



Clinical trial results:

A Randomised, Controlled, Open-Label, Rater-Blinded, Phase 3b Study of the Efficacy, Safety, and Tolerability of 6-Week Extended Interval Dosing (EID) of Natalizumab (BG00002) in Subjects With Relapsing-Remitting Multiple Sclerosis Switching From Treatment With 4-Week Natalizumab Standard Interval Dosing (SID) in Relation to Continued SID Treatment - Followed by an Open-Label Crossover Extension Study Comprising Subcutaneous and Intravenous Natalizumab Administration Summary

EudraCT number	2018-002145-11
Trial protocol	GB DE FR NL ES IT
Global end of trial date	24 July 2023

Results information

Result version number	v1 (current)
This version publication date	13 July 2024
First version publication date	13 July 2024

Trial information

Trial identification

Sponsor protocol code	101MS329
-----------------------	----------

Additional study identifiers

ISRCTN number	-
ClinicalTrials.gov id (NCT number)	NCT03689972
WHO universal trial number (UTN)	-

Notes:

Sponsors

Sponsor organisation name	Biogen
Sponsor organisation address	22 Binney Street, Cambridge, United States, 02142
Public contact	Biogen Study Medical Director, Biogen, clinicaltrials@biogen.com
Scientific contact	Biogen Study Medical Director, Biogen, clinicaltrials@biogen.com

Notes:

Paediatric regulatory details

Is trial part of an agreed paediatric investigation plan (PIP)	No
Does article 45 of REGULATION (EC) No 1901/2006 apply to this trial?	No
Does article 46 of REGULATION (EC) No 1901/2006 apply to this trial?	No

Notes:

Results analysis stage

Analysis stage	Final
Date of interim/final analysis	24 July 2023
Is this the analysis of the primary completion data?	No
Global end of trial reached?	Yes
Global end of trial date	24 July 2023
Was the trial ended prematurely?	No

Notes:

General information about the trial

Main objective of the trial:

Part 1:Primary objective=evaluate efficacy of natalizumab extended interval dosing(EID)(every 6 weeks[Q6W])in participants who have previously been treated with natalizumab standard interval dosing(SID)(every 4 weeks[Q4W])for at least 12 months,in relation to continued Q4W treatment.Secondary objectives=evaluate relapse-based clinical efficacy measures,disability worsening,additional magnetic resonance imaging(MRI)-lesion efficacy measures & safety of Q6W in participants who have previously been treated with natalizumab Q4W for at least 12 months,in relation to continued Q4W treatment.Part 2:Primary objective=evaluate participant preference for subcutaneous(SC)/intravenous(IV) route of natalizumab administration.Secondary objectives=evaluate treatment satisfaction,drug preparation & administration time,safety & immunogenicity,efficacy & characterise pharmacokinetic(PK) & pharmacodynamic(PD) drug preparation and administration time of SC versus IV routes of natalizumab administration.

Protection of trial subjects:

Written informed consent was obtained from each participant or participant`s legally authorised representative, as applicable, prior to evaluations performed for eligibility. Participants or the participant`s legally authorised representative were given adequate time to review the information in the informed consent/assent and were allowed to ask, and have answered, questions concerning all portions of the conduct of the study.

Background therapy:

N/A

Evidence for comparator:

N/A

Actual start date of recruitment	27 November 2018
Long term follow-up planned	No
Independent data monitoring committee (IDMC) involvement?	No

Notes:

Population of trial subjects

Subjects enrolled per country

Country: Number of subjects enrolled	United States: 237
Country: Number of subjects enrolled	Spain: 65
Country: Number of subjects enrolled	Germany: 61
Country: Number of subjects enrolled	Israel: 41
Country: Number of subjects enrolled	Canada: 37
Country: Number of subjects enrolled	Italy: 37
Country: Number of subjects enrolled	Australia: 31
Country: Number of subjects enrolled	France: 30
Country: Number of subjects enrolled	Netherlands: 18
Country: Number of subjects enrolled	Belgium: 16

Country: Number of subjects enrolled	United Kingdom: 12
Worldwide total number of subjects	585
EEA total number of subjects	227

Notes:

Subjects enrolled per age group	
In utero	0
Preterm newborn - gestational age < 37 wk	0
Newborns (0-27 days)	0
Infants and toddlers (28 days-23 months)	0
Children (2-11 years)	0
Adolescents (12-17 years)	0
Adults (18-64 years)	585
From 65 to 84 years	0
85 years and over	0

Subject disposition

Recruitment

Recruitment details:

Participants were enrolled at the investigative sites in Australia, Belgium, Canada, France, Germany, Israel, Italy, Netherlands, Spain, the United Kingdom, and the United States from 27 November 2018 to 20 June 2021.

Pre-assignment

Screening details:

585 participants were enrolled in the study, out of which 499 participants were randomised in Part 1. A total of 396 participants completed Part 1 of the study, out of which 67 participants entered Part 2 of the study. A total of 153 participants (including 86 new participants) entered Part 2 crossover period and 123 participants completed the study.

Period 1

Period 1 title	Part 1 (Day 1 up to Week 72)
Is this the baseline period?	Yes
Allocation method	Randomised - controlled
Blinding used	Not blinded

Arms

Are arms mutually exclusive?	Yes
Arm title	Part 1: IV Q4W

Arm description:

Participants received natalizumab 300 mg IV infusion Q4W up to Week 72.

Arm type	Experimental
Investigational medicinal product name	Natalizumab
Investigational medicinal product code	
Other name	BG00002, AN100226
Pharmaceutical forms	Concentrate for solution for infusion
Routes of administration	Intravenous use

Dosage and administration details:

Administered as specified in the treatment arm.

Arm title	Part 1: IV Q6W
------------------	----------------

Arm description:

Participants received natalizumab 300 mg IV infusion Q6W up to Week 72.

Arm type	Experimental
Investigational medicinal product name	Natalizumab
Investigational medicinal product code	
Other name	BG00002, AN100226
Pharmaceutical forms	Concentrate for solution for infusion
Routes of administration	Intravenous use

Dosage and administration details:

Administered as specified in the treatment arm.

Number of subjects in period 1 ^[1]	Part 1: IV Q4W	Part 1: IV Q6W
Started	248	251
Completed	194	202
Not completed	54	49
Randomised but not Dosed	1	1
Adverse event, non-fatal	1	3
Pregnancy	5	1
Protocol-Defined Rescue Criteria	-	6
Developed Persistent Anti-Natalizumab Antibodies	1	3
Unwilling to Comply With Protocol	3	2
Investigator Decision	9	6
Lost to follow-up	-	2
Reason not Specified	20	16
Consent Withdrawn	14	9

Notes:

[1] - The number of subjects reported to be in the baseline period are not the same as the worldwide number enrolled in the trial. It is expected that these numbers will be the same.

Justification: 585 participants were enrolled in the study, out of which 499 participants were randomised in Part 1.

Period 2

Period 2 title	Part 2:Run-in Period(Week 73-Week 107)
Is this the baseline period?	No
Allocation method	Not applicable
Blinding used	Not blinded

Arms

Arm title	Part 2: Run-in Period: IV Q6W
------------------	-------------------------------

Arm description:

Participants who completed Part 1 or were newly enrolled in Part 2 received natalizumab 300 mg IV infusion Q6W from Week 72 through Week 102.

Arm type	Experimental
Investigational medicinal product name	Natalizumab
Investigational medicinal product code	
Other name	BG00002, AN100226
Pharmaceutical forms	Concentrate for solution for infusion
Routes of administration	Intravenous use

Dosage and administration details:

Administered as specified in the treatment arm.

Number of subjects in period 2	Part 2: Run-in Period: IV Q6W
Started	158
Completed	153
Not completed	5
Reason not Specified	2
Pregnancy	1
Consent Withdrawn	2

Period 3

Period 3 title	Part 2:Crossover Period(Week108-Week156)
Is this the baseline period?	No
Allocation method	Randomised - controlled
Blinding used	Not blinded

Arms

Are arms mutually exclusive?	Yes
Arm title	Part 2: Crossover Period: IV Q6W then SC Q6W

Arm description:

Participants who completed run-in period of Part 2 were randomised to receive natalizumab 300 mg IV infusion Q6W from Week 108 through Week 126 followed by natalizumab 300 mg SC injection Q6W from Week 132 through Week 150 along with a single dose of natalizumab 300 mg SC injection or IV infusion as per participant's choice at Week 156.

