

## Supplemental Online Content

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**eAppendix 1.** Magnetic Resonance Imaging Secondary Endpoints in Full Analysis Set Population

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This supplemental material has been provided by the authors to give readers additional information about their work.

## eAppendix 1. Magnetic Resonance Imaging Secondary Endpoints in Full Analysis Set Population

eTable 1.1. Cumulative Number of New Active Lesions by Visit by Primary Randomization

Cumulative number of new active lesions	Biosim-NTZ (n=131)	Ref-NTZ (n=133)
<b>... up to Week 8</b>		
<b>n</b>	125	128
<b>Mean</b>	1.3	1.7
<b>SD</b>	3.14	3.09
<b>Median</b>	0.0	0.0
<b>Min/Max</b>	0/25	0/16
<b>... up to Week 16</b>		
<b>n</b>	124	128
<b>Mean</b>	1.4	1.8
<b>SD</b>	3.54	3.42
<b>Median</b>	0.0	0.0
<b>Min/Max</b>	0/30	0/17
<b>... up to Week 20</b>		
<b>n</b>	126	128
<b>Mean</b>	1.4	1.8
<b>SD</b>	3.57	3.42
<b>Median</b>	0.0	0.0
<b>Min/Max</b>	0/30	0/17
<b>... up to Week 24</b>		
<b>n</b>	126	127
<b>Mean</b>	1.4	1.9
<b>SD</b>	3.62	3.98
<b>Median</b>	0.0	0.0
<b>Min/Max</b>	0/30	0/29
<b>... up to Week 48</b>		
<b>n</b>	122	96
<b>Mean</b>	1.5	2.3
<b>SD</b>	3.72	5.68
<b>Median</b>	0.0	0.0
<b>Min/Max</b>	0/30	0/39

For timepoints after Week 24, patients who switch from Ref-NTZ to Biosim-NTZ are excluded from this table.

Biosim-NTZ, biosimilar natalizumab; n, number of patients in population/treatment group; Ref-NTZ, reference natalizumab; SD, standard deviation.

**eTable 1.2. Cumulative Number of New Active Lesions by Number of MRI Scans by Visit by Primary Randomization**

<b>Cumulative number of new active lesions/MRI scans</b>	<b>Biosim-NTZ (n=131)</b>	<b>Ref-NTZ (n=133)</b>
<b>... up to Week 8</b>		
<b>n</b>	129	133
<b>Cumulative number of new active lesions</b>	157	215
<b>Total number of MRI scans</b>	125	128
<b>Mean number of new active lesions per MRI scan</b>	1.3	1.7
<b>... up to Week 16</b>		
<b>n</b>	126	132
<b>Cumulative number of new active lesions</b>	170	234
<b>Total number of MRI scans</b>	243	252
<b>Mean number of new active lesions per MRI scan</b>	0.7	0.9
<b>... up to Week 20</b>		
<b>n</b>	126	131
<b>Cumulative number of new active lesions</b>	174	233
<b>Total number of MRI scans</b>	363	374
<b>Mean number of new active lesions per MRI scan</b>	0.5	0.6
<b>... up to Week 24</b>		
<b>n</b>	126	130
<b>Cumulative number of new active lesions</b>	178	245
<b>Total number of MRI scans</b>	485	497
<b>Mean number of new active lesions per MRI scan</b>	0.4	0.5
<b>... up to Week 48</b>		
<b>n</b>	122	99
<b>Cumulative number of new active lesions</b>	181	223
<b>Total number of MRI scans</b>	588	466
<b>Mean number of new active lesions per MRI scan</b>	0.3	0.5

For timepoints after Week 24, patients who switched from Ref-NTZ to Biosim-NTZ are excluded from this table.

Biosim-NTZ, biosimilar natalizumab, MRI, magnetic resonance imaging; n, number of patients in population/treatment group; Ref-NTZ, reference natalizumab.

**eTable 1.3. Number of Patients with New Active Lesions by Visit by Primary Randomization**

Number of patients with new active lesions/MRI scans (%)	Biosim-NTZ (n=131)	Ref-NTZ (n=133)
<b>Week 8</b>		
<b>N</b>	125	128
<b>No new lesions</b>	75 (60.0)	74 (57.8)
<b>1–3 new lesions</b>	39 (31.2)	30 (23.4)
<b>4–6 new lesions</b>	5 (4.0)	13 (10.2)
<b>7–9 new lesions</b>	2 (1.6)	5 (3.9)
<b>10–12 new lesions</b>	2 (1.6)	4 (3.1)
<b>&gt;12 new lesions</b>	2 (1.6)	2 (1.6)
<b>Week 16</b>		
<b>N</b>	121	124
<b>No new lesions</b>	116 (95.9)	118 (95.2)
<b>1–3 new lesions</b>	3 (2.5)	5 (4.0)
<b>4–6 new lesions</b>	2 (1.7)	0
<b>7–9 new lesions</b>	0	0
<b>10–12 new lesions</b>	0	1 (0.8)
<b>&gt;12 new lesions</b>	0	0
<b>Week 20</b>		
<b>N</b>	120	124
<b>No new lesions</b>	118 (98.3)	124 (100)
<b>1–3 new lesions</b>	2 (1.7)	0
<b>4–6 new lesions</b>	0	0
<b>7–9 new lesions</b>	0	0
<b>10–12 new lesions</b>	0	0
<b>&gt;12 new lesions</b>	0	0
<b>Week 24</b>		
<b>N</b>	121	126
<b>No new lesions</b>	118 (97.5)	125 (99.2)
<b>1–3 new lesions</b>	3 (2.5)	0
<b>4–6 new lesions</b>	0	0
<b>7–9 new lesions</b>	0	0
<b>10–12 new lesions</b>	0	1 (0.8)
<b>&gt;12 new lesions</b>	0	0
<b>Week 48</b>		
<b>N</b>	118	93
<b>No new lesions</b>	116 (98.3)	88 (94.6)
<b>1–3 new lesions</b>	2 (1.7)	2 (2.2)
<b>4–6 new lesions</b>	0	1 (1.1)
<b>7–9 new lesions</b>	0	0
<b>10–12 new lesions</b>	0	1 (1.1)
<b>&gt;12 new lesions</b>	0	1 (1.1)

For timepoints after Week 24, patients who switched from Ref-NTZ to Biosim-NTZ are excluded from this table.

