Introducing the biosimilar paradigm to neurology – The totality of evidence for the first biosimilar natalizumab

BioDrugs

Krzysztof Selmaj[1], *Karsten Roth*[2], *Josef Höfler*[3], *Klaus Vitzithum*[2], *Rafal Derlacz*[2], *Oliver von Richter*[4], *Cyrill Hornuss*[4], *Johann Poetzl*[4], *Barry Singer*[5], *Laura Jacobs*[4]*

[1]Department of Neurology, University of Warmia & Mazury, Olsztyn, and Center of Neurology, Lodz, Poland

[2]Polpharma Biologics S.A., Gdansk, Poland

[3]Staburo GmbH, Munich, Germany

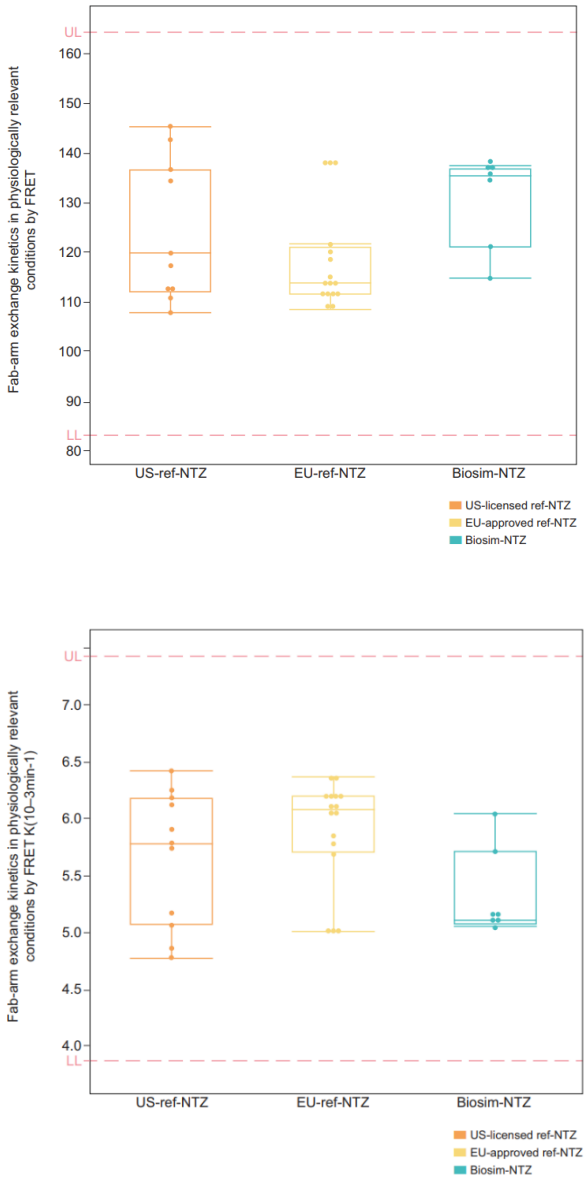
[4]Hexal AG (a Sandoz company), Holzkirchen, Germany

[5]The MS Center for Innovations in Care, Missouri Baptist Medical Center, St Louis, Missouri, USA

*Corresponding author: Laura Jacobs

Email: laura.jacobs@sandoz.com

Supplementary figure 1 Fab-arm exchange kinetics in physiologically relevant conditions by FRET



Biosim-NTZ, biosimilar natalizumab; FRET, Förster resonance energy transfer; ref-NTZ, reference natalizumab.

The boxes indicate quartiles and the horizontal line in each box represents the median value; the whiskers show data distribution; the circles represent the individual batches of US-ref-NTZ, EU-ref-NTZ, and biosim-NTZ.

Supplementary table 1 Fab-arm exchange kinetics in physiologically relevant conditions by FRET

Sample	Half-life (min)			K (10^{-3} min^{-1})		
	Biosim-NTZ (n=7)	**US-ref-NTZ (n=11)**	**EU-ref-NTZ (n=16)**	**Biosim-NTZ (n=7)**	**US-ref-NTZ (n=11)**	**EU-ref-NTZ (n=16)**
Min	114.7	108.0	108.7	5.056	4.778	5.012
Max	137.3	145.2	138.3	6.053	6.424	6.382
Mean	130.9	123.8	118.5	5.321	5.665	5.891
SD	9.080	13.514	10.356	0.398	0.595	0.470

Biosim-NTZ, biosimilar natalizumab; FRET, Förster resonance energy transfer; ref-NTZ, reference natalizumab; SD, standard deviation.