Arm type	Experimental
Investigational medicinal product name	Natalizumab
Investigational medicinal product code	
Other name	BG00002, AN100226
Pharmaceutical forms	Concentrate for solution for infusion
Routes of administration	Intravenous use, Subcutaneous use

Dosage and administration details:

Administered as specified in the treatment arm.

Arm title	Part 2: Crossover Period: SC Q6W then IV Q6W
------------------	--

Arm description:

Participants who completed run-in period of Part 2 were randomised to receive natalizumab 300 mg SC injection Q6W from Week 108 through Week 126 followed by natalizumab 300 mg IV infusion Q6W from Week 132 through Week 150 along with a single dose of natalizumab 300 mg SC injection or IV infusion as per participant's choice at Week 156.

Arm type	Experimental
Investigational medicinal product name	Natalizumab
Investigational medicinal product code	
Other name	BG00002, AN100226
Pharmaceutical forms	Concentrate for solution for infusion
Routes of administration	Subcutaneous use, Intravenous use

Dosage and administration details:

Administered as specified in the treatment arm.

Number of subjects in period 3	Part 2: Crossover Period: IV Q6W then SC Q6W	Part 2: Crossover Period: SC Q6W then IV Q6W
Started	75	78
Completed	63	60
Not completed	12	18
Randomised but not Dosed	-	12
Adverse event, non-fatal	1	1
Pregnancy	-	1
Investigator Decision	2	2
Reason not Specified	2	1
Consent Withdrawn	7	1

Baseline characteristics

Reporting groups

Reporting group title	Part 1: IV Q4W
Reporting group description: Participants received natalizumab 300 mg IV infusion Q4W up to Week 72.	
Reporting group title	Part 1: IV Q6W
Reporting group description: Participants received natalizumab 300 mg IV infusion Q6W up to Week 72.	

Reporting group values	Part 1: IV Q4W	Part 1: IV Q6W	Total
Number of subjects	248	251	499
Age Categorical Units: Subjects			

Age continuous			
Part 1: All randomised population included all the randomised participants in Part 1 of the study. Part 2: Included all the newly enrolled randomised participants in the crossover period of Part 2 of the study.			
Units: years			
arithmetic mean	40.5	41.0	
standard deviation	± 10.03	± 9.66	-
Gender categorical Units: Subjects			
Male	67	73	140
Female	181	178	359
Ethnicity Units: Subjects			
Hispanic or Latino	10	9	19
Not Hispanic or Latino	223	224	447
Unknown or Not Reported	15	18	33
Race Units: Subjects			
American Indian or Alaska Native	1	1	2
Asian	1	4	5
Black or African American	23	14	37
White	211	211	422
Not reported due to confidentiality regulations	11	15	26
Other	1	6	7

Subject analysis sets

Subject analysis set title	Part 2: Crossover Period
Subject analysis set type	Intention-to-treat
Subject analysis set description: Participants who were newly enrolled in Part 2 received natalizumab 300 mg IV infusion Q6W from Week 108 through Week 126 followed by natalizumab 300 mg SC injection Q6W from Week 132 through Week 150, or natalizumab 300 mg SC injection Q6W from Week 108 through Week 126 followed by natalizumab 300 mg IV infusion Q6W from Week 132 through Week 150, along with a single dose of natalizumab 300 mg SC injection or IV infusion as per participant's choice at Week 156.	

Subject analysis set title	Part 2: Crossover Period: IV Q6W
Subject analysis set type	Intention-to-treat
Subject analysis set description:	
Participants received natalizumab 300 mg IV infusion Q6W for 24 weeks.	
Subject analysis set title	Part 2: Crossover Period: SC Q6W
Subject analysis set type	Intention-to-treat
Subject analysis set description:	
Participants received natalizumab 300 mg SC injection Q6W for 24 weeks.	

Reporting group values	Part 2: Crossover Period	Part 2: Crossover Period: IV Q6W	Part 2: Crossover Period: SC Q6W
Number of subjects	86	153	153
Age Categorical			
Units: Subjects			

Age continuous			
Part 1: All randomised population included all the randomised participants in Part 1 of the study. Part 2: Included all the newly enrolled randomised participants in the crossover period of Part 2 of the study.			
Units: years			
arithmetic mean	37.6	0	0
standard deviation	± 9.85	± 0	± 0
Gender categorical			
Units: Subjects			
Male	28	0	0
Female	58	0	0
Ethnicity			
Units: Subjects			
Hispanic or Latino	1	0	0
Not Hispanic or Latino	67	0	0
Unknown or Not Reported	18	0	0
Race			
Units: Subjects			
American Indian or Alaska Native	0	0	0
Asian	0	0	0
Black or African American	0	0	0
White	71	0	0
Not reported due to confidentiality regulations	14	0	0
Other	1	0	0

End points

End points reporting groups

Reporting group title	Part 1: IV Q4W
Reporting group description: Participants received natalizumab 300 mg IV infusion Q4W up to Week 72.	
Reporting group title	Part 1: IV Q6W
Reporting group description: Participants received natalizumab 300 mg IV infusion Q6W up to Week 72.	
Reporting group title	Part 2: Run-in Period: IV Q6W
Reporting group description: Participants who completed Part 1 or were newly enrolled in Part 2 received natalizumab 300 mg IV infusion Q6W from Week 72 through Week 102.	
Reporting group title	Part 2: Crossover Period: IV Q6W then SC Q6W
Reporting group description: Participants who completed run-in period of Part 2 were randomised to receive natalizumab 300 mg IV infusion Q6W from Week 108 through Week 126 followed by natalizumab 300 mg SC injection Q6W from Week 132 through Week 150 along with a single dose of natalizumab 300 mg SC injection or IV infusion as per participant's choice at Week 156.	
Reporting group title	Part 2: Crossover Period: SC Q6W then IV Q6W
Reporting group description: Participants who completed run-in period of Part 2 were randomised to receive natalizumab 300 mg SC injection Q6W from Week 108 through Week 126 followed by natalizumab 300 mg IV infusion Q6W from Week 132 through Week 150 along with a single dose of natalizumab 300 mg SC injection or IV infusion as per participant's choice at Week 156.	
Subject analysis set title	Part 2: Crossover Period
Subject analysis set type	Intention-to-treat
Subject analysis set description: Participants who were newly enrolled in Part 2 received natalizumab 300 mg IV infusion Q6W from Week 108 through Week 126 followed by natalizumab 300 mg SC injection Q6W from Week 132 through Week 150, or natalizumab 300 mg SC injection Q6W from Week 108 through Week 126 followed by natalizumab 300 mg IV infusion Q6W from Week 132 through Week 150, along with a single dose of natalizumab 300 mg SC injection or IV infusion as per participant's choice at Week 156.	
Subject analysis set title	Part 2: Crossover Period: IV Q6W
Subject analysis set type	Intention-to-treat
Subject analysis set description: Participants received natalizumab 300 mg IV infusion Q6W for 24 weeks.	
Subject analysis set title	Part 2: Crossover Period: SC Q6W
Subject analysis set type	Intention-to-treat
Subject analysis set description: Participants received natalizumab 300 mg SC injection Q6W for 24 weeks.	

Primary: Part 1: Mean Number of New or Newly Enlarging T2 Hyperintense Lesions at Week 72

End point title	Part 1: Mean Number of New or Newly Enlarging T2 Hyperintense Lesions at Week 72
End point description: T2 hyperintense lesions were analysed by magnetic resonance imaging (MRI) scans of brain. New MRI scans were compared with the prior MRI scans to analyse the number of new or newly enlarging T2 hyperintense lesions at Week 72 relative to baseline. Modified intent to treat (mITT) population included all randomised participants who received at least one dose of study treatment and had at least 1 postbaseline result in Part 1. Here, 'subjects analysed' signifies the number of participants with data available for endpoint analysis.	
End point type	Primary

End point timeframe:

Week 72

End point values	Part 1: IV Q4W	Part 1: IV Q6W		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	197	211		
Units: number of T2 lesions				
arithmetic mean (confidence interval 95%)	0.05 (0.01 to 0.22)	0.20 (0.07 to 0.63)		

Statistical analyses

Statistical analysis title	Statistical Analysis 1
Comparison groups	Part 1: IV Q4W v Part 1: IV Q6W
Number of subjects included in analysis	408
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.0755 ^[1]
Method	Negative Binomial Regression
Parameter estimate	Ratio of Mean
Point estimate	4.24
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.86
upper limit	20.85

Notes:

[1] - The model included treatment as classification variable & baseline body weight, duration of natalizumab exposure at baseline, & region as covariates.