Biosim-NTZ, biosimilar natalizumab; MRI, magnetic resonance imaging; n, number of patients in population/treatment group; Ref-NTZ, reference natalizumab.

**eTable 1.4. Cumulative Number of New GdE T1-weighted Lesions by Visit by Primary Randomization**

Cumulative number of new GdE T1-weighted lesions	Biosim-NTZ (n=131)	Ref-NTZ (n=133)
<b>... up to Week 8</b>		
n	125	128
Mean	0.2	0.3
SD	0.78	1.19
Median	0.0	0.0
Min/Max	0/6	0/11
<b>... up to Week 16</b>		
n	124	128
Mean	0.3	0.4
SD	0.97	1.22
Median	0.0	0.0
Min/Max	0/8	0/11
<b>... up to Week 20</b>		
n	126	128
Mean	0.3	0.4
SD	1.01	1.22
Median	0.0	0.0
Min/Max	0/8	0/11
<b>... up to Week 24</b>		
n	126	127
Mean	0.3	0.4
SD	1.01	1.25
Median	0.0	0.0
Min/Max	0/8	0/11
<b>... up to Week 48</b>		
n	122	96
Mean	0.3	0.4
SD	1.02	1.39
Median	0.0	0.0
Min/Max	0/8	0/11

For timepoints after Week 24, patients who switched from Ref-NTZ to Biosim-NTZ are excluded from this table.

Biosim-NTZ, biosimilar natalizumab; GdE, gadolinium-enhancing; n, number of patients in population/treatment group; Ref-NTZ, reference natalizumab; SD, standard deviation.

**eTable 1.5. Cumulative Number of New GdE T1-weighted Lesions by Number of MRI Scans by Visit by Primary Randomization**

Cumulative number of new GdE T1-weighted lesions/MRI scans	Biosim-NTZ (n=131)	Ref-NTZ (n=133)
<b>... up to Week 8</b>		
n	129	133
Cumulative number of new GdE T1-weighted lesions	26	43
Total number of MRI scans	125	128
Mean number of new GdE T1-weighted lesions per MRI scan	0.2	0.3
<b>... up to Week 16</b>		
n	126	132
Cumulative number of new GdE T1-weighted lesions	31	47
Total number of MRI scans	243	252
Mean number of new GdE T1-weighted lesions per MRI scan	0.1	0.2
<b>... up to Week 20</b>		
n	126	131
Cumulative number of new GdE T1-weighted lesions	33	47
Total number of MRI scans	363	374
Mean number of new GdE T1-weighted lesions per MRI scan	0.1	0.1
<b>... up to Week 24</b>		
n	126	130
Cumulative number of new GdE T1-weighted lesions	34	49
Total number of MRI scans	485	497
Mean number of new GdE T1-weighted lesions per MRI scan	0.1	0.1
<b>... up to Week 48</b>		
n	122	99
Cumulative number of new GdE T1-weighted lesions	34	41
Total number of MRI scans	588	466
Mean number of new GdE T1-weighted lesions per MRI scan	0.1	0.1

For timepoints after Week 24, patients who switched from Ref-NTZ to Biosim-NTZ are excluded from this table.

Biosim-NTZ, biosimilar natalizumab; GdE, gadolinium-enhancing; MRI, magnetic resonance imaging; n, number of patients in population/treatment group; Ref-NTZ, reference natalizumab.

**eTable 1.6. Number of Patients with New GdE T1-weighted Lesions by Visit by Primary Randomization**

Number of patients (%)	Biosim-NTZ (n=131)	Ref-NTZ (n=133)
<b>Week 8</b>		
n	125	128
No new lesions	110 (88.0)	108 (84.4)
1–3 new lesions	13 (10.4)	17 (13.3)
4–6 new lesions	2 (1.6)	2 (1.6)
7–9 new lesions	0	0
10–12 new lesions	0	1 (0.8)
>12 new lesions	0	0
<b>Week 16</b>		
n	121	124
No new lesions	118 (97.5)	121 (97.6)
1–3 new lesions	3 (2.5)	3 (2.4)
4–6 new lesions	0	0
7–9 new lesions	0	0
10–12 new lesions	0	0
>12 new lesions	0	0
<b>Week 20</b>		
n	120	124
No new lesions	119 (99.2)	124 (100)
1–3 new lesions	1 (0.8)	0
4–6 new lesions	0	0
7–9 new lesions	0	0
10–12 new lesions	0	0
>12 new lesions	0	0
<b>Week 24</b>		
n	121	126
No new lesions	120 (99.2)	125 (99.2)
1–3 new lesions	1 (0.8)	1 (0.8)
4–6 new lesions	0	0
7–9 new lesions	0	0
10–12 new lesions	0	0
>12 new lesions	0	0
<b>Week 48</b>		
n	117	93
No new lesions	117 (100)	92 (98.9)
1–3 new lesions	0	1 (1.1)
4–6 new lesions	0	0
7–9 new lesions	0	0
10–12 new lesions	0	0
>12 new lesions	0	0



For timepoints after Week 24, patients who switched from Ref-NTZ to Biosim-NTZ are excluded from this table.  
Biosim-NTZ, biosimilar natalizumab; GdE, gadolinium-enhancing; n, number of patients in population/treatment group; Ref-NTZ, reference natalizumab.

