0 RTX/CT-P10 0	**n/a**	**Trial CT-P10 3.2** ADAb-positive vs ADAb-negative: <u>IRR, 1st treatment course</u> RTX: 6.1% vs 8.7% CT-P10: 16.7% vs 14.9% <u>IRR, 2nd treatment course</u> RTX: 4.1% vs 4.1% CT-P10: 11.5% vs 7.8%

Biosimilar / Manufacturer	Participants	cDMARD or Previous Therapy	Trial Registration and Design	Patients with ADAbs (% of total patients per treatment group, [n_1/N]x100)		Patients with nAbs (% of ADAb-positive patients per treatment group, [n_2/n1]x100)		PK by ADAb Status	Effect of ADAbs on PD, efficacy, and safety parameters
				Reference product	Biosimilar	Reference product	Biosimilar		
			initially randomized to receive US-RTX were re-randomized (1:1) to continue treatment or switch to CT-P10 (follow-up until Week 72)						
Rixathon (GP2013) Hexal/Sandoz	RA, poor response to TNFi	MTX	GP13-201 (NCT01274182) [50] N=312 Part 1: Randomized (1:1) to receive GP2013 or RTX-EU Part 2: Randomized (1:2) to receive GP2013 or RTX-US	**Overall post-BL (Week 24)**: 15.1% (25/166)	**Overall post-BL (Week 24):** 16.5% (21/127)	**Overall post-BL (Week 24)**: 4.0% (1/25)	**Overall post-BL (Week 24):** 23.8% (5/21)	ADAb-positive patients had a 21-37% lower $AUC_{0\text{-}inf}$ than ADAb–negative patients	n/a
Rixathon (GP2013) Hexal/Sandoz	RA, receiving RTX	MTX	GP13-302 (NCT02514772) [51] N=107 RTX-treated patients were randomized (1:1) to continue with	**Week 24:** RTX/RTX 1.9% (1/53)	**Week 24:** RTX/GP2013 0	**Week 24:** RTX/RTX 0	**Week 24:** RTX/GP2013 0	n/a	n/a

Biosimilar / Manufacturer	Participants	cDMARD or Previous Therapy	Trial Registration and Design	Patients with ADAbs (% of total patients per treatment group, [n_1/N]x100)		Patients with nAbs (% of ADAb-positive patients per treatment group, [n_2/n1]x100)		PK by ADAb Status	Effect of ADAbs on PD, efficacy, and safety parameters
				Reference product	Biosimilar	Reference product	Biosimilar		
			RTX or switch to GP2013 (follow-up 24 weeks)						
PF-05280586 Pfizer	RA, poor response to TNFi	MTX	REFLECTIONS B328-01 (NCT01526057) [52] N=220 Randomized (1:1:1) for DB treatment with RTX-EU, RTX-US, and PF-05280586 at days 1 and 15 (follow-up 24 weeks)	**Week 24:** RTX-EU: 13.5% (10/74) RTX-US: 12.3% (9/73)	**Week 24:** 9.6% (7/73)	**Week 24:** RTX-EU 0 RTX-US 0	**Week 24:** 0	ADAb-positive patients had lower $AUC_{0-\infty}$ and higher clearance rate than ADAb-negative patients	No
PF-05280586 Pfizer	RA, poor response to TNFi	MTX	REFLECTIONS B328-04 (NCT01643928) [53] N=185 Extension of REFLECTIONS B238-01 All patients were offered 3 courses of treatment, each course divided into 2 infusions 2 weeks	**Courses 1-3:** 13.3% n/N data are not available	**Courses 1-3:** 10.0% n/N data are not available	**Courses 1-3:** 0	**Courses 1-3:** 0	ADAb-positive patients had slightly lower drug concentrations, but data should be interpreted with caution due to a small number of patients with ADAbs	**n/a**

Biosimilar / Manufacturer	Participants	cDMARD or Previous Therapy	Trial Registration and Design	Patients with ADAbs (% of total patients per treatment group, [n_1/N]x100)		Patients with nAbs (% of ADAb-positive patients per treatment group, [n_2/n1]x100)		PK by ADAb Status	Effect of ADAbs on PD, efficacy, and safety parameters
				Reference product	Biosimilar	Reference product	Biosimilar		
			apart and separated from the next course by 24 ± 8 weeks Course 1: Patients initially randomized to PF-05280586 remained on that treatment; those randomized to RTX-EU or RTX-US were re-randomized (1:1) to continue treatment or receive PF-05280586 Courses 2-3: All patients who continued treatment after Course 1 received PF-05280586						

[a]Drug tolerance level of the ADA assay was close to the mean trough concentrations at Weeks 4 and 8. Therefore, an observed difference in between-group concentrations at Weeks 4 and 8 may have caused a bias in the ADAb results.
[b]ADAb/Nab prevalence higher than that of historic controls probably due to a higher-sensitivity assays.
[c]ADAb Occurrence in patients who were ADA-negative during weeks 1-54.
[d]For patients with CD, there was a significant difference in the occurrence of ADAbs at Baseline (P<0.001), Week 14 (P<0.001), Week 30 (P=0.03), and Week 54 (P=0.03)
[e]For patients with UC, there was a significant difference in the occurrence of ADAbs at Baseline (P<0.001)

Biosimilar / Manufacturer	Participants	cDMARD or Previous Therapy	Trial Registration and Design	Patients with ADAbs (% of total patients per treatment group, [n_1/N]x100)		Patients with nAbs (% of ADAb-positive patients per treatment group, [n_2/n1]x100)		PK by ADAb Status	Effect of ADAbs on PD, efficacy, and safety parameters
				Reference product	Biosimilar	Reference product	Biosimilar		
ACR, American College of Rheumatology; ADAb, anti-drug antibody; ADA, adalimumab; AS, ankylosing spondylitis; ASAS, Assessment of Spondyloarthritis International Society; AUC, area under the curve; BL, baseline; CD, Crohn's disease; CDAI, Clinical Disease Activity Index; C_{max}, maximum concentration; CRP, C-reactive protein; DAS28, 28-joint Disease Activity Score; EPAR, European Public Assessment Report; ESR, erythrocyte sedimentation rate; EULAR, European League Against Rheumatism; ETN, etanercept; IBD, inflammatory bowel disease; INF, infliximab; IRR, incidence rate ratio; LDA, low disease activity; MTX, methotrexate; n/a, data not available; nAb, neutralizing antibody; PD, pharmacodynamics; PK, pharmacokinetics; RTX, rituximab; RA, rheumatoid arthritis; SDAI, Simple Disease Activity Index; TNFi, tumor necrosis factor α inhibitor; UC, ulcerative colitis.									

1. REFERENCES (greyed out items pertain to manuscript text, but not supplementary tables)

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