Primary: Part 2: Percentage of Participants Indicating a Preference for Natalizumab SC Administration at the End of Crossover Period of Part 2

End point title	Part 2: Percentage of Participants Indicating a Preference for Natalizumab SC Administration at the End of Crossover Period of Part 2
-----------------	---

End point description:

mITT population included all randomised participants who received at least one dose of SC natalizumab after randomisation in Part 2 and who completed at least the first question in the Patient Preference Questionnaire (PPQ) on one occasion. Here, 'subjects analysed' signifies the number of participants with data available for endpoint analysis. (Confidence interval=CI)

End point type	Primary
----------------	---------

End point timeframe:

Week 150

End point values	Part 2: Crossover Period: IV Q6W then SC Q6W	Part 2: Crossover Period: SC Q6W then IV Q6W		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	62	61		
Units: percentage of participants				
number (not applicable)				
SC	83.9	91.8		

Statistical analyses

Statistical analysis title	Statistical Analysis 2
Comparison groups	Part 2: Crossover Period: IV Q6W then SC Q6W v Part 2: Crossover Period: SC Q6W then IV Q6W
Number of subjects included in analysis	123
Analysis specification	Pre-specified
Analysis type	superiority
Method	Exact Binomial Method
Parameter estimate	Percentage
Point estimate	87.8
Confidence interval	
level	95 %
sides	2-sided
lower limit	80.68
upper limit	93.01

Secondary: Part 1: Time to First Relapse as Adjudicated by an Independent Neurology Evaluation Committee (INEC)

End point title	Part 1: Time to First Relapse as Adjudicated by an Independent Neurology Evaluation Committee (INEC)
End point description:	
Relapse is defined as the onset of new or recurrent neurological symptoms, not associated with fever, infection, severe stress, or drug toxicity, lasting at least 24 hours, accompanied by new objective abnormalities on a neurological examination. Only relapses confirmed by an INEC were included in the analysis. Time to First Relapse was estimated by Kaplan-Meier method. mITT population included all randomised participants who received at least one dose of study treatment and had at least 1 postbaseline result in Part 1. 99999= Median, Q1 and Q3 were not reached in the Kaplan-Meier curve due to insufficient number of relapses.	
End point type	Secondary
End point timeframe:	
Up to Week 72	

End point values	Part 1: IV Q4W	Part 1: IV Q6W		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	242	247		
Units: weeks				
median (inter-quartile range (Q1-Q3))	99999 (99999 to 99999)	99999 (99999 to 99999)		

Statistical analyses

No statistical analyses for this end point

Secondary: Part 1: Annualised Relapse Rate at Week 72

End point title	Part 1: Annualised Relapse Rate at Week 72
End point description:	
Annualised relapse rate is calculated as the total number of INEC-confirmed relapses that occurred during the treatment period divided by the total number of participant-years followed in the period. mITT population included all randomised participants who received at least one dose of study treatment and had at least 1 postbaseline result in Part 1.	
End point type	Secondary
End point timeframe:	
Week 72	

End point values	Part 1: IV Q4W	Part 1: IV Q6W		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	242	247		
Units: relapses per participant-year				
number (confidence interval 95%)	0.00010 (0.00004 to 0.00024)	0.00013 (0.00006 to 0.00027)		

Statistical analyses

Statistical analysis title	Statistical Analysis 3
Comparison groups	Part 1: IV Q4W v Part 1: IV Q6W
Number of subjects included in analysis	489
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.6312 [2]
Method	Poisson Regression
Parameter estimate	Ratio of annualised relapse rate
Point estimate	1.32481

Confidence interval	
level	95 %
sides	2-sided
lower limit	0.42016
upper limit	4.17725

Notes:

[2] - Poisson regression model was adjusted for baseline body weight (≤ 80 kg versus >80 kg), duration of natalizumab exposure at baseline (≤ 3 years versus > 3 years), and region.

Secondary: Part 1: Time to Expanded Disability Status Scale (EDSS) Worsening

End point title	Part 1: Time to Expanded Disability Status Scale (EDSS) Worsening
-----------------	---

End point description:

Confirmed EDSS worsening is defined as an increase of at least 1.0 point from a baseline EDSS score ≥ 1.0 or an increase of at least 1.5 points from a baseline EDSS score of 0 that is confirmed after at least 24 weeks. Time to EDSS worsening is estimated by Kaplan-Meier method. mITT population included all randomised participants who received at least one dose of study treatment and had at least 1 postbaseline result in Part 1. 99999= Median, Q1 and Q3 were not reached in the Kaplan-Meier curve due to insufficient number of events.

End point type	Secondary
----------------	-----------

End point timeframe:

Up to Week 72

End point values	Part 1: IV Q4W	Part 1: IV Q6W		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	242	247		
Units: weeks				
median (inter-quartile range (Q1-Q3))	99999 (99999 to 99999)	99999 (99999 to 99999)		

Statistical analyses

No statistical analyses for this end point

Secondary: Part 1: Mean Number of New T1 Hypointense Lesions at Weeks 24, 48, and 72

End point title	Part 1: Mean Number of New T1 Hypointense Lesions at Weeks 24, 48, and 72
-----------------	---

End point description:

T1 hypointense lesions on brain were analysed by MRI scans of brain. New MRI scans were compared with the prior MRI scans to analyse the number of new T1 hypointense lesions at Weeks 24, 48, and 72 relative to baseline. mITT population included all randomised participants who received at least one dose of study treatment and had at least 1 postbaseline result in Part 1. 'Subjects analysed' signifies the number of participants with data available for endpoint analysis. Here, 'number analysed (n)' signifies the number of participants with data available for analysis at specified time point.

End point type	Secondary
----------------	-----------

End point timeframe:

Weeks 24, 48, and 72

End point values	Part 1: IV Q4W	Part 1: IV Q6W		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	227	241		
Units: number of T1 lesions				
arithmetic mean (standard deviation)				
Week 24 (n=227,241)	0.0 (± 0.13)	0.0 (± 0.06)		
Week 48 (n=202,218)	0.0 (± 0.16)	0.0 (± 0.07)		
Week 72 (n=191,209)	0.0 (± 0.16)	0.0 (± 0.32)		

Statistical analyses

No statistical analyses for this end point

Secondary: Part 1: Mean Number of New or Newly Enlarging T2 Hyperintense Lesions at Weeks 24 and 48

End point title	Part 1: Mean Number of New or Newly Enlarging T2 Hyperintense Lesions at Weeks 24 and 48
-----------------	--

End point description:

T2 hyperintense lesions were analysed by MRI scans of brain. New MRI scans were compared with the prior MRI scans to analyse the number of new or newly enlarging T2 hyperintense lesions at Weeks 24 and 48 relative to baseline. mITT population included all randomised participants who received at least one dose of study treatment and had at least 1 postbaseline result in Part 1. 'Subjects analysed' signifies the number of participants with data available for endpoint analysis Here, 'number analysed (n)' signifies the number of participants with data available for analysis at specified time point.

End point type	Secondary
----------------	-----------

End point timeframe:

Weeks 24 and 48

End point values	Part 1: IV Q4W	Part 1: IV Q6W		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	229	242		
Units: number of T2 lesions				
arithmetic mean (standard deviation)				
Week 24 (n=229,242)	0.0 (± 0.16)	0.0 (± 0.35)		
Week 48 (n=206,221)	0.0 (± 0.21)	0.1 (± 1.03)		

Statistical analyses

No statistical analyses for this end point

Secondary: Part 1: Mean Number of New Gadolinium (Gd) Enhancing Lesions at

Weeks 24, 48, and 72

End point title	Part 1: Mean Number of New Gadolinium (Gd) Enhancing Lesions at Weeks 24, 48, and 72
-----------------	--

End point description:

Gd enhancing lesions on brain were analysed by MRI scans of brain. New MRI scans were compared with the prior MRI scans to analyse the number of new Gd enhancing lesions at Weeks 24, 48, and 72 relative to baseline. mITT population included all randomised participants who received at least one dose of study treatment and had at least 1 postbaseline result in Part 1. 'Subjects analysed' signifies the number of participants with data available for endpoint analysis Here, 'number analysed' signifies the number of participants with data available for analysis at specified time point.