**eTable 1.7. Number of Patients Without New GdE T1-weighted Lesions Over 24 and 48 Weeks**

	<b>Biosim-NTZ (n=131)</b>	<b>Ref-NTZ (n=133)</b>
<b>... Over 24 weeks</b>		
<b>n</b>	131	133
<b>Number of patients without new GdE T1-weighted lesions (%)</b>	109 (83.2)	105 (78.9)
<b>Number of patients with at least one new GdE T1-weighted lesion (%)</b>	17 (13.0)	22 (16.5)
<b>Number of patients without sufficient MRI data (%)</b>	5 (3.8)	6 (4.5)
<b>... Over 48 weeks</b>		
<b>n</b>	131	103
<b>Number of patients without new GdE T1-weighted lesions (%)</b>	105 (80.2)	80 (77.7)
<b>Number of patients with at least one new GdE T1-weighted lesion (%)</b>	17 (13.0)	16 (15.5)
<b>Number of patients without sufficient MRI data (%)</b>	9 (6.9)	7 (6.8)

For timepoints after Week 24, patients who switched from Ref-NTZ to Biosim-NTZ are excluded from this table.

Biosim-NTZ, biosimilar natalizumab; GdE, gadolinium-enhancing; MRI, magnetic resonance imaging; n, number of patients in population/treatment group; Ref-NTZ, reference natalizumab; SD, standard deviation.

**eTable 1.8. Cumulative Number of New/Enlarging T2-weighted Lesions by Visit by Primary Randomization**

Cumulative number of new/enlarging T2-weighted lesions	Biosim-NTZ (n=131)	Ref-NTZ (n=133)
<b>... up to Week 8</b>		
n	125	128
Mean	1.3	1.8
SD	3.34	3.28
Median	0.0	0.0
Min/Max	0/26	0/16
<b>... up to Week 16</b>		
n	124	128
Mean	1.4	1.9
SD	3.72	3.59
Median	0.0	0.0
Min/Max	0/31	0/17
<b>... up to Week 20</b>		
n	126	128
Mean	1.5	1.9
SD	3.75	3.59
Median	0.0	0.0
Min/Max	0/31	0/17
<b>... up to Week 24</b>		
n	126	127
Mean	1.5	2.0
SD	3.79	4.12
Median	0.0	0.0
Min/Max	0/31	0/29
<b>... up to Week 48</b>		
n	122	96
Mean	1.6	2.4
SD	3.90	5.79
Median	0.0	0.0
Min/Max	0/31	0/39

For timepoints after Week 24, patients who switched from Ref-NTZ to Biosim-NTZ are excluded from this table.

Biosim-NTZ, biosimilar natalizumab; n, number of patients in population/treatment group; Ref-NTZ, reference natalizumab; SD, standard deviation.

**eTable 1.9. Cumulative Number of New/Enlarging T2-weighted Lesions by Number of MRI Scans by Visit by Primary Randomization**

<b>Cumulative number of new/enlarging T2-weighted lesions/MRI scans</b>	<b>Biosim-NTZ (n=131)</b>	<b>Ref-NTZ (n=133)</b>
<b>... up to Week 8</b>		
<b>n</b>	129	133
<b>Cumulative number of new/enlarging T2-weighted lesions</b>	166	229
<b>Total number of MRI scans</b>	125	128
<b>Mean number of new/enlarging T2-weighted lesions per MRI scan</b>	1.3	1.8
<b>... up to Week 16</b>		
<b>n</b>	126	132
<b>Cumulative number of new/enlarging T2-weighted lesions</b>	179	248
<b>Total number of MRI scans</b>	243	252
<b>Mean number of new/enlarging T2-weighted lesions per MRI scan</b>	0.7	1.0
<b>... up to Week 20</b>		
<b>n</b>	126	131
<b>Cumulative number of new/enlarging T2-weighted lesions</b>	183	247
<b>Total number of MRI scans</b>	363	374
<b>Mean number of new/enlarging T2-weighted lesions per MRI scan</b>	0.5	0.7
<b>... up to Week 24</b>		
<b>n</b>	126	130
<b>Cumulative number of new/enlarging T2-weighted lesions</b>	187	259
<b>Total number of MRI scans</b>	485	497
<b>Mean number of new/enlarging T2-weighted lesions per MRI scan</b>	0.4	0.5
<b>... up to Week 48</b>		
<b>n</b>	122	99
<b>Cumulative number of new/enlarging T2-weighted lesions</b>	190	234
<b>Total number of MRI scans</b>	588	466
<b>Mean number of new/enlarging T2-weighted lesions per MRI scan</b>	0.3	0.5

For timepoints after Week 24, patients who switched from Ref-NTZ to Biosim-NTZ are excluded from this table.

Biosim-NTZ, biosimilar natalizumab; MRI, magnetic resonance imaging; n, number of patients in population/treatment group; Ref-NTZ, reference natalizumab.

**eTable 1.10. Number of Patients with New/Enlarging T2-weighted Lesions by Visit by Primary Randomization**

Number of patients (%)	Biosim-NTZ (n=131)	Ref-NTZ (n=133)
<b>Week 8</b>		
n	125	128
No new lesions	74 (59.2)	73 (57.0)
1–3 new lesions	40 (32.0)	31 (24.2)
4–6 new lesions	5 (4.0)	13 (10.2)
7–9 new lesions	2 (1.6)	4 (3.1)
10–12 new lesions	1 (0.8)	4 (3.1)
>12 new lesions	3 (2.4)	3 (2.3)
<b>Week 16</b>		
n	121	124
No new lesions	116 (95.9)	119 (96.0)
1–3 new lesions	3 (2.5)	4 (3.2)
4–6 new lesions	2 (1.7)	0
7–9 new lesions	0	0
10–12 new lesions	0	1 (0.8)
>12 new lesions	0	0
<b>Week 20</b>		
n	120	124
No new lesions	118 (98.3)	124 (100)
1–3 new lesions	2 (1.7)	0
4–6 new lesions	0	0
7–9 new lesions	0	0
10–12 new lesions	0	0
>12 new lesions	0	0
<b>Week 24</b>		
n	122	126
No new lesions	119 (97.5)	125 (99.2)
1–3 new lesions	3 (2.5)	0
4–6 new lesions	0	0
7–9 new lesions	0	0
10–12 new lesions	0	1 (0.8)
>12 new lesions	0	0
<b>Week 48</b>		
n	118	93
No new lesions	116 (98.3)	88 (94.6)
1–3 new lesions	2 (1.7)	2 (2.2)
4–6 new lesions	0	1 (1.1)
7–9 new lesions	0	0
10–12 new lesions	0	1 (1.1)
>12 new lesions	0	1 (1.1)

For timepoints after Week 24, patients who switched from Ref-NTZ to Biosim-NTZ are excluded from this table.  
Biosim-NTZ, biosimilar natalizumab; n, number of patients in population/treatment group; Ref-NTZ, reference natalizumab.

