Clinical trial results:
A Multicenter, Randomized, Double-Blind, Placebo-Controlled Study of the Efficacy of Natalizumab on Reducing Disability Progression in Subjects With Secondary Progressive Multiple Sclerosis, With Optional Open-Label Extension

Summary

EudraCT number	2010-021978-11
Trial protocol	SE GB DE FI CZ DK BE ES PL IT IE
Global end of trial date	13 April 2016

Results information

Result version number	v2
This version publication date	11 June 2017
First version publication date	29 April 2017
Version creation reason	

Trial information

Trial identification

Sponsor protocol code	101MS326

Additional study identifiers

ISRCTN number	-
ClinicalTrials.gov id (NCT number)	NCT01416181
WHO universal trial number (UTN)	-

Notes:

Sponsors

Sponsor organisation name	Biogen
Sponsor organisation address	225 Binney Street, Cambridge, Massachusetts, 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	13 April 2016
Is this the analysis of the primary completion data?	No

Global end of trial reached?	Yes
Global end of trial date	13 April 2016
Was the trial ended prematurely?	Yes

Notes:

General information about the trial

Main objective of the trial:

Part 1: The primary objective of the study is to investigate whether treatment with natalizumab slows the accumulation of disability not related to relapses in participants with secondary progressive multiple sclerosis (SPMS).

Part 2: The primary objective of Part 2 of the study is to evaluate the safety profile of natalizumab in participants with SPMS.

Protection of trial subjects:

Written informed consent was obtained from each subject prior to evaluations being performed for eligibility. Subjects were given adequate time to review the information in the informed consent and were allowed to ask, and have answered, questions concerning all portions of the conduct of the study. Through the informed consent process each subject was made aware of the purpose of the study, the procedures, the benefits and risks of the study, the discomforts and the precautions taken. Any side effects or other health issues occurring during the study were followed up by the study doctor. Subjects were able to stop taking part in the study at any time without giving any reason.

Background therapy: -

Evidence for comparator: -

Actual start date of recruitment	13 September 2011
Long term follow-up planned	No
Independent data monitoring committee (IDMC) involvement?	Yes

Notes:

Population of trial subjects

Subjects enrolled per country

Country: Number of subjects enrolled	Poland: 188
Country: Number of subjects enrolled	United Kingdom: 126
Country: Number of subjects enrolled	United States: 87
Country: Number of subjects enrolled	Canada: 82
Country: Number of subjects enrolled	Italy: 75
Country: Number of subjects enrolled	Russian Federation: 55
Country: Number of subjects enrolled	France: 51
Country: Number of subjects enrolled	Germany: 51
Country: Number of subjects enrolled	Sweden: 46
Country: Number of subjects enrolled	Spain: 26
Country: Number of subjects enrolled	Israel: 18
Country: Number of subjects enrolled	Netherlands: 17
Country: Number of subjects enrolled	Denmark: 16
Country: Number of subjects enrolled	Czech Republic: 14

Country: Number of subjects enrolled	Ireland: 14
Country: Number of subjects enrolled	Finland: 12
Country: Number of subjects enrolled	Belgium: 11
Worldwide total number of subjects	889
EEA total number of subjects	647

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)	889
From 65 to 84 years	0
85 years and over	0

Subject disposition

Recruitment

Recruitment details: -

Pre-assignment

Screening details:

Subject eligibility for Part 1 of the study was determined within 6 weeks prior to study entry into Part 1. Eligible subjects from Part 1 who consented to participate in Part 2 were enrolled at the Part 1 Week 96 Visit. The Part 1 Week 108 Visit served as the Baseline Visit for Part 2.

Period 1

Period 1 title	Part 1
Is this the baseline period?	Yes
Allocation method	Randomised - controlled
Blinding used	Double blind
Roles blinded	Subject, Investigator

Blinding implementation details:

For Part 1, subjects and all study staff were blinded to the subject treatment assignments. On request, Investigators were to be notified of subject treatment assignments after finalization of the CSR for Part 1 of the study. Precautions were taken with the study treatment to maintain blinding.