End point type	Secondary
----------------	-----------

End point timeframe:

Weeks 24, 48, and 72

End point values	Part 1: IV Q4W	Part 1: IV Q6W		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	227	241		
Units: number of Gd lesions				
arithmetic mean (standard deviation)				
Week 24 (n=227,241)	0.0 (± 0.07)	0.0 (± 0.00)		
Week 48 (n=203,218)	0.0 (± 0.07)	0.0 (± 0.00)		
Week 72 (n=191,210)	0.0 (± 0.07)	0.1 (± 0.83)		

Statistical analyses

No statistical analyses for this end point

Secondary: Part 1: Percentage of Participants With Treatment-Emergent Adverse Events (TEAEs) and Serious Adverse Events (SAEs)

End point title	Part 1: Percentage of Participants With Treatment-Emergent Adverse Events (TEAEs) and Serious Adverse Events (SAEs)
-----------------	---

End point description:

AE is any untoward medical occurrence in participant/clinical investigation participant administered a pharmaceutical product & that does not necessarily have causal relationship with this treatment. It can therefore be any unfavorable & unintended sign (including an abnormal laboratory finding), symptom/disease temporally associated with use of medicinal (investigational) product, whether or not related to medicinal (investigational) product. TEAE is any event occurring on/after first dose after randomisation up to 12 weeks (or 24 weeks for PML [progressive multifocal leukoencephalopathy] events) following last dose on study. SAE is any untoward medical occurrence that at any dose results in death, is life-threatening event, requires inpatient hospitalization/prolongation of existing hospitalization, results in significant disability/incapacity/congenital anomaly, is medically important event. Safety population = all randomised participants who received at least one dose of study

End point type	Secondary
----------------	-----------

End point timeframe:

Baseline up to Week 96

End point values	Part 1: IV Q4W	Part 1: IV Q6W		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	247	250		
Units: percentage of participants				
number (not applicable)				
TEAEs	76.9	77.6		
SAEs	6.9	6.8		

Statistical analyses

No statistical analyses for this end point

Secondary: Part 2: Change From Baseline in Treatment Satisfaction Questionnaire for Medication (TSQM) Scores During the Crossover Period

End point title	Part 2: Change From Baseline in Treatment Satisfaction Questionnaire for Medication (TSQM) Scores During the Crossover Period
-----------------	---

End point description:

TSQM has 14 questions that assesses participants' global satisfaction level with their treatment in 4 domains: side effects (5 questions in the side effects domain, 1 of them is Yes/No question & there are 4 sub-components, hence maximum score of 20), effectiveness (3 questions), global satisfaction (3 questions), convenience (3 questions). All questions are scored from 1 (least satisfied) to 5/7 (most satisfied). Total score is summed for each domain to obtain: side effects (1-20), effectiveness (1-21), global satisfaction (1-17), convenience (1-21), using transformed scores between 0 & 100 for effectiveness. Lower total scores in each domain indicate dissatisfaction with study medication & higher total scores indicate satisfaction. Full analysis set (FAS) = all randomised participants who received at least one dose of study treatment during at least one study period & had at least 1 baseline assessment in Part 2. Here, subjects analysed = number of participants with data available for endpoint analysis.

End point type	Secondary
----------------	-----------

End point timeframe:

Part 2 Baseline (Week 108) up to Week 156

End point values	Part 2: Crossover Period: IV Q6W	Part 2: Crossover Period: SC Q6W		
Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed	127	127		
Units: Score on a scale				
least squares mean (standard error)	0.17 (± 0.899)	0.64 (± 0.902)		

Statistical analyses

Statistical analysis title	Statistical Analysis 4
Comparison groups	Part 2: Crossover Period: IV Q6W v Part 2: Crossover Period: SC Q6W

Number of subjects included in analysis	254
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.764 ^[3]
Method	Linear Mixed Effects Model
Parameter estimate	Difference
Point estimate	0.47
Confidence interval	
level	95 %
sides	2-sided
lower limit	-2.61
upper limit	3.54

Notes:

[3] - Performed with factors:route of administration,period,sequence,body weight,duration of natalizumab exposure,stratification factor,baseline TSQM score.

Secondary: Part 2: Mean Time for Drug Preparation and Drug Administration During the Crossover Period

End point title	Part 2: Mean Time for Drug Preparation and Drug Administration During the Crossover Period
End point description: FAS included all randomised participants who received at least one dose of study treatment during at least one study period and had at least one baseline assessment in Part 2.	
End point type	Secondary
End point timeframe: Week 108 up to Week 156	

End point values	Part 2: Crossover Period: IV Q6W	Part 2: Crossover Period: SC Q6W		
Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed	136	132		
Units: Minutes				
arithmetic mean (standard deviation)				
Drug Preparation Time	4.9 (± 3.86)	0 (± 0)		
Drug Administration Time	62.6 (± 10.45)	4.3 (± 5.11)		

Statistical analyses

No statistical analyses for this end point

Secondary: Part 2: Percentage of Participants With Treatment-Emergent Adverse Events (TEAEs)

End point title	Part 2: Percentage of Participants With Treatment-Emergent Adverse Events (TEAEs)
End point description: An AE is any untoward medical occurrence in a participant or clinical investigation participant administered a pharmaceutical product and that does not necessarily have a causal relationship with this	

treatment. An AE can therefore be any unfavorable and unintended sign (including an abnormal laboratory finding), symptom, or disease temporally associated with the use of a medicinal (investigational) product, whether or not related to the medicinal (investigational) product. A TEAE is any event occurring on or after first dose after randomisation up to and including 12 weeks (or 24 weeks for PML events) following the last dose on the study. Safety population included all randomised participants who received at least one dose of study treatment during the crossover period of Part 2.

End point type	Secondary
----------------	-----------

End point timeframe:

Part 2: Baseline (Week 108) up to Week 180

End point values	Part 2: Crossover Period: IV Q6W	Part 2: Crossover Period: SC Q6W		
Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed	136	132		
Units: percentage of participants				
number (not applicable)	57.4	62.9		

Statistical analyses

No statistical analyses for this end point

Secondary: Part 2: Percentage of Participants With Anti-Natalizumab Antibodies During the Crossover Period

End point title	Part 2: Percentage of Participants With Anti-Natalizumab Antibodies During the Crossover Period
-----------------	---

End point description:

Immunogenicity population included all participants who received at least one dose of SC or IV natalizumab and had at least one assessment for anti-drug antibody during crossover period of Part 2.

End point type	Secondary
----------------	-----------

End point timeframe:

Part 2: Baseline (Week 108) up to Week 156

End point values	Part 2: Crossover Period: IV Q6W	Part 2: Crossover Period: SC Q6W		
Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed	136	132		
Units: percentage of participants				
number (not applicable)	0	0		

Statistical analyses

No statistical analyses for this end point

Secondary: Part 2: Mean Number of New or Newly Enlarging T2 Hyperintense Lesions During the Crossover Period

End point title	Part 2: Mean Number of New or Newly Enlarging T2 Hyperintense Lesions During the Crossover Period
-----------------	---

End point description:

T2 hyperintense lesions were analysed by MRI scans of brain. New MRI scans were compared with the prior MRI scans to analyse the number of new or newly enlarging T2 hyperintense lesions during the crossover period of Part 2 relative to baseline. FAS included all randomised participants who received at least one dose of study treatment during at least one study period and had at least one baseline assessment in Part 2. Here, 'subjects analysed' signifies the number of participants with data available for endpoint analysis.

End point type	Secondary
----------------	-----------

End point timeframe:

Part 2: Baseline (Week 108) up to Week 156

End point values	Part 2: Crossover Period: IV Q6W	Part 2: Crossover Period: SC Q6W		
Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed	131	128		
Units: number of T2 lesions				
arithmetic mean (standard deviation)	0.0 (± 0.09)	0.0 (± 0.22)		

Statistical analyses

No statistical analyses for this end point

Secondary: Part 2: Time to First Relapse During the Crossover Period

End point title	Part 2: Time to First Relapse During the Crossover Period
-----------------	---

End point description:

Relapse is defined as the onset of new or recurrent neurological symptoms, not associated with fever, infection, severe stress, or drug toxicity, lasting at least 24 hours. The time to first relapse was defined as the time from the first randomised dose in Part 2 up to the first relapse. Time to First Relapse is estimated by Kaplan-Meier method. FAS: all randomised participants receiving ≥ 1 dose of study treatment during at least one study period; had ≥ 1 baseline assessment in Part 2. Overall number analysed: participants without any relapse at beginning of crossover period of Part 2. As pre-specified in Statistical Analysis Plan (SAP), time to event analyses was planned by 'per treatment sequence' rather than 'per intervention' in Part 2 as protocol-specified analysis does not account for correlation of within participant effect. 9999 = Median, Q1 and Q3 were not reached in the Kaplan-Meier curve due to one relapse. 99999 = Data is not available as no participant in this group had a relapse.

