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Supplementary information

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The devolution of biosimilars regulations

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Supplementary information

Supplemental Table 1: EU biosimilars on the market (Aug 2023) and their reference products with quality differences.

Reference product (bold) / biosimilar				**Quality differences**			
Name	**Marketing authorization holder**	**Formulation**	**Analytical**	**Receptor binding**	**Biological activity**	**HMW/particles/ aggregates**	**Comment**
Enbrel (entanercept)	Pfizer						
Benepali	Samsung	Y	Y	Y (FcγR)	Y (ADCC)	Y	ADCC not MOA
Erelzi	Sandoz	Y	Y	N	Y (ADCC and CDC)	Y	ADCC and CDC not MOA
Nepexto	Mylan IRE	Y	Y	N	Y (ADCC)	N[a]	ADCC not MOA
Remicade (infliximab)	Jansen Biologics						
Remsima, Inflectra	Celltrion / Hospira	N	Y	Y (FcγR)	Y (ADCC)	Y	Additional functional testing: no difference
Flixabi	Samsung	N	Y	Y (FcγR, FcRn, C1q)	N	Y	
Zessly	Sandoz	Y	Y	Y (FcγR, FcRn)	N	N	
Humira (adalimumab)	AbbVie						
Amgevita	Amgen	Y	Y	(-)	N	N	
Imraldi	Samsung	Y	Y	N	Y (CDC)	Y	Similarity justified (no details)
Cyltezo	Boehringer	Y	(-)	Y (FcγR)	Y (reverse signaling, CDC, ADCP)	Y	Similarity justified (no details)
Halimatoz, Hefiya, Hymiroz	Sandoz	Y	Y	Y (mTNFa, C1q)	Y (ADCC)	Y	Limits set to control ADCC
Hulio	Viatris	Y	Y	N	N	Y	
Idacio	Fresenius	Y	Y	Y (FcγR)	Y (ADCC)	N	Additional functional testing: no difference and stringent control of ADCC
Libmyris, Hukyndra	Stada Arzneimittel	Y	Y	Y (FcγR)	Y (ADCC)	Y[b]	
Amsparity	Pfizer	Y	Y	N	Y (ADCC)	Y	Additional functional testing: overlap in function
Yuflyma	Celltrion	Y	Y	N	N	N	
Avastin (bevacizumab)	Roche						
Mvasi	Amgen	N	Y	Y (FcγR)	Y (growth inhibition)	Y	
Zirabev	Pfizer	Y	Y	Y (FcγR)	N	Y	Comparable potency
Abvemy	Mylan IRE	N	Y	Y (FcγR)	N	Y	Comparable potency; lower amount

Reference product (bold) / biosimilar				**Quality differences**			
Name	**Marketing authorization holder**	**Formulation**	**Analytical**	**Receptor binding**	**Biological activity**	**HMW/particles/ aggregates**	**Comment**
							of HMW
Vegzelma	Celltrion	N	Y	N	N	N	
Aybintio, Onbevzi	Samsung	Y	Y	N	N	Y	Higher count of subvisible particles
Oyavas, Alymsys	Stada Arzneimittel / Mabxience	N	Y	Y (FcγR)	N	Y	Comparable potency; lower amount of HMW
Herceptin (trastuzumab)	Roche						
Ontruzant	Samsung	N	Y	Y (FcγR)	Y (ADCC)	N	Comparable ADCC, except for cluster Herceptin batches with lower ADCC, CDC
Herzuma	Celltrion	Y	Y	Y (FcγR)	N	Y	
Kanjinti	Amgen	N	Y				Comparable ADCC, except for cluster Herceptin batches with lower ADCC, CDC not MOA
Trazimera	Pfizer	Y	Y	N	N	N	
Ogivri	Viatris	Y	Y	N	N	N	
Zercepac	Accord	N	Y				
MabThera (rituximab)	Roche						
Truxima,Blitzima	Celltrion	N	(-)	N	N	(-)	
Rixathon, Riximyo	Sandoz	N	Y	N	N	N	
Ruxience	Pfizer	Y	Y	N	N	Y	Lower HMW, higher monomer for Ruxience
Lucentis (ranibizumab)	Roche						
Ranvisio	Midas Pharma	N	Y	Y (VEGF-A111)	N	N	Comparable potency
Byooviz	Samsung	N	Y	N	N	Y	Incidental lower monomer and higher HMW for Byooviz
Ximluci	Stada Arzneimittel	N	Y	N	N	N	
Soliris (eculizumab)	AstraZeneca						
Epysqli	Samsung	N	Y	N	N	N	Slight difference in N-glycan profile
Bekemv	Amgen	N	Y	N	N	N	Slight difference in afucolysation, galactosylation, sialylation
Eprex (epoetin alfa)	Jansen Cilag						
Retacrit, Silapo	Pfizer / Stada	N	Y	N	N	N	Glycoforms without O-glycan chain slightly higher and ‘unwanted’ glycoforms lower
Abseamed, Binocrit	Medice	N	Y	N	N	N	Presence of mannose type glycan