Arms

Are arms mutually exclusive?	Yes
Arm title	Placebo

Arm description:

Part 1: subjects were randomized to receive placebo intravenously (IV) every 4 weeks for 96 weeks. Part 2: subjects transitioned to receive open-label natalizumab 300 mg IV every 4 weeks for at least 96 weeks.

Arm type	Placebo
Investigational medicinal product name	placebo
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Concentrate for solution for infusion
Routes of administration	Intravenous use

Dosage and administration details:

Placebo was administered through IV infusion. The individual preparing study treatment carefully reviewed the instructions provided in the Directions for Handling and Administration.

Arm title	Natalizumab 300 mg

Arm description:

Part 1: subjects were randomized to receive 300 mg of natalizumab IV every 4 weeks for 96 weeks. Part 2: subjects transitioned to receive open-label natalizumab 300 mg IV every 4 weeks for at least 96 weeks.

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

Dosage and administration details:

Natalizumab was administered through IV infusion. The individual preparing study treatment carefully reviewed the instructions provided in the Directions for Handling and Administration

Number of subjects in period 1[1]	Placebo	Natalizumab 300 mg
Started	449	439
Completed	312	326
Not completed	137	113
Adverse event, serious fatal	-	1
Consent withdrawn by subject	74	47
Adverse event, non-fatal	15	18
Not specified	10	24
Investigator Decision	7	6
Ongoing in Follow-Up	14	8
Lost to follow-up	1	1
Lack of efficacy	16	8

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: 1 subject withdrew prior to dosing

Period 2

Period 2 title	Part 2
Is this the baseline period?	No
Allocation method	Not applicable
Blinding used	Not blinded

Arms

Are arms mutually exclusive?	Yes
Arm title	Placebo

Arm description:

Part 1: subjects were randomized to receive placebo IV every 4 weeks for 96 weeks. Part 2: subjects transitioned to receive open-label natalizumab 300 mg IV every 4 weeks for at least 96 weeks.

Arm type	Placebo
Investigational medicinal product name	natalizumab
Investigational medicinal product code	BG00002
Other name	Tysabri
Pharmaceutical forms	Concentrate and solvent for concentrate for solution for infusion
Routes of administration	Intravenous use

Dosage and administration details:

Natalizumab was administered through IV infusion. The individual preparing study treatment carefully reviewed the instructions provided in the Directions for Handling and Administration.

Arm title	Natalizumab 300 mg

Arm description:

Part 1: subjects were randomized to receive 300 mg of natalizumab IV every 4 weeks for 96 weeks. Part 2: subjects transitioned to receive open-label natalizumab 300 mg IV every 4 weeks for at least 96 weeks.

Arm type	Experimental

Investigational medicinal product name	natalizumab
Investigational medicinal product code	BG00002
Other name	Tysabri
Pharmaceutical forms	Concentrate and solvent for concentrate for solution for infusion
Routes of administration	Intravenous use

Dosage and administration details:

Natalizumab was administered through IV infusion. The individual preparing study treatment carefully reviewed the instructions provided in the Directions for Handling and Administration.

Number of subjects in period 2[2]	Placebo	Natalizumab 300 mg
Started	274	292
Completed Treatment for 48 Weeks	98	111
Completed Treatment for 96 Weeks	1 [3]	0 [4]
Completed Treatment for > 96 Weeks	1 [5]	0 [6]
Completed	3	6
Not completed	271	286
Consent withdrawn by subject	14	5
Adverse event, non-fatal	11	4
Not specified	234	267
Investigator Decision	6	7
Lost to follow-up	2	2
Lack of efficacy	4	1

Notes:

[2] - The number of subjects starting the period is not consistent with the number completing the preceding period. It is expected the number of subjects starting the subsequent period will be the same as the number completing the preceding period.

Justification: Only subjects who transitions into Part 2 of the study are presented in period 2.