End point type	Secondary
----------------	-----------

End point timeframe:

Part 2: Baseline (Week 108) up to Week 156

End point values	Part 2: Crossover Period: IV Q6W then SC Q6W	Part 2: Crossover Period: SC Q6W then IV Q6W		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	71	63		
Units: weeks				
median (inter-quartile range (Q1-Q3))	9999 (9999 to 9999)	99999 (99999 to 99999)		

Statistical analyses

No statistical analyses for this end point

Secondary: Part 2: Annualized Relapse Rate During the Crossover Period

End point title	Part 2: Annualized Relapse Rate During the Crossover Period
End point description: Annualised relapse rate is calculated as the total number of relapses that occurred during the treatment period divided by the total number of participant-years followed in the period.	
End point type	Secondary
End point timeframe: Part 2 Baseline (Week 108) up to Week 156	

End point values	Part 2: Crossover Period: IV Q6W then SC Q6W	Part 2: Crossover Period: SC Q6W then IV Q6W		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	0 ^[4]	0 ^[5]		
Units: relapses per-participant year				
number (not applicable)				

Notes:

[4] - Data was not analysed for this endpoint as only 1 relapse was observed in Part 2 crossover period.

[5] - Data was not analysed for this endpoint as only 1 relapse was observed in 1 Part 2 crossover period.

Statistical analyses

No statistical analyses for this end point

Secondary: Part 2: Change From Baseline in EDSS Score During the Crossover Period

End point title	Part 2: Change From Baseline in EDSS Score During the Crossover Period
-----------------	--

End point description:

The EDSS is a scale based on standardised neurological examination which comprised of optic, brain stem, pyramidal, cerebellar, sensory and cerebral functions, as well as walking ability. It measures the MS disability status on a scale ranging from 0 (normal) to 10 (death due to MS), with higher scores indicating more disability. FAS included all randomised participants who received at least one dose of study treatment during at least one study period and had at least one baseline assessment in Part 2. Here, 'subjects analysed' signifies the number of participants with data available for endpoint analysis.

End point type	Secondary
End point timeframe:	
Part 2 Baseline (Week 108) up to Week 156	

End point values	Part 2: Crossover Period: IV Q6W	Part 2: Crossover Period: SC Q6W		
Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed	135	132		
Units: Score on a scale				
least squares mean (standard error)	0.02 (± 0.055)	0.10 (± 0.056)		

Statistical analyses

Statistical analysis title	Statistical Analysis 5
Comparison groups	Part 2: Crossover Period: IV Q6W v Part 2: Crossover Period: SC Q6W
Number of subjects included in analysis	267
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.357 ^[6]
Method	Linear Mixed Effects Model
Parameter estimate	Difference
Point estimate	0.08
Confidence interval	
level	95 %
sides	2-sided
lower limit	-0.09
upper limit	0.25

Notes:

[6] - Performed with factors:route of administration,period,sequence,body weight,duration of natalizumab exposure,stratification factor,baseline TSQM score.

Secondary: Part 2: Mean Number of New Gd Enhancing Lesions During the Crossover Period

End point title	Part 2: Mean Number of New Gd Enhancing Lesions During the Crossover Period
End point description:	
Gd enhancing lesions on brain were analysed by MRI scans of brain. New MRI scans were compared with the prior MRI scans to analyse the number of new Gd enhancing lesions during the crossover period of Part 2 relative to baseline. FAS included all randomised participants who received at least one dose of study treatment during at least one study period and had at least one baseline assessment in Part 2. Here, 'subjects analysed' signifies the number of participants with data available for endpoint analysis.	
End point type	Secondary
End point timeframe:	
Week 108 up to Week 156	

End point values	Part 2: Crossover Period: IV Q6W	Part 2: Crossover Period: SC Q6W		
Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed	131	128		
Units: number of Gd lesions				
arithmetic mean (standard deviation)	0.0 (\pm 0.00)	0.0 (\pm 0.00)		

Statistical analyses

No statistical analyses for this end point

Secondary: Part 2: Mean Number of New T1 Hypointense Lesions During the Crossover Period

End point title	Part 2: Mean Number of New T1 Hypointense Lesions During the Crossover Period
-----------------	---

End point description:

T1 hypointense lesions on brain were analysed by MRI scans of brain. New MRI scans were compared with the prior MRI scans to analyse the number of new T1 hypointense lesions during the crossover period of Part 2 relative to baseline. FAS included all randomised participants who received at least one dose of study treatment during at least one study period and had at least one baseline assessment in Part 2. Here, 'subjects analysed' signifies the number of participants with data available for endpoint analysis.

End point type	Secondary
----------------	-----------

End point timeframe:

Week 108 up to Week 156

End point values	Part 2: Crossover Period: IV Q6W	Part 2: Crossover Period: SC Q6W		
Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed	131	128		
Units: number of T1 lesions				
arithmetic mean (standard deviation)	0.0 (\pm 0.09)	0.0 (\pm 0.00)		

Statistical analyses

No statistical analyses for this end point

Secondary: Part 2: Mean Percentage Change From Baseline in Brain Volume During the Crossover Period

End point title	Part 2: Mean Percentage Change From Baseline in Brain
-----------------	---

End point description:

FAS included all randomised participants who received at least one dose of study treatment during at least one study period and had at least one baseline assessment in Part 2. Here, 'subjects analysed' signifies the number of participants with data available for endpoint analysis.

End point type	Secondary
----------------	-----------

End point timeframe:

Part 2 Baseline (Week 108) up to Week 156

End point values	Part 2: Crossover Period: IV Q6W	Part 2: Crossover Period: SC Q6W		
Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed	112	108		
Units: percent change				
least squares mean (standard error)	-0.11 (\pm 0.042)	-0.10 (\pm 0.042)		

Statistical analyses

No statistical analyses for this end point

Secondary: Part 2: Change From Baseline in Cortical and Thalamic Brain Region Volume During the Crossover Period

End point title	Part 2: Change From Baseline in Cortical and Thalamic Brain Region Volume During the Crossover Period
-----------------	---

End point description:

FAS included all randomised participants who received at least one dose of study treatment during at least one study period and had at least one baseline assessment in Part 2. 'Subjects analysed' signifies the number of participants with data available for endpoint analysis. Here 'number analysed (n)' signifies the number of participants with data available for analysis at specified categories.

End point type	Secondary
----------------	-----------

End point timeframe:

Part 2 Baseline (Week 108) up to Week 156

End point values	Part 2: Crossover Period: IV Q6W	Part 2: Crossover Period: SC Q6W		
Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed	111	107		
Units: cubic centimetres (cm ³)				
least squares mean (standard error)				
Cortical Brain Region (n=111,107)	-1478.82 (\pm 363.714)	-881.34 (\pm 367.155)		
Thalamic Brain Region (n=108,104)	-25.98 (\pm 14.582)	-17.96 (\pm 14.796)		

Statistical analyses

No statistical analyses for this end point

Secondary: Part 2: Trough Serum Concentration of Natalizumab (Ctrough) During the Crossover Period

End point title	Part 2: Trough Serum Concentration of Natalizumab (Ctrough) During the Crossover Period
-----------------	---

End point description:

Pharmacokinetic (PK) population included all participants who received at least one dose of SC or IV natalizumab and had at least one assessment for the concentration of natalizumab in serum during the crossover period of Part 2.

End point type	Secondary
----------------	-----------

End point timeframe:

Pre-dose at Weeks 108, 114, 120, 126, 132, 138, 144, 150, and 156

End point values	Part 2: Crossover Period: IV Q6W	Part 2: Crossover Period: SC Q6W		
Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed	136	132		
Units: micrograms per millilitre (µg/mL)				
arithmetic mean (standard deviation)	11.9 (± 11.50)	10.3 (± 10.94)		

Statistical analyses

No statistical analyses for this end point

Secondary: Part 2: Mean Trough α4 Integrin Saturation During the Crossover Period

End point title	Part 2: Mean Trough α4 Integrin Saturation During the Crossover Period
-----------------	--

End point description:

Pharmacodynamic (PD) population included all participants who received at least 1 dose of SC or IV natalizumab after randomisation in Part 2 and had at least 1 post-baseline assessment of the PD parameter. Here 'subjects analysed' indicates the number of participants without any relapse at the beginning of the crossover period of Part 2.