Reference product (bold) / biosimilar				Quality differences			
Name	**Marketing authorization holder**	**Formulation**	**Analytical**	**Receptor binding**	**Biological activity**	**HMW/particles/ aggregates**	**Comment**
	Arzneimittel Pütter / Sandoz						structures on Asn-24. Not clinically relevant (weak binding to HM6P receptor)
Neulasta (pegfilgrastim)	Amgen						
Grasustek	Juta Pharma	Y	Y	N	N	Y	Lower amount of HMW and hydrophobic impurities
Ziextenzo	Sandoz	N	Y	N	N	Y	Lower amount of HMW and other product related impurities
Stimufend	Fresenius Kabi	N[c]	Y	N	N	Y	Lower amount of HMW and other product related impurities
Fulphila	Viatris	Y	Y	N	N	Y	Marginally higher HMW
Pelmeg, Cegfila	Mundipharma	N (pH 4.2)	Y	N	N	N	
Nyvepria	Pfizer	Y	Y	N	N	Y	HMW and product related impurities lower
Pelgraz	Accord Healthcare	Y	Y	N	N	Y	Product related impurities lower
Forsteo (teriparatide)	Eli Lilly						
Movymia, Terrosa	Stada Arzneimittel / Gedeon Richter	N	N	N	N	N	

Not included are biosimilars of Enoxaparin Sodium (LMW Heparins), Filgrastim (G-CSF), and Insulin as product specific EU guidance exists stipulating that PK/PD studies are sufficient to demonstrate clinical similarity. ADCC, Antibody-Dependent Cell-Mediated Cytotoxicity; CDC, Complement-dependent cytotoxicity; HMW, high-molecular weight; MOA, mechanism of action. Y, yes; N, no; (–), no details.

[a] Equivalent or lower amounts of aggregates

[b] Reported as ‘slightly higher HMWs’ - RP (0.29-0.5 %) vs Libmyris (0.7 – 1.3%)

[c] The Stimufend EPAR suggests quantitative but not qualitative differences

Supplemental Table 2. EU biosimilars on the market (Aug 2023) and their reference products with PK/PD clinical studies and confirmatory clinical studies performed, and their relevance demonstrating biosimilarity.