**eTable 1.11. Number of Patients without New/Enlarging T2-weighted Lesions by Primary Randomization**

	<b>Biosim-NTZ (n=131)</b>	<b>Ref-NTZ (n=133)</b>
<b>... Over 24 weeks</b>		
<b>n</b>	131	133
<b>Number of patients without new/enlarging T2-weighted lesions (%)</b>	75 (57.3)	72 (54.1)
<b>Number of patients with at least one new/enlarging T2-weighted lesion (%)</b>	51 (38.9)	55 (41.4)
<b>Number of patients without sufficient MRI data (%)</b>	5 (3.8)	6 (4.5)
<b>... Over 48 weeks</b>		
<b>n</b>	131	103
<b>Number of patients without new/enlarging T2-weighted lesions (%)</b>	71 (54.2)	52 (50.5)
<b>Number of patients with at least one new/enlarging T2-weighted lesion (%)</b>	51 (38.9)	44 (42.7)
<b>Number of patients without sufficient MRI data (%)</b>	9 (6.9)	7 (6.8)

For timepoints after Week 24, patients who switched from Ref-NTZ to Biosim-NTZ are excluded from this table.

Biosim-NTZ, biosimilar natalizumab; MRI, magnetic resonance imaging; n, number of patients in population/treatment group; Ref-NTZ, reference natalizumab.

**eTable 1.12. Number of Persistent Lesions by Visit by Primary Randomization**

Number of persistent lesions	Biosim-NTZ (n=131)	Ref-NTZ (n=133)
<b>... up to Week 8</b>		
n	125	128
Mean	0.3	0.3
SD	1.59	1.34
Median	0.0	0.0
Min/Max	0/16	0/14
<b>... up to Week 16</b>		
n	124	128
Mean	0.4	0.4
SD	1.97	2.38
Median	0.0	0.0
Min/Max	0/19	0/26
<b>... up to Week 20</b>		
n	126	128
Mean	0.4	0.4
SD	2.28	2.90
Median	0.0	0.0
Min/Max	0/22	0/32
<b>... up to Week 24</b>		
n	126	127
Mean	0.5	0.4
SD	2.46	2.92
Median	0.0	0.0
Min/Max	0/23	0/32
<b>... up to Week 48</b>		
n	122	96
Mean	0.5	0.6
SD	2.55	3.35
Median	0.0	0.0
Min/Max	0/23	0/32

For timepoints after Week 24, patients who switched from Ref-NTZ to Biosim-NTZ are excluded from this table.

Biosim-NTZ, biosimilar natalizumab; n, number of patients in population/treatment group; Ref-NTZ, reference natalizumab; SD, standard deviation.



**eTable 1.13. Cumulative Number of Persistent Lesions by Number of MRI Scans by Visit by Primary Randomization**

<b>Cumulative number of persistent lesions/MRI scan</b>	<b>Biosim-NTZ (n=131)</b>	<b>Ref-NTZ (n=133)</b>
<b>... up to Week 8</b>		
<b>n</b>	129	133
<b>Cumulative number of persistent lesions</b>	37	32
<b>Total number of MRI scans</b>	125	128
<b>Mean number of persistent lesions per MRI scan</b>	0.3	0.3
<b>... up to Week 16</b>		
<b>n</b>	126	132
<b>Cumulative number of persistent lesions</b>	49	49
<b>Total number of MRI scans</b>	243	252
<b>Mean number of persistent lesions per MRI scan</b>	0.2	0.2
<b>... up to Week 20</b>		
<b>n</b>	126	131
<b>Cumulative number of persistent lesions</b>	56	56
<b>Total number of MRI scans</b>	363	374
<b>Mean number of persistent lesions per MRI scan</b>	0.2	0.2
<b>... up to Week 24</b>		
<b>n</b>	126	130
<b>Cumulative number of persistent lesions</b>	61	57
<b>Total number of MRI scans</b>	485	497
<b>Mean number of persistent lesions per MRI scan</b>	0.1	0.1
<b>... up to Week 48</b>		
<b>n</b>	122	99
<b>Cumulative number of persistent lesions</b>	63	54
<b>Total number of MRI scans</b>	588	466
<b>Mean number of persistent lesions per MRI Scan</b>	0.1	0.1

For timepoints after Week 24, patients who switched from Ref-NTZ to Biosim-NTZ are excluded from this table.

Biosim-NTZ, biosimilar natalizumab; MRI, magnetic resonance imaging; n, number of patients in population/treatment group; Ref-NTZ, reference natalizumab.