End point type	Secondary
----------------	-----------

End point timeframe:

Pre-dose at Weeks 108, 114, 120, 126, 132, 138, 144, 150, and 156

End point values	Part 2: Crossover Period: IV Q6W	Part 2: Crossover Period: SC Q6W		
Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed	135	132		
Units: percentage				
arithmetic mean (standard deviation)	71.2 (± 15.31)	67.2 (± 17.80)		

Statistical analyses

No statistical analyses for this end point

Adverse events

Adverse events information

Timeframe for reporting adverse events:

From first dose of study drug up to Week 180

Adverse event reporting additional description:

Safety population included all randomised participants who received at least one dose of study treatment. MedDRA version 24.0 applied for Part 1 and MedDRA version 26.0 applied for Part 2.

Assessment type	Systematic
-----------------	------------

Dictionary used

Dictionary name	MedDRA
-----------------	--------

Dictionary version	24.0, 26.0
--------------------	------------

Reporting groups

Reporting group title	Part 1: IV Q4W
-----------------------	----------------

Reporting group description:

Participants received natalizumab 300 mg IV infusion Q4W up to Week 72.

Reporting group title	Part 2: Crossover Period: SC Q6W
-----------------------	----------------------------------

Reporting group description:

Participants received natalizumab 300 mg SC injection Q6W for 24 weeks.

Reporting group title	Part 2: Crossover Period: IV Q6W
-----------------------	----------------------------------

Reporting group description:

Participants received natalizumab 300 mg IV infusion Q6W for 24 weeks.

Reporting group title	Part 1: IV Q6W
-----------------------	----------------

Reporting group description:

Participants received natalizumab 300 mg IV infusion Q6W up to Week 72.

Reporting group title	Part 2: Run-in period: IV Q6W
-----------------------	-------------------------------

Reporting group description:

Participants who completed Part 1 or were newly enrolled in Part 2 received natalizumab 300 mg IV infusion Q6W from Week 72 through Week 102.

Serious adverse events	Part 1: IV Q4W	Part 2: Crossover Period: SC Q6W	Part 2: Crossover Period: IV Q6W
Total subjects affected by serious adverse events			
subjects affected / exposed	17 / 247 (6.88%)	4 / 132 (3.03%)	2 / 136 (1.47%)
number of deaths (all causes)	0	0	0
number of deaths resulting from adverse events	0	0	0
Neoplasms benign, malignant and unspecified (incl cysts and polyps)			
Benign lung neoplasm			
subjects affected / exposed	1 / 247 (0.40%)	0 / 132 (0.00%)	0 / 136 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Invasive ductal breast carcinoma			

subjects affected / exposed	0 / 247 (0.00%)	0 / 132 (0.00%)	1 / 136 (0.74%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Leiomyoma			
subjects affected / exposed	1 / 247 (0.40%)	0 / 132 (0.00%)	0 / 136 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Lipoma			
subjects affected / exposed	0 / 247 (0.00%)	0 / 132 (0.00%)	0 / 136 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Ovarian germ cell teratoma benign			
subjects affected / exposed	0 / 247 (0.00%)	1 / 132 (0.76%)	0 / 136 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Uterine leiomyoma			
subjects affected / exposed	1 / 247 (0.40%)	0 / 132 (0.00%)	0 / 136 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Vascular disorders			
Venous thrombosis limb			
subjects affected / exposed	1 / 247 (0.40%)	0 / 132 (0.00%)	0 / 136 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Pregnancy, puerperium and perinatal conditions			
Abortion spontaneous			
subjects affected / exposed	1 / 247 (0.40%)	0 / 132 (0.00%)	0 / 136 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Immune system disorders			
Drug hypersensitivity			
subjects affected / exposed	1 / 247 (0.40%)	0 / 132 (0.00%)	0 / 136 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0

Reproductive system and breast disorders			
Adnexal torsion			
subjects affected / exposed	0 / 247 (0.00%)	1 / 132 (0.76%)	0 / 136 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Endometriosis			
subjects affected / exposed	1 / 247 (0.40%)	0 / 132 (0.00%)	0 / 136 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Respiratory, thoracic and mediastinal disorders			
Hyperventilation			
subjects affected / exposed	1 / 247 (0.40%)	0 / 132 (0.00%)	0 / 136 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Pneumothorax			
subjects affected / exposed	0 / 247 (0.00%)	0 / 132 (0.00%)	0 / 136 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Pulmonary embolism			
subjects affected / exposed	1 / 247 (0.40%)	0 / 132 (0.00%)	0 / 136 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Psychiatric disorders			
Depression			
subjects affected / exposed	0 / 247 (0.00%)	0 / 132 (0.00%)	0 / 136 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Suicidal ideation			
subjects affected / exposed	0 / 247 (0.00%)	0 / 132 (0.00%)	0 / 136 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Suicide attempt			

subjects affected / exposed	0 / 247 (0.00%)	0 / 132 (0.00%)	0 / 136 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Injury, poisoning and procedural complications			
Ankle fracture			
subjects affected / exposed	0 / 247 (0.00%)	0 / 132 (0.00%)	0 / 136 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Craniocerebral injury			
subjects affected / exposed	0 / 247 (0.00%)	0 / 132 (0.00%)	0 / 136 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Fall			
subjects affected / exposed	1 / 247 (0.40%)	0 / 132 (0.00%)	0 / 136 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Humerus fracture			
subjects affected / exposed	1 / 247 (0.40%)	0 / 132 (0.00%)	0 / 136 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Respiratory tract procedural complication			
subjects affected / exposed	0 / 247 (0.00%)	0 / 132 (0.00%)	0 / 136 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Post lumbar puncture syndrome			
subjects affected / exposed	1 / 247 (0.40%)	0 / 132 (0.00%)	0 / 136 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Tendon rupture			
subjects affected / exposed	0 / 247 (0.00%)	0 / 132 (0.00%)	0 / 136 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Road traffic accident			

subjects affected / exposed	0 / 247 (0.00%)	0 / 132 (0.00%)	0 / 136 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Cardiac disorders			
Coronary artery dissection			
subjects affected / exposed	0 / 247 (0.00%)	0 / 132 (0.00%)	0 / 136 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Nervous system disorders			
Hemiparesis			
subjects affected / exposed	0 / 247 (0.00%)	0 / 132 (0.00%)	0 / 136 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Lumbar radiculopathy			
subjects affected / exposed	1 / 247 (0.40%)	0 / 132 (0.00%)	0 / 136 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Migraine			
subjects affected / exposed	1 / 247 (0.40%)	0 / 132 (0.00%)	0 / 136 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Lumbosacral radiculopathy			
subjects affected / exposed	1 / 247 (0.40%)	0 / 132 (0.00%)	0 / 136 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Multiple sclerosis pseudo relapse			
subjects affected / exposed	0 / 247 (0.00%)	0 / 132 (0.00%)	0 / 136 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Multiple sclerosis relapse			
subjects affected / exposed	0 / 247 (0.00%)	0 / 132 (0.00%)	0 / 136 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Neuropathy peripheral			

subjects affected / exposed	0 / 247 (0.00%)	0 / 132 (0.00%)	0 / 136 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Optic neuritis			
subjects affected / exposed	0 / 247 (0.00%)	0 / 132 (0.00%)	0 / 136 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Blood and lymphatic system disorders			
Splenomegaly			
subjects affected / exposed	0 / 247 (0.00%)	0 / 132 (0.00%)	0 / 136 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Anaemia			
subjects affected / exposed	1 / 247 (0.40%)	0 / 132 (0.00%)	0 / 136 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Eye disorders			
Papilloedema			
subjects affected / exposed	0 / 247 (0.00%)	0 / 132 (0.00%)	0 / 136 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Gastrointestinal disorders			
Diarrhoea			
subjects affected / exposed	0 / 247 (0.00%)	0 / 132 (0.00%)	0 / 136 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Hiatus hernia			
subjects affected / exposed	0 / 247 (0.00%)	0 / 132 (0.00%)	1 / 136 (0.74%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Hepatobiliary disorders			
Cholecystitis			

subjects affected / exposed	0 / 247 (0.00%)	0 / 132 (0.00%)	0 / 136 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Cholelithiasis			
subjects affected / exposed	0 / 247 (0.00%)	0 / 132 (0.00%)	0 / 136 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Renal and urinary disorders			
Renal colic			
subjects affected / exposed	0 / 247 (0.00%)	0 / 132 (0.00%)	0 / 136 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Ureterolithiasis			
subjects affected / exposed	1 / 247 (0.40%)	0 / 132 (0.00%)	0 / 136 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Endocrine disorders			
Goitre			
subjects affected / exposed	0 / 247 (0.00%)	1 / 132 (0.76%)	0 / 136 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Musculoskeletal and connective tissue disorders			
Flank pain			
subjects affected / exposed	0 / 247 (0.00%)	0 / 132 (0.00%)	0 / 136 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Intervertebral disc protrusion			
subjects affected / exposed	1 / 247 (0.40%)	0 / 132 (0.00%)	0 / 136 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Osteoarthritis			
subjects affected / exposed	1 / 247 (0.40%)	0 / 132 (0.00%)	0 / 136 (0.00%)
occurrences causally related to treatment / all	0 / 2	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0