Reference product (bold) / biosimilar	**Results of clinical trials**				**Added value of trials**	
Name	**PK equivalence: number and type of subjects (source of RP)**	**Efficacy equivalence: indication and combined treatment (number of patients)**	**Safety similarity**	**Immunogenicity similarity**	**PK trial**	**Efficacy trial**
Enbrel (entanercept)						
Benepali	Y: n = 138 HV (EU/US RP)	Y: RA + MTX; n=596	Similar	Similar (low)	Formulation, immunogenicity	N
Erelzi	N: n = 108 HV (EU RP)	Y: Psoriasis; n = 531	Similar	No ADA detected with biosimilar	Formulation, immunogenicity, clearance	N
Nepexto	Y: n = 52 HV (EU RP)	Y: RA + MTX; n = 528	Similar	Similar	Clearance	N
Remicade (infliximab)						
Remsima, Inflectra	Y: AS; n = 250 (EU RP)	Y: RA + MTX; n = 606	Similar	Similar	Immunogenicity	N
Flixabi	Y: n = 159 HV (EU/US RP)	Y: RA + MTX; n = 584	Similar	ADA + rate ↑ in both trials	Clearance, immunogenicity	N
Zessly	Y: n = 151 HV (EU/US RP)	Y: RA + MTX; n = 650	Similar	Similar	Formulation, clearance, immunogenicity	N
Humira (adalimumab)						
Amgevita	Y: n= 203 HV (EU/US RP)	Y: Psoriasis; n= 350	Similar	ADA + rate ↓ in PK trial, similar in efficacy trial	Formulation, local tolerance, immunogenicity	N
Imraldi	Y: n = 189 HV (EU/US RP)	Y: RA + MTX; n = 544	Similar	Similar	Local tolerance, immunogenicity, formulation	N
Halimatoz, Hefiya, Hymiroz	N: n = 219 HV Y: n = 318 HV (EU/US RP)	Y[a]: Psoriasis; n= 465	Similar	ADA + rate ↑ in PK and efficacy trials	Formulation, clearance, local tolerance, immunogenicity	N
Hulio	Y: n = 180 HV (EU/US RP)	Y: RA + MTX; n = 728	Similar	Similar	Formulation, local tolerance	Y[b]
Idacio	Y: n = 237 HV (EU/US RP)	Y[c]: Psoriasis; n = 443	Similar	Similar	Formulation, clearance, local tolerance	N
Libmyris, Hukyndra	Y: n = 380 HV (EU/US RP)	Y: Psoriasis; n = 412	Similar	Similar	Clearance, immunogenicity	N
Amsparity	N: n = 208 HV (EU/US RP) Y: n= 340 HV (EU/US RP)	Y: RA + MTX; n = 596	Similar	Similar	Clearance, local tolerance, immunogenicity	N
Yuflyma	Y: n = 312 HV (EU/US RP)	Y: RA + MTX; n = 648	Similar	Similar	Local tolerance, immunogenicity	N
Avastin (bevacizumab)						
Mvasi	Y: n = 202 HV (EU/US RP)	Y: Metastatic NSCLC + chemo; n = 642	Similar	Similar	Clearance	N
Zirabev	Y: n = 102 HV (EU/US RP)	Y: Metastatic NSCLC + chemo; n = 719	Similar	Similar	Clearance	N
Abvemy	Y: n = 111 HV (EU/US RP)	Y: Metastatic NSCLC + chemo; n = 671	Similar	Similar	Clearance, immunogenicity	N
Vegzelma	Y: n = 141 HV (EU/US RP)	Y: Metastatic NSCLC + chemo; n = 689	Similar	Similar	Clearance, immunogenicity	N