**eTable 1.14. Number of Patients with Persistent Lesions by Visit by Primary Randomization**

Number of patients (%)	Biosim-NTZ (n=131)	Ref-NTZ (n=133)
<b>Week 8</b>		
<b>n</b>	125	128
<b>No new lesions</b>	114 (91.2)	114 (89.1)
<b>1–3 new lesions</b>	9 (7.2)	12 (9.4)
<b>4–6 new lesions</b>	1 (0.8)	1 (0.8)
<b>7–9 new lesions</b>	0	0
<b>10–12 new lesions</b>	0	0
<b>&gt;12 new lesions</b>	1 (0.8)	1 (0.8)
<b>Week 16</b>		
<b>n</b>	121	124
<b>No new lesions</b>	114 (94.2)	119 (96.0)
<b>1–3 new lesions</b>	7 (5.8)	4 (3.2)
<b>4–6 new lesions</b>	0	0
<b>7–9 new lesions</b>	0	0
<b>10–12 new lesions</b>	0	1 (0.8)
<b>&gt;12 new lesions</b>	0	0
<b>Week 20</b>		
<b>n</b>	120	124
<b>No new lesions</b>	116 (96.7)	122 (98.4)
<b>1–3 new lesions</b>	4 (3.3)	1 (0.8)
<b>4–6 new lesions</b>	0	1 (0.8)
<b>7–9 new lesions</b>	0	0
<b>10–12 new lesions</b>	0	0
<b>&gt;12 new lesions</b>	0	0
<b>Week 24</b>		
<b>n</b>	121	126
<b>No new lesions</b>	117 (96.7)	125 (99.2)
<b>1–3 new lesions</b>	4 (3.3)	1 (0.8)
<b>4–6 new lesions</b>	0	0
<b>7–9 new lesions</b>	0	0
<b>10–12 new lesions</b>	0	0
<b>&gt;12 new lesions</b>	0	0
<b>Week 48</b>		
<b>n</b>	117	93
<b>No new lesions</b>	115 (98.3)	93 (100)
<b>1–3 new lesions</b>	2 (1.7)	0
<b>4–6 new lesions</b>	0	0
<b>7–9 new lesions</b>	0	0
<b>10–12 new lesions</b>	0	0
<b>&gt;12 new lesions</b>	0	0

For timepoints after Week 24, patients who switched from Ref-NTZ to Biosim-NTZ are excluded from this table.  
Biosim-NTZ, biosimilar natalizumab; n, number of patients in population/treatment group; Ref-NTZ, reference natalizumab.

**eAppendix 2. Cumulative Number of New Active Lesions Over 24 Weeks by Corrected Stratification Variables – Sensitivity Analysis (Per-Protocol Population)**

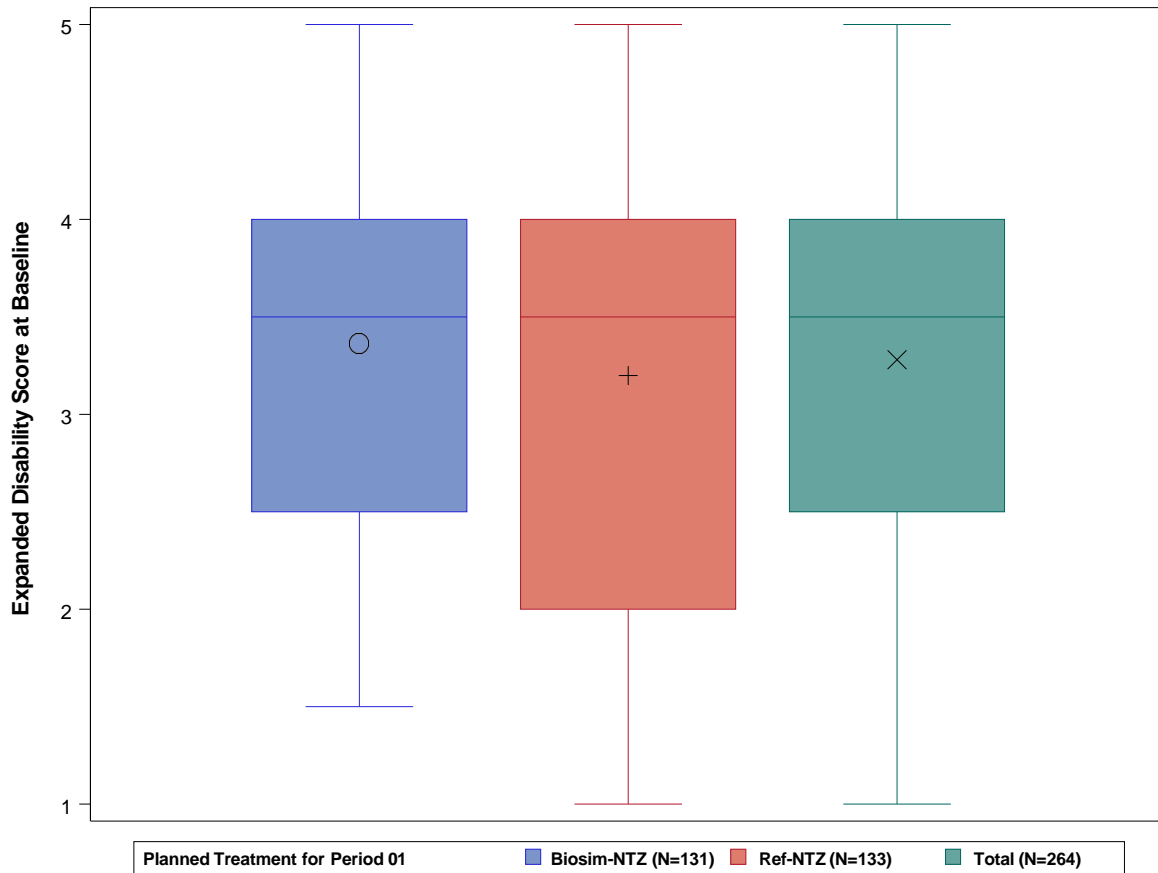
<b>Cumulative number of new active lesions over 24 weeks</b>	<b>Estimate (SE)</b>	<b>90% Confidence interval</b>	<b>95% Confidence interval</b>
<b>Least square means</b>			
<b>Biosim-NTZ</b>	-1.31 (0.642)		
<b>Ref-NTZ</b>	-1.10 (0.630)		
<b>Difference Biosim-NTZ–Ref-NTZ</b>	0.21 (0.247)	-0.198; 0.615	-0.276; 0.692
<b>Exponentiated difference Biosim-NTZ–Ref-NTZ</b>	0.06 (0.083)	-0.073; 0.199	-0.099; 0.225

Biosim-NTZ, biosimilar natalizumab; Ref-NTZ, reference natalizumab; SE, standard error.