[3] - The number of subjects at this milestone seems inconsistent with the number of subjects in the arm. It is expected that the number of subjects will be greater than, or equal to the number that completed, minus those who left.

Justification: Milestones present the number of subjects who completed given number of weeks of treatment.

[4] - The number of subjects at this milestone seems inconsistent with the number of subjects in the arm. It is expected that the number of subjects will be greater than, or equal to the number that completed, minus those who left.

Justification: Milestones present the number of subjects who completed given number of weeks of treatment.

[5] - The number of subjects at this milestone seems inconsistent with the number of subjects in the arm. It is expected that the number of subjects will be greater than, or equal to the number that completed, minus those who left.

Justification: Milestones present the number of subjects who completed given number of weeks of treatment.

[6] - The number of subjects at this milestone seems inconsistent with the number of subjects in the arm. It is expected that the number of subjects will be greater than, or equal to the number that completed, minus those who left.

Justification: Milestones present the number of subjects who completed given number of weeks of treatment.

Baseline characteristics

Reporting groups	
Reporting group title	Placebo
Reporting group description:	
Part 1: subjects were randomized to receive placebo intravenously (IV) every 4 weeks for 96 weeks. Part 2: subjects transitioned to receive open-label natalizumab 300 mg IV every 4 weeks for at least 96 weeks.	
Reporting group title	Natalizumab 300 mg
Reporting group description:	
Part 1: subjects were randomized to receive 300 mg of natalizumab IV every 4 weeks for 96 weeks. Part 2: subjects transitioned to receive open-label natalizumab 300 mg IV every 4 weeks for at least 96 weeks.	

Reporting group values	Placebo	Natalizumab 300 mg	Total
Number of subjects	449	439	888
Age categorical Units: Subjects			
20 - 29 years	10	10	20
30 - 39 years	73	50	123
40 - 49 years	162	194	356
≥ 50 years	204	185	389
Gender, Male/Female Units: Subjects			
Female	280	270	550
Male	169	169	338

End points

End points reporting groups

Reporting group title	Placebo
Reporting group description:	
Part 1: subjects were randomized to receive placebo intravenously (IV) every 4 weeks for 96 weeks. Part 2: subjects transitioned to receive open-label natalizumab 300 mg IV every 4 weeks for at least 96 weeks.	
Reporting group title	Natalizumab 300 mg
Reporting group description:	
Part 1: subjects were randomized to receive 300 mg of natalizumab IV every 4 weeks for 96 weeks. Part 2: subjects transitioned to receive open-label natalizumab 300 mg IV every 4 weeks for at least 96 weeks.	
Reporting group title	Placebo
Reporting group description:	
Part 1: subjects were randomized to receive placebo IV every 4 weeks for 96 weeks. Part 2: subjects transitioned to receive open-label natalizumab 300 mg IV every 4 weeks for at least 96 weeks.	
Reporting group title	Natalizumab 300 mg
Reporting group description:	
Part 1: subjects were randomized to receive 300 mg of natalizumab IV every 4 weeks for 96 weeks. Part 2: subjects transitioned to receive open-label natalizumab 300 mg IV every 4 weeks for at least 96 weeks.	

Primary: Part 1: Percentage of Subjects With Confirmed Progression of Disability in One or More of the Expanded Disability Status Scale (EDSS), Timed 25-Foot Walk (T25FW), or 9-Hole Peg Test (9HPT)

End point title	Part 1: Percentage of Subjects With Confirmed Progression of Disability in One or More of the Expanded Disability Status Scale (EDSS), Timed 25-Foot Walk (T25FW), or 9-Hole Peg Test (9HPT)
End point description:	
Confirmed disability progression, defined as ≥1 of the following criteria (confirmed at a second visit ≥6 months later and at Week 96): - Confirmed progression in EDSS (EDSS score increased from baseline [BL] by ≥1 point if BL EDSS ≤5.5 or by ≥0.5 points if BL EDSS ≥6); - Confirmed progression in T25FW (T25FW increased by ≥20% of the BL walk); - Confirmed progression in 9HPT (9HPT increased by ≥20% of the time taken at BL on either hand and confirmed on the same hand). The EDSS measures disability status on a scale ranging from 0 to 10, with higher scores indicating more disability. The T25FW is a quantitative mobility and leg function performance test where the participant is timed while walking for 25 feet. The 9HPT is a quantitative test of upper extremity function that measures the time it takes to place 9 pegs into 9 holes and then remove the pegs. The 95% confidence interval (CI) of the percentage is based on normal approximation.	
End point type	Primary
End point timeframe:	
Up to 96 weeks (2 years)	