Reference product (bold) / biosimilar	**Results of clinical trials**				**Added value of trials**	
Name	**PK equivalence: number and type of subjects (source of RP)**	**Efficacy equivalence: indication and combined treatment (number of patients)**	**Safety similarity**	**Immunogenicity similarity**	**PK trial**	**Efficacy trial**
Aybintio, Onbevzi	Y: n = 119 HV (EU/US RP)	Y: Metastatic NSCLC + chemo; n = 341	Similar	Similar	Clearance, immunogenicity	N
Oyavas, Alymsys	Y: n = 114 HV (EU/US RP)	Y: Metastatic NSCLC + chemo; n = 627	Similar	Similar	Clearance, immunogenicity	N
Herceptin (trastuzumab)						
Ontruzant	Y: n = 108 HV (EU/US RP)	N[d]: HER2 + EBC or locally advanced BC + chemo; n = 875	Similar	Similar (low)	Clearance, IRR	N
Herzuma	Y: n = 70 HV (US RP)	Y: HER2 + EBC or locally advanced BC + chemo; n = 549	Similar	Similar (low)	Clearance, formulation, IRR, immunogenicity	N
Kanjinti	Y: n = 157 HV (EU/US RP)	N[d]: HER2 + MBC or locally advanced BC + chemo; n = 725	Similar	Similar (low)	Clearance, IRR, immunogenicity	N
Trazimera	Y: n = 105 HV (EU/US RP)	Y: HER2 + MBC or locally advanced BC + chemo; n = 707	Similar	Similar (low)	Clearance, formulation, IRR	N
Ogivri	Y: n = 132 HV (EU/US RP)	Y: HER2 + MBC or locally advanced BC + chemo; n = 500	Similar	Similar (low)	PK, clearance, formulation, IRR	N
Zercepac	Y: n = 111 HV (EU RP)	Y: HER2 + MBC or locally advanced BC + chemo; n = 549	Similar	Similar[g]	PK, clearance, immunogenicity	N
MabThera (rituximab)						
Truxima, Blitzima	Y: RA + MTX; n = 154 (pivotal; EU RP) n = 189 (supportive, EU/US RP) RA + MTX; n = 173	Y: RA +MTX; n = 372 Y[e]: AFL +chemo; n = 140	Similar	Similar	IRR, immunogenicity	N
Rixathon, Riximyo	Y: RA + MTX, N = 173 (EU RP)	Y[f]: AFL + chemo; n = 629	Similar	ADA + rate ↓	Clearance, immunogenicity	N
Ruxience	Y: RA + MTX; n=198 (pivotal; EU/US RP)	Y: AFL + chemo; N=393 (pivotal; EU RP)	Similar	Similar	Clearance, immunogenicity, PD, safety	N
Lucentis (ranibizumab)						
Ranvisio	Y: Compartive systemic exposure in efficacy study, n = 59	Y[h]: Subfoveal nAMD; n= 477 (US RP)	Similar	ADA rate low, too limited data (n=54) for definitive conclusion	Not applicable	N
Byooviz	Y: Compartive systemic exposure in efficacy study, n = 54	Y: Neovascular AMD, n = 705 (EU RP)	Similar	ADA rate low, incidental high ADA. No difference between groups	Not applicable	N
Ximluci	Y: Compartive systemic exposure in efficacy study, n = 70	Y[i]: Neovascular AMD, n = 583 (EU/US RP)	Similar	Similar	Not applicable	N
Soliris (eculizumab)						