**eAppendix 3. Kurtzke Expanded Disability Status Scale Score at Baseline by Primary Randomization (Full Analysis Set)**

	<b>Biosim-NTZ (n=131)</b>	<b>Ref-NTZ (n=133)</b>	<b>Total (N=264)</b>
<b>Baseline EDSS</b>			
<b>Mean (SD)</b>	3.4 (1.1)	3.2 (1.2)	3.3 (1.1)
<b>Median</b>	3.5	3.5	3.5
<b>Q1/Q3</b>	2.5/4.0	2.0/4.0	2.5/4.0
<b>Interquartile range</b>	1.5	2.0	1.5
<b>Minimum/maximum</b>	2/5	1/5	1/5

Biosim-NTZ, biosimilar natalizumab; EDSS, Kurtzke Expanded Disability Status Scale; Ref-NTZ, reference natalizumab; SD, standard deviation.



**eAppendix 4. Common TEAEs (>1% of Patients in any Treatment Group) by System Organ Class and Preferred Term by Treatment Sequence (Safety population)**

	<b>Biosim-NTZ (n=131)</b>		<b>Biosim-NTZ after switch from Ref-NTZ (n=30)</b>		<b>Ref-NTZ (n=103)</b>	
<b>System organ class Preferred term</b>	<b>Patients with event n (%)</b>	<b>Number of events / rate per 100 PY<sup>a</sup></b>	<b>Patients with event n (%)</b>	<b>Number of events / rate per 100 PY<sup>a</sup></b>	<b>Patients with event n (%)</b>	<b>Number of events / rate per 100 PY<sup>a</sup></b>
<b>Any event</b>	<b>85 (64.9)</b>	<b>221 / 192.3</b>	<b>22 (73.3)</b>	<b>60 / 219.6</b>	<b>71 (68.9)</b>	<b>176 / 194.7</b>
<b>Blood and lymphatic system disorders</b>	<b>5 (3.8)</b>	<b>5 / 4.4</b>	<b>0 (0.0)</b>	<b>0 / 0</b>	<b>4 (3.9)</b>	<b>4 / 4.4</b>
Anemia	4 (3.1)	4 / 3.5	0 (0.0)	0 / 0	0 (0.0)	0 / 0
<b>Ear and labyrinth disorders</b>	<b>2 (1.5)</b>	<b>2 / 1.7</b>	<b>0 (0.0)</b>	<b>0 / 0</b>	<b>0 (0.0)</b>	<b>0 / 0</b>
<b>Gastrointestinal disorders</b>	<b>13 (9.9)</b>	<b>17 / 14.8</b>	<b>0 (0.0)</b>	<b>0 / 0</b>	<b>12 (11.7)</b>	<b>18 / 19.9</b>
Diarrhea	3 (2.3)	3 / 2.6	0 (0.0)	0 / 0	5 (4.9)	5 / 5.5
Nausea	4 (3.1)	4 / 3.5	0 (0.0)	0 / 0	3 (2.9)	3 / 3.3
Constipation	2 (1.5)	2 / 1.7	0 (0.0)	0 / 0	3 (2.9)	4 / 4.4
Vomiting	0 (0.0)	0 / 0	0 (0.0)	0 / 0	2 (1.9)	2 / 2.2
<b>General disorders and administration site conditions</b>	<b>13 (9.9)</b>	<b>14 / 12.2</b>	<b>7 (23.3)</b>	<b>8 / 29.3</b>	<b>5 (4.9)</b>	<b>5 / 5.5</b>
Asthenia	5 (3.8)	5 / 4.4	1 (3.3)	1 / 3.7	1 (1.0)	1 / 1.1
Fatigue	5 (3.8)	5 / 4.4	0 (0.0)	0 / 0	1 (1.0)	1 / 1.1
Pyrexia	1 (0.8)	1 / 0.9	1 (3.3)	1 / 3.7	3 (2.9)	3 / 3.3
Hyperthermia	2 (1.5)	2 / 1.7	1 (3.3)	1 / 3.7	0 (0.0)	0 / 0
Feeling hot	0 (0.0)	0 / 0	2 (6.7)	2 / 7.3	0 (0.0)	0 / 0
Edema peripheral	1 (0.8)	1 / 0.9	1 (3.3)	1 / 3.7	0 (0.0)	0 / 0
Discomfort	0 (0.0)	0 / 0	1 (3.3)	1 / 3.7	0 (0.0)	0 / 0
Infusion site pain	0 (0.0)	0 / 0	1 (3.3)	1 / 3.7	0 (0.0)	0 / 0
<b>Hepatobiliary disorders</b>	<b>2 (1.5)</b>	<b>2 / 1.7</b>	<b>1 (3.3)</b>	<b>1 / 3.7</b>	<b>1 (1.0)</b>	<b>1 / 1.1</b>
Hyperbilirubinemia	1 (0.8)	1 / 0.9	1 (3.3)	1 / 3.7	0	0 / 0
<b>Immune system disorders</b>	<b>0 (0.0)</b>	<b>0 / 0</b>	<b>1 (3.3)</b>	<b>1 / 3.7</b>	<b>0 (0.0)</b>	<b>0 / 0</b>
Hypersensitivity	0	0 / 0	1 (3.3)	1 / 3.7	0	0 / 0
<b>Infections and infestations</b>	<b>39 (29.8)</b>	<b>54 / 47.0</b>	<b>15 (50.0)</b>	<b>19 / 69.6</b>	<b>34 (33.0)</b>	<b>44 / 48.7</b>
Nasopharyngitis	11 (8.4)	16 / 13.9	5 (16.7)	5 / 18.3	8 (7.8)	9 / 10.0
COVID-19	11 (8.4)	11 / 9.6	4 (13.3)	4 / 14.6	6 (5.8)	6 / 6.6
Upper respiratory tract infection	2 (1.5)	2 / 1.7	1 (3.3)	1 / 3.7	3 (2.9)	3 / 3.3
Pharyngitis	1 (0.8)	2 / 1.7	1 (3.3)	1 / 3.7	3 (2.9)	4 / 4.4
Pneumonia	3 (2.3)	3 / 2.6	0 (0.0)	0 / 0	1 (1.0)	1 / 1.1