Supplementary table 2 Pivotal PK/PD study %Fab-arm exchange over time

Scheduled study time/day	Biosim-NTZ				US-ref-NTZ				EU-ref-NTZ			
	n	nmiss	mean	SD	n	nmiss	mean	SD	n	nmiss	mean	SD
Hour 5	141	1	13.8	16.400	148	0	15.4	13.600	146	1	16.5	12.300
Hour 6	142	0	30.6	19.700	148	0	31.4	16.300	146	1	31.4	18.200
Hour 12	142	0	50.6	15.000	148	0	51.1	13.400	147	0	52.0	14.500
Day 2	142	0	60.2	14.800	147	1	61.5	14.900	145	2	60.9	15.100
Day 3	141	1	77.8	16.300	148	0	80.9	14.000	145	2	79.5	14.900
Day 5	138	4	91.2	13.800	143	5	93.5	11.800	142	5	92.6	11.400
Day 8	140	2	95.4	8.360	148	0	96.2	7.440	146	1	95.9	7.160
Day 15	140	2	98.9	3.490	143	5	99.3	1.400	145	2	99.2	1.720
Day 22	137	5	99.6	0.533	144	4	99.7	0.370	143	4	99.6	0.425
Day 29	135	7	99.9	0.280	142	6	99.9	0.245	142	5	99.9	0.272
Day 36	139	3	99.9	0.478	144	4	100	0.110	141	6	100.0	0.196
Day 43	134	8	99.9	1.160	144	4	100	0.190	144	3	99.9	0.348

Biosim-NTZ, biosimilar natalizumab; nmiss, number of missing values; PD, pharmacodynamics; PK, pharmacokinetics; ref-NTZ, reference natalizumab; SD, standard deviation.

Supplementary table 3 Summary of the Antelope study safety and immunogenicity results to Week 48[a]

Safety population	No. (%)		
	Biosim-NTZ (n=131)	**EU-ref-NTZ/biosim-NTZ switch (n=30)**	**EU-ref-NTZ (n=103)**
Any TEAE	85 (64.9)	22 (73.3)	71 (68.9)
Any related TEAE	31 (23.7)	8 (26.7)	22 (21.4)
Any TEAE ≥Grade 3	4 (3.1)	0	1 (1.0)
Investigations	2 (1.5)	0	0
Musculoskeletal and connective tissue disorders	0	0	1 (1.0)
Respiratory, thoracic, and mediastinal disorders	1 (0.8)	0	0
Skin and subcutaneous tissue disorders	1 (0.8)	0	0
Any TEAE of special interest	6 (4.6)	2 (6.7)	6 (5.8)
Immune system disorders	0	1 (3.3)	0
Infections and infestations	2 (1.5)	1 (3.3)	5 (4.9)
Investigations	1 (0.8)	0	0
Skin and subcutaneous tissue disorders	3 (2.3)	0	1 (1.0)
Any TEAE leading to permanent study drug discontinuation	8 (6.1)[b]	1 (3.3)[c]	3 (2.9)[d]
Any TEAE leading to withdrawal from study[e]	0	0	0
ADA prevalence at baseline	9 (7)	1 (3)	7 (7)
Treatment-emergent ADA positivity, total incidence	104 (79)	23 (77)	76 (74)
Neutralizing ADA (NAb)	90 (69)	20 (67)	69 (67)
% of ADA positive	87	87	91

[a]The number and percentage of patients with TEAEs, AEs of special interest (i.e. PML, John Cunningham virus granule cell neuronopathy, opportunistic infections, liver injury, hypersensitivity, encephalitis, meningitis, and acute retinal necrosis), and serious AEs that occurred after the start of the first infusion and through 4 weeks after the last infusion date of the study drug (visit 13, end of study visit), were summarized by MedDRA system organ class and preferred term overall, by severity, and by relationship to study drug for each treatment group.
[b]Urticaria (n=2); pruritus (n=2); asthenia, hyperhidrosis, blood pressure fluctuations, and dizziness (n=1); trigeminal neuralgia, herpes simplex, and ear infection (n=1); COVID-19 (n=1); hypotension (n=1).
[c]Hypersensitivity (n=1).
[d]Urinary tract infection (n=1); pharyngitis (n=1); urticaria and angioedema (n=1).
[e]A TEAE was considered to lead to withdrawal from the study only if the patient did not proceed to PML follow-up because of this event.

ADA, anti-drug antibody; AE, adverse event; biosim-NTZ, biosimilar natalizumab; COVID-19, coronavirus disease 2019; NAb, neutralizing antibody; PML, progressive multifocal leukoencephalopathy; ref-NTZ, reference natalizumab; TEAE, treatment-emergent adverse event.

Hemmer B, Wiendl H, Roth K, Wessels H, Höfler J, Hornuss C, Liedert B, Selmaj K. Efficacy and Safety of Proposed Biosimilar Natalizumab (PB006) in Patients With Relapsing-Remitting Multiple Sclerosis: The Antelope Phase 3 Randomized Clinical Trial. JAMA Neurology. 2023;80:298–307. Reprinted by permission of JAMA Network