Infections and infestations Cholangitis infective subjects affected / exposed occurrences causally related to treatment / all deaths causally related to treatment / all	0 / 247 (0.00%) 0 / 0 0 / 0	1 / 132 (0.76%) 1 / 1 0 / 0	0 / 136 (0.00%) 0 / 0 0 / 0
Covid-19 pneumonia subjects affected / exposed occurrences causally related to treatment / all deaths causally related to treatment / all	0 / 247 (0.00%) 0 / 0 0 / 0	0 / 132 (0.00%) 0 / 0 0 / 0	0 / 136 (0.00%) 0 / 0 0 / 0
Pneumonia subjects affected / exposed occurrences causally related to treatment / all deaths causally related to treatment / all	1 / 247 (0.40%) 0 / 1 0 / 0	0 / 132 (0.00%) 0 / 0 0 / 0	0 / 136 (0.00%) 0 / 0 0 / 0
Herpes zoster subjects affected / exposed occurrences causally related to treatment / all deaths causally related to treatment / all	1 / 247 (0.40%) 0 / 1 0 / 0	0 / 132 (0.00%) 0 / 0 0 / 0	0 / 136 (0.00%) 0 / 0 0 / 0
Gastroenteritis subjects affected / exposed occurrences causally related to treatment / all deaths causally related to treatment / all	1 / 247 (0.40%) 0 / 1 0 / 0	0 / 132 (0.00%) 0 / 0 0 / 0	0 / 136 (0.00%) 0 / 0 0 / 0
Respiratory tract infection subjects affected / exposed occurrences causally related to treatment / all deaths causally related to treatment / all	0 / 247 (0.00%) 0 / 0 0 / 0	0 / 132 (0.00%) 0 / 0 0 / 0	0 / 136 (0.00%) 0 / 0 0 / 0
Progressive multifocal leukoencephalopathy subjects affected / exposed occurrences causally related to treatment / all deaths causally related to treatment / all	0 / 247 (0.00%) 0 / 0 0 / 0	0 / 132 (0.00%) 0 / 0 0 / 0	0 / 136 (0.00%) 0 / 0 0 / 0
Metabolism and nutrition disorders Dehydration subjects affected / exposed occurrences causally related to treatment / all deaths causally related to treatment / all	0 / 247 (0.00%) 0 / 0 0 / 0	0 / 132 (0.00%) 0 / 0 0 / 0	0 / 136 (0.00%) 0 / 0 0 / 0

Serious adverse events	Part 1: IV Q6W	Part 2: Run-in period: IV Q6W	
Total subjects affected by serious adverse events			
subjects affected / exposed	17 / 250 (6.80%)	3 / 158 (1.90%)	
number of deaths (all causes)	0	0	
number of deaths resulting from adverse events	0	0	
Neoplasms benign, malignant and unspecified (incl cysts and polyps)			
Benign lung neoplasm			
subjects affected / exposed	0 / 250 (0.00%)	0 / 158 (0.00%)	
occurrences causally related to treatment / all	0 / 0	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Invasive ductal breast carcinoma			
subjects affected / exposed	0 / 250 (0.00%)	0 / 158 (0.00%)	
occurrences causally related to treatment / all	0 / 0	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Leiomyoma			
subjects affected / exposed	0 / 250 (0.00%)	0 / 158 (0.00%)	
occurrences causally related to treatment / all	0 / 0	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Lipoma			
subjects affected / exposed	1 / 250 (0.40%)	0 / 158 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Ovarian germ cell teratoma benign			
subjects affected / exposed	0 / 250 (0.00%)	0 / 158 (0.00%)	
occurrences causally related to treatment / all	0 / 0	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Uterine leiomyoma			
subjects affected / exposed	0 / 250 (0.00%)	0 / 158 (0.00%)	
occurrences causally related to treatment / all	0 / 0	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Vascular disorders			
Venous thrombosis limb			

subjects affected / exposed	0 / 250 (0.00%)	0 / 158 (0.00%)	
occurrences causally related to treatment / all	0 / 0	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pregnancy, puerperium and perinatal conditions			
Abortion spontaneous			
subjects affected / exposed	0 / 250 (0.00%)	0 / 158 (0.00%)	
occurrences causally related to treatment / all	0 / 0	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Immune system disorders			
Drug hypersensitivity			
subjects affected / exposed	0 / 250 (0.00%)	0 / 158 (0.00%)	
occurrences causally related to treatment / all	0 / 0	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Reproductive system and breast disorders			
Adnexal torsion			
subjects affected / exposed	0 / 250 (0.00%)	0 / 158 (0.00%)	
occurrences causally related to treatment / all	0 / 0	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Endometriosis			
subjects affected / exposed	0 / 250 (0.00%)	0 / 158 (0.00%)	
occurrences causally related to treatment / all	0 / 0	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Respiratory, thoracic and mediastinal disorders			
Hyperventilation			
subjects affected / exposed	0 / 250 (0.00%)	0 / 158 (0.00%)	
occurrences causally related to treatment / all	0 / 0	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pneumothorax			
subjects affected / exposed	1 / 250 (0.40%)	0 / 158 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pulmonary embolism			

subjects affected / exposed	0 / 250 (0.00%)	0 / 158 (0.00%)	
occurrences causally related to treatment / all	0 / 0	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Psychiatric disorders			
Depression			
subjects affected / exposed	1 / 250 (0.40%)	0 / 158 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Suicidal ideation			
subjects affected / exposed	1 / 250 (0.40%)	0 / 158 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Suicide attempt			
subjects affected / exposed	1 / 250 (0.40%)	0 / 158 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Injury, poisoning and procedural complications			
Ankle fracture			
subjects affected / exposed	1 / 250 (0.40%)	0 / 158 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Craniocerebral injury			
subjects affected / exposed	1 / 250 (0.40%)	0 / 158 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Fall			
subjects affected / exposed	1 / 250 (0.40%)	0 / 158 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Humerus fracture			
subjects affected / exposed	0 / 250 (0.00%)	0 / 158 (0.00%)	
occurrences causally related to treatment / all	0 / 0	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	

Respiratory tract procedural complication			
subjects affected / exposed	1 / 250 (0.40%)	0 / 158 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Post lumbar puncture syndrome			
subjects affected / exposed	0 / 250 (0.00%)	0 / 158 (0.00%)	
occurrences causally related to treatment / all	0 / 0	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Tendon rupture			
subjects affected / exposed	1 / 250 (0.40%)	0 / 158 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Road traffic accident			
subjects affected / exposed	1 / 250 (0.40%)	0 / 158 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cardiac disorders			
Coronary artery dissection			
subjects affected / exposed	0 / 250 (0.00%)	1 / 158 (0.63%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Nervous system disorders			
Hemiparesis			
subjects affected / exposed	1 / 250 (0.40%)	0 / 158 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Lumbar radiculopathy			
subjects affected / exposed	0 / 250 (0.00%)	0 / 158 (0.00%)	
occurrences causally related to treatment / all	0 / 0	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Migraine			
subjects affected / exposed	0 / 250 (0.00%)	0 / 158 (0.00%)	
occurrences causally related to treatment / all	0 / 0	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	