Respiratory tract infection	2 (1.5)	2 / 1.7	1 (3.3)	1 / 3.7	1 (1.0)	1 / 1.1
Urinary tract infection	2 (1.5)	2 / 1.7	0 (0.0)	0 / 0	2 (1.9)	3 / 3.3
Bronchitis	0 (0.0)	0 / 0	1 (3.3)	1 / 3.7	2 (1.9)	3 / 3.3
Cystitis	2 (1.5)	2 / 1.7	0 (0.0)	0 / 0	1 (1.0)	1 / 1.1
Oral herpes	1 (0.8)	1 / 0.9	1 (3.3)	1 / 3.7	1 (1.0)	1 / 1.1
Rhinitis	1 (0.8)	1 / 0.9	1 (3.3)	1 / 3.7	1 (1.0)	1 / 1.1
Respiratory tract infection viral	1 (0.8)	1 / 0.9	1 (3.3)	1 / 3.7	0 (0.0)	0 / 0
COVID-19 pneumonia	0 (0.0)	0 / 0	1 (3.3)	1 / 3.7	0 (0.0)	0 / 0
Laryngitis	0 (0.0)	0 / 0	1 (3.3)	1 / 3.7	0 (0.0)	0 / 0
Pyoderma streptococcal	0 (0.0)	0 / 0	1 (3.3)	1 / 3.7	0 (0.0)	0 / 0
<b>Injury, poisoning and procedural complications</b>	<b>2 (1.5)</b>	<b>4 / 3.5</b>	<b>1 (3.3)</b>	<b>1 / 3.7</b>	<b>3 (2.9)</b>	<b>3 / 3.3</b>
Contusion	0 (0.0)	0 / 0	1 (3.3)	1 / 3.7	1 (1.0)	1 / 1.1
<b>Investigations</b>	<b>8 (6.1)</b>	<b>11 / 9.6</b>	<b>2 (6.7)</b>	<b>3 / 11.0</b>	<b>9 (8.7)</b>	<b>11 / 12.2</b>
Weight decreased	2 (1.5)	2 / 1.7	1 (3.3)	1 / 3.7	3 (2.9)	3 / 3.3
Alanine aminotransferase increased	2 (1.5)	2 / 1.7	0 (0.0)	0 / 0	1 (1.0)	2 / 2.2
Blood pressure increased	1 (0.8)	1 / 0.9	0 (0.0)	0 / 0	2 (1.9)	2 / 2.2
C-reactive protein increased	2 (1.5)	2 / 1.7	0 (0.0)	0 / 0	1 (1.0)	1 / 1.1
Gamma-glutamyl transferase increased	1 (0.8)	1 / 0.9	1 (3.3)	2 / 7.3	0 (0.0)	0 / 0
<b>Metabolism and nutrition disorders</b>	<b>1 (0.8)</b>	<b>1 / 0.9</b>	<b>1 (3.3)</b>	<b>1 / 3.7</b>	<b>2 (1.9)</b>	<b>3 / 3.3</b>
Hyperlipidemia	0 (0.0)	0 / 0	1 (3.3)	1 / 3.7	0 (0.0)	0 / 0
<b>Musculoskeletal and connective tissue disorders</b>	<b>17 (13.0)</b>	<b>21 / 18.3</b>	<b>1 (3.3)</b>	<b>1 / 3.7</b>	<b>9 (8.7)</b>	<b>13 / 14.4</b>
Back pain	7 (5.3)	7 / 6.1	1 (3.3)	1 / 3.7	3 (2.9)	3 / 3.3
Pain in extremity	2 (1.5)	2 / 1.7	0 (0.0)	0 / 0	4 (3.9)	4 / 4.4
Muscle spasms	2 (1.5)	2 / 1.7	0 (0.0)	0 / 0	1 (1.0)	1 / 1.1
Myalgia	2 (1.5)	2 / 1.7	0 (0.0)	0 / 0	1 (1.0)	1 / 1.1
Neck pain	1 (0.8)	2 / 1.7	0 (0.0)	0 / 0	2 (1.9)	2 / 2.2
Arthralgia	2 (1.5)	2 / 1.7	0 (0.0)	0 / 0	0 (0.0)	0 / 0
Musculoskeletal stiffness	0 (0.0)	0 / 0	0 (0.0)	0 / 0	2 (1.9)	2 / 2.2
<b>Neoplasms benign, malignant, and</b>	<b>2 (1.5)</b>	<b>2 / 1.7</b>	<b>0 (0.0)</b>	<b>0 / 0</b>	<b>0 (0.0)</b>	<b>0 / 0</b>