Reference product (bold) / biosimilar	Results of clinical trials				Added value of trials	
Name	**PK equivalence: number and type of subjects (source of RP)**	**Efficacy equivalence: indication and combined treatment (number of patients)**	**Safety similarity**	**Immunogenicity similarity**	**PK trial**	**Efficacy trial**
Epysqli	Y: n = 240 HV (EU/US RP)	Y[j]: PHN; n=49 (EU RP)	Similar	Safety data collected only provide limited information on comparability of safety and immunogenicity	Clearance, safety, tolerability, immunogenicity, PD	N
Bekemv	Y: n = 217 HV (EU/US RP)	Y[k]: PHN; n=42	Similar	Similar	Clearance, safety, tolerability, immunogenicity	N
Eprex (epoetin alfa)						
Retacrit, Silapo	Y: n=24 HV (EU RP)	Y: Correction and maintenance of anemia in renal failure patients; n = 598 Safety (maintenance); n = 282	Similar	Similar	Clearance	N
Abseamed, Binocrit	Y: n=80 HV (EU RP) – iv Y: n=74 HV EU RP) - sc	Y: Correction of anemia in renal failure patients; n = 403	Similar	Similar	Clearance, PD (reticulocyte count)	N
Neulasta (pegfilgrastim)						
Grasustek	Y: n=156 HV (EU RP)	Y: Breast cancer patients undergoing myelosuppressive chemotherapy; n=248	Similar	Similar	Clearance, PD (ANC, CD34+ cells), immunogenicity	N
Ziextenzo	Y: n=184 HV (EU/US RP)	Y: Breast cancer patients undergoing myelosuppressive chemotherapy; n=316	Similar	Similar	Clearance, PD (ANC), immunogenicity	N
Stimufend	Y: n=192 HV (US RP), n= 336 HV (US RP)	No efficacy trial	Similar	Similar	Clearance, PD (ANC), tolerability, safety, immunogenicity	---
Fulphila	Y: n=216 HV (EU/US RP),	Stage II/III invasive breast cancer in the adjuvant/neo- adjuvant setting who were receiving TAC; n=194	Similar	Similar	2nd study: immunogenicity, safety, tolerability, clearance, PD (NAC), safety tolerability + separate immunogenicity study (n=50 HV, US RP)	N
Pelmeg, Cegfila	Y: n=172 HV (EU RP), n= 96 HV (EU RP)	No efficacy trial	Similar	Similar	Clearance, PD (ANC), safety, immunogenicity	---
Nyvepria	Y: n=153 HV (EU/US RP), n= 422 HV (US RP	No efficacy trial	Similar	Similar	2nd study: PD (ANC), immunogenicity, safety, clearance	---
Pelgraz	Y: n=66 HV (EU/US RP)	Y: Early breast cancer pts, receiving TAC; n=589	Similar	Similar	2nd study: immunogenicity[L], clearance, PD (ANC, CD34+).	Y[m]
Forsteo (teriparatide)						
Movymia, Terrosa	n=51 HV (EU RP)	No efficacy trial	Similar	Not analyzed	Clearance, safety, tolerability	---

Not included are biosimilars of Enoxaparin Sodium (LMW Heparins), Filgrastim (G-CSF), and Insulin as product specific EU guidance exists stipulating that PK/PD studies are sufficient to demonstrate clinical similarity. AFL, advanced follicular lymphoma; ANC, absolute neutrophil count; AS, ankylosing spondylitis; chemo, chemotherapy; EBC, early breast cancer; EU RP, EU-sourced reference product; IRR, infusion-related reaction; MBC, metastatic breast cancer; mTNFa, membrane tumour necrosis factor a; MTX, methotrexate; TAC, docetaxel, doxorubicin and cyclophosphamide, NSCLC, nonsmall cell lung cancer; PHN, paroxysmal nocturnal haemoglobinuria; US RP, US-sourced reference product.

Y, yes; N, no; (–), no details.

↑ or ↓: increased or decreased for the biosimilar compared with the RP.

N = total number of subjects randomized in the trial.

[a] Equivalence in the US group; lower for the biosimilar in the small EU group.

[b] Immunogenicity because of unreliable assays in the PK trial.

[c] Much higher efficacy response than expected.

[d] Upper limit of equivalence margin exceeded.

[e] Non-inferiority trial.

[f] Equivalence for overall response rate (primary endpoint) but lower progression-free survival for the biosimilar

[g] Number of subjects with positive ADA and or NAb too small to draw clinically meaningful conclusion

[h] Lower efficacy for Ranivisio, not of clinical relevance

[i] Lucentis over performed in study; Ximluci results similar to meta-analysis of RCTs (3500 subjects)

[j] Apparent lower efficacy of Epsyqli, breakthrough haemolysis higher, small sample size – divergent opinion added to EPAR

[k] Small sample size, evidence moderate, still similar efficacy concluded / biosimilarity largely relying on quality similarity

[l] Immunogenicity study was performed based on FDA interactions as a non-inferiority study, which is not a formal CHMP request

[m] Safety monitored in phase III study only