Lumbosacral radiculopathy			
subjects affected / exposed	0 / 250 (0.00%)	0 / 158 (0.00%)	
occurrences causally related to treatment / all	0 / 0	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Multiple sclerosis pseudo relapse			
subjects affected / exposed	0 / 250 (0.00%)	1 / 158 (0.63%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Multiple sclerosis relapse			
subjects affected / exposed	1 / 250 (0.40%)	0 / 158 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Neuropathy peripheral			
subjects affected / exposed	1 / 250 (0.40%)	0 / 158 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Optic neuritis			
subjects affected / exposed	0 / 250 (0.00%)	1 / 158 (0.63%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Blood and lymphatic system disorders			
Splenomegaly			
subjects affected / exposed	0 / 250 (0.00%)	1 / 158 (0.63%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Anaemia			
subjects affected / exposed	0 / 250 (0.00%)	0 / 158 (0.00%)	
occurrences causally related to treatment / all	0 / 0	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Eye disorders			
Papilloedema			
subjects affected / exposed	1 / 250 (0.40%)	0 / 158 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	

Gastrointestinal disorders			
Diarrhoea			
subjects affected / exposed	1 / 250 (0.40%)	0 / 158 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hiatus hernia			
subjects affected / exposed	0 / 250 (0.00%)	0 / 158 (0.00%)	
occurrences causally related to treatment / all	0 / 0	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hepatobiliary disorders			
Cholecystitis			
subjects affected / exposed	1 / 250 (0.40%)	0 / 158 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cholelithiasis			
subjects affected / exposed	2 / 250 (0.80%)	0 / 158 (0.00%)	
occurrences causally related to treatment / all	0 / 2	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Renal and urinary disorders			
Renal colic			
subjects affected / exposed	1 / 250 (0.40%)	0 / 158 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Ureterolithiasis			
subjects affected / exposed	0 / 250 (0.00%)	0 / 158 (0.00%)	
occurrences causally related to treatment / all	0 / 0	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Endocrine disorders			
Goitre			
subjects affected / exposed	0 / 250 (0.00%)	0 / 158 (0.00%)	
occurrences causally related to treatment / all	0 / 0	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Musculoskeletal and connective tissue disorders			
Flank pain			

subjects affected / exposed	1 / 250 (0.40%)	0 / 158 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Intervertebral disc protrusion			
subjects affected / exposed	1 / 250 (0.40%)	0 / 158 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Osteoarthritis			
subjects affected / exposed	0 / 250 (0.00%)	0 / 158 (0.00%)	
occurrences causally related to treatment / all	0 / 0	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Infections and infestations			
Cholangitis infective			
subjects affected / exposed	0 / 250 (0.00%)	0 / 158 (0.00%)	
occurrences causally related to treatment / all	0 / 0	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Covid-19 pneumonia			
subjects affected / exposed	1 / 250 (0.40%)	0 / 158 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pneumonia			
subjects affected / exposed	0 / 250 (0.00%)	0 / 158 (0.00%)	
occurrences causally related to treatment / all	0 / 0	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Herpes zoster			
subjects affected / exposed	0 / 250 (0.00%)	0 / 158 (0.00%)	
occurrences causally related to treatment / all	0 / 0	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Gastroenteritis			
subjects affected / exposed	0 / 250 (0.00%)	0 / 158 (0.00%)	
occurrences causally related to treatment / all	0 / 0	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Respiratory tract infection			

subjects affected / exposed	1 / 250 (0.40%)	0 / 158 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Progressive multifocal leukoencephalopathy			
subjects affected / exposed	1 / 250 (0.40%)	0 / 158 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Metabolism and nutrition disorders			
Dehydration			
subjects affected / exposed	1 / 250 (0.40%)	0 / 158 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	

Frequency threshold for reporting non-serious adverse events: 5 %

Non-serious adverse events	Part 1: IV Q4W	Part 2: Crossover Period: SC Q6W	Part 2: Crossover Period: IV Q6W
Total subjects affected by non-serious adverse events			
subjects affected / exposed	104 / 247 (42.11%)	56 / 132 (42.42%)	48 / 136 (35.29%)
Injury, poisoning and procedural complications			
Fall			
subjects affected / exposed	13 / 247 (5.26%)	2 / 132 (1.52%)	2 / 136 (1.47%)
occurrences (all)	14	2	2
Nervous system disorders			
Headache			
subjects affected / exposed	23 / 247 (9.31%)	4 / 132 (3.03%)	7 / 136 (5.15%)
occurrences (all)	45	7	7
General disorders and administration site conditions			
Fatigue			
subjects affected / exposed	8 / 247 (3.24%)	2 / 132 (1.52%)	3 / 136 (2.21%)
occurrences (all)	8	2	6
Respiratory, thoracic and mediastinal disorders			
Cough			
subjects affected / exposed	4 / 247 (1.62%)	1 / 132 (0.76%)	2 / 136 (1.47%)
occurrences (all)	4	1	2

Musculoskeletal and connective tissue disorders			
Arthralgia			
subjects affected / exposed	9 / 247 (3.64%)	8 / 132 (6.06%)	2 / 136 (1.47%)
occurrences (all)	11	8	2
Pain in extremity			
subjects affected / exposed	7 / 247 (2.83%)	1 / 132 (0.76%)	1 / 136 (0.74%)
occurrences (all)	7	1	1
Infections and infestations			
Covid-19			
subjects affected / exposed	6 / 247 (2.43%)	31 / 132 (23.48%)	28 / 136 (20.59%)
occurrences (all)	6	32	28
Nasopharyngitis			
subjects affected / exposed	32 / 247 (12.96%)	13 / 132 (9.85%)	3 / 136 (2.21%)
occurrences (all)	44	13	3
Upper respiratory tract infection			
subjects affected / exposed	17 / 247 (6.88%)	4 / 132 (3.03%)	2 / 136 (1.47%)
occurrences (all)	21	5	2
Urinary tract infection			
subjects affected / exposed	19 / 247 (7.69%)	2 / 132 (1.52%)	7 / 136 (5.15%)
occurrences (all)	24	4	9

Non-serious adverse events	Part 1: IV Q6W	Part 2: Run-in period: IV Q6W	
Total subjects affected by non-serious adverse events			
subjects affected / exposed	105 / 250 (42.00%)	42 / 158 (26.58%)	
Injury, poisoning and procedural complications			
Fall			
subjects affected / exposed	13 / 250 (5.20%)	5 / 158 (3.16%)	
occurrences (all)	18	5	
Nervous system disorders			
Headache			
subjects affected / exposed	26 / 250 (10.40%)	4 / 158 (2.53%)	
occurrences (all)	43	4	
General disorders and administration site conditions			
Fatigue			
subjects affected / exposed	25 / 250 (10.00%)	4 / 158 (2.53%)	
occurrences (all)	30	5	

Respiratory, thoracic and mediastinal disorders Cough subjects affected / exposed occurrences (all)	14 / 250 (5.60%) 14	4 / 158 (2.53%) 5	
Musculoskeletal and connective tissue disorders Arthralgia subjects affected / exposed occurrences (all) Pain in extremity subjects affected / exposed occurrences (all)	18 / 250 (7.20%) 24 14 / 250 (5.60%) 14	1 / 158 (0.63%) 1 4 / 158 (2.53%) 4	
Infections and infestations Covid-19 subjects affected / exposed occurrences (all) Nasopharyngitis subjects affected / exposed occurrences (all) Upper respiratory tract infection subjects affected / exposed occurrences (all) Urinary tract infection subjects affected / exposed occurrences (all)	5 / 250 (2.00%) 5 27 / 250 (10.80%) 31 12 / 250 (4.80%) 14 24 / 250 (9.60%) 42	19 / 158 (12.03%) 19 4 / 158 (2.53%) 5 1 / 158 (0.63%) 1 6 / 158 (3.80%) 7	

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

Date	Amendment
27 February 2019	1. Updated the timing of the primary efficacy endpoint to Week 72. 2. Updated time to EDSS worsening as a secondary endpoint. 3. Specified and clarified the study's statistical analysis plan within the protocol. 4. Extended the screening period from Day -42 to Day -1. 5. Added Week 84 EDSS and neurological examination assessments and Week 60 assessments for anti-natalizumab antibodies. 6. Clarified stratification on the factor 'country/region' and used a lower cut-off for body weight. 7. Clarified the screening assessments' timing.
08 July 2020	Added an open-label extension (OLE) part (Part 2) comprising a crossover analysis of natalizumab administered by IV infusion and SC injection under every 6 weeks (Q6W).
20 August 2020	1. Added details regarding the Screening visit for new participants who did not participate in Part 1 of the study and were being enrolled in Part 2. 2. Revised instructions for postdosing observation requirements. 3. Revised the nominal study day for the screening visit.

Notes:

Interruptions (globally)

Were there any global interruptions to the trial? No

Limitations and caveats

None reported