unspecified (incl. cysts and polyps)						
<b>Nervous system disorders</b>	<b>33 (25.2)</b>	<b>48 / 41.8</b>	<b>8 (26.7)</b>	<b>13 / 47.6</b>	<b>24 (23.3)</b>	<b>56 / 62.0</b>
Headache	25 (19.1)	36 / 31.3	4 (13.3)	5 / 18.3	19 (18.4)	47 / 52.0
Dizziness	3 (2.3)	3 / 2.6	2 (6.7)	2 / 7.3	1 (1.0)	2 / 2.2
Hypoesthesia	2 (1.5)	2 / 1.7	1 (3.3)	1 / 3.7	1 (1.0)	1 / 1.1
Paranesthesia	1 (0.8)	1 / 0.9	1 (3.3)	1 / 3.7	0 (0.0)	0 / 0
Presyncope	1 (0.8)	1 / 0.9	1 (3.3)	1 / 3.7	0 (0.0)	0 / 0
Tension headache	1 (0.8)	2 / 1.7	1 (3.3)	3 / 11.0	0 (0.0)	0 / 0
<b>Psychiatric disorders</b>	<b>7 (5.3)</b>	<b>10 / 8.7</b>	<b>4 (13.3)</b>	<b>4 / 14.6</b>	<b>2 (1.9)</b>	<b>2 / 2.2</b>
Depression	3 (2.3)	3 / 2.6	3 (10.0)	3 / 11.0	1 (1.0)	1 / 1.1
Insomnia	4 (3.1)	6 / 5.2	0 (0.0)	0 / 0	1 (1.0)	1 / 1.1
Sleep disorder	0 (0.0)	0 / 0	1 (3.3)	1 / 3.7	0 (0.0)	0 / 0
<b>Renal and urinary disorders</b>	<b>1 (0.8)</b>	<b>1 / 0.9</b>	<b>3 (10.0)</b>	<b>4 / 14.6</b>	<b>2 (1.9)</b>	<b>4 / 4.4</b>
Leukocyturia	0 (0.0)	0 / 0	1 (3.3)	1 / 3.7	1 (1.0)	1 / 1.1
Dysuria	0 (0.0)	0 / 0	1 (3.3)	1 / 3.7	0 (0.0)	0 / 0
Hematuria	0 (0.0)	0 / 0	1 (3.3)	1 / 3.7	0 (0.0)	0 / 0
Urinary retention	0 (0.0)	0 / 0	1 (3.3)	1 / 3.7	0 (0.0)	0 / 0
<b>Reproductive system and breast disorders</b>	<b>3 (2.3)</b>	<b>3 / 2.6</b>	<b>0 (0.0)</b>	<b>0 / 0</b>	<b>1 (1.0)</b>	<b>1 / 1.1</b>
<b>Respiratory, thoracic, and mediastinal disorders</b>	<b>10 (7.6)</b>	<b>11 / 9.6</b>	<b>1 (3.3)</b>	<b>1 / 3.7</b>	<b>4 (3.9)</b>	<b>5 / 5.5</b>
Oropharyngeal pain	5 (3.8)	5 / 4.4	0 (0.0)	0 / 0	3 (2.9)	3 / 3.3
Rhinorrhea	1 (0.8)	1 / 0.9	1 (3.3)	1 / 3.7	0 (0.0)	0 / 0
<b>Skin and subcutaneous tissue disorders</b>	<b>8 (6.1)</b>	<b>10 / 8.7</b>	<b>2 (6.7)</b>	<b>2 / 7.3</b>	<b>3 (2.9)</b>	<b>4 / 4.4</b>
Urticaria	2 (1.5)	2 / 1.7	0 (0.0)	0 / 0	1 (1.0)	1 / 1.1
Erythema	1 (0.8)	1 / 0.9	1 (3.3)	1 / 3.7	0 (0.0)	0 / 0
Hyperhidrosis	1 (0.8)	1 / 0.9	1 (3.3)	1 / 3.7	0 (0.0)	0 / 0
Pruritus	2 (1.5)	2 / 1.7	0 (0.0)	0 / 0	0 (0.0)	0 / 0
<b>Vascular disorders</b>	<b>4 (3.1)</b>	<b>4 / 3.5</b>	<b>1 (3.3)</b>	<b>1 / 3.7</b>	<b>0 (0.0)</b>	<b>0 / 0</b>
Hypotension	2 (1.5)	2 / 1.7	0	0 / 0	0 (0.0)	0 / 0
Hypertension	0 (0.0)	0 / 0	1 (3.3)	1 / 3.7	0 (0.0)	0 / 0

<sup>a</sup>Patient-years calculated as the sum of (last day of follow-up – first day of exposure + 1)/365.25 for all patients in group. AEs are summarized according to the randomized study drug sequence.

AE, adverse event; Biosim-NTZ, biosimilar natalizumab; PY, patient-years; Ref-NTZ, reference natalizumab; TEAEs, treatment-emergent adverse event.



**eAppendix 5. Anti-John Cunningham Virus Antibodies by Visit by Primary Randomization (Safety Population)**

Number of patients (%)	Biosim-NTZ (n=131)	Ref-NTZ (n=133)	Total (N=264)
<b>Baseline</b>			
<b>n</b>	131 (100)	133 (100)	264 (100)
<b>Positive, index &gt;1.5</b>	0	0	0
<b>Positive, index between 0.9 and 1.5</b>	16 (12.2)	18 (13.5)	34 (12.9)
<b>Positive, index ≤0.9</b>	35 (26.7)	37(27.8)	72 (27.3)
<b>Negative</b>	80 (61.1)	78 (58.6)	158 (59.8)
<b>Week 24</b>			
<b>n</b>	103 (100)	111 (100)	214 (100)
<b>Positive, index &gt;1.5</b>	5 (4.9)	5 (4.5)	10 (4.7)
<b>Positive, index between 0.9 and 1.5</b>	7 (6.8)	13 (11.7)	20 (9.3)
<b>Positive, index ≤0.9</b>	35 (34.0)	29 (26.1)	64 (29.9)
<b>Negative</b>	56 (54.4)	63 (56.8)	119 (55.6)
<b>Indeterminate</b>	0	1 (0.9)	1 (0.5)
<b>Week 48</b>			
<b>n</b>	116 (100)	119 (100)	235 (100)
<b>Positive, index &gt;1.5</b>	7 (6.0)	7 (5.9)	14 (6.0)
<b>Positive, index between 0.9 and 1.5</b>	4 (3.4)	9 (7.6)	13 (5.5)
<b>Positive, index ≤0.9</b>	38 (32.8)	34 (28.6)	72 (30.6)
<b>Negative</b>	67 (57.8)	69 (58.0)	136 (57.9)

Biosim-NTZ, biosimilar natalizumab; n, number of patients in population/treatment group; Ref-NTZ, reference natalizumab.