End point values	Placebo	Natalizumab 300 mg		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	448	439		
Units: percentage of subjects				
number (confidence interval 95%)				

Confirmed on ≥1 of EDSS, T25FW, or 9HPT at 2 years	48 (43.1 to 52.4)	44 (39.8 to 49.1)		
Confirmed on EDSS at 2 years	15 (11.7 to 18.3)	16 (12.3 to 19.1)		
Confirmed on T25FW at 2 years	35 (30.8 to 39.7)	35 (30.4 to 39.3)		
Confirmed on 9HPT (either hand) at 2 years	23 (19.3 to 27.1)	15 (11.3 to 17.9)		
Confirmed on 9HPT (dominant hand) at 2 years	13 (10.2 to 16.5)	10 (7.2 to 12.8)		
Confirmed on 9HPT (non-dominant hand) at 2 years	16 (12.5 to 19.2)	10 (7.2 to 12.8)		

Statistical analyses

Statistical analysis title	Statistical Analysis 1
Statistical analysis description:	
Confirmed progressors on ≥ 1 of EDSS, T25FW, or 9HPT at 2 years	
Comparison groups	Placebo v Natalizumab 300 mg
Number of subjects included in analysis	887
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.2866 [1]
Method	Regression, Logistic
Parameter estimate	Odds ratio (OR)
Point estimate	0.86
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.66
upper limit	1.13

Notes:

[1] - Based on logistic regression, adjusted for Baseline EDSS (<=5.5 or >=6) and/or T25FW and/or 9HPT (either hand).

Statistical analysis title	Statistical Analysis 2
Statistical analysis description:	
Confirmed progressors on EDSS	
Comparison groups	Placebo v Natalizumab 300 mg
Number of subjects included in analysis	887
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.753 [2]
Method	Regression, Logistic
Parameter estimate	Odds ratio (OR)
Point estimate	1.06
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.74
upper limit	1.53

Notes:

[2] - Based on logistic regression, adjusted for Baseline EDSS (<=5.5 or >=6) and/or T25FW and/or 9HPT (either hand).

Statistical analysis title	Statistical Analysis 3
Statistical analysis description:	
Confirmed progressors on T25FW	
Comparison groups	Placebo v Natalizumab 300 mg
Number of subjects included in analysis	887
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.9137 [3]
Method	Regression, Logistic
Parameter estimate	Odds ratio (OR)
Point estimate	0.98
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.74
upper limit	1.3

Notes:

[3] - Based on logistic regression, adjusted for Baseline EDSS (<=5.5 or >=6) and/or T25FW and/or 9HPT (either hand).

Statistical analysis title	Statistical Analysis 4
Statistical analysis description:	
Confirmed progressors on 9HPT (either hand)	
Comparison groups	Placebo v Natalizumab 300 mg
Number of subjects included in analysis	887
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.0012 [4]
Method	Regression, Logistic
Parameter estimate	Odds ratio (OR)
Point estimate	0.56
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.4
upper limit	0.8

Notes:

[4] - Based on logistic regression, adjusted for Baseline EDSS (<=5.5 or >=6) and/or T25FW and/or 9HPT (either hand).

Statistical analysis title	Statistical Analysis 5
Statistical analysis description:	
Confirmed progressors on 9HPT (dominant hand)	
Comparison groups	Placebo v Natalizumab 300 mg

Number of subjects included in analysis	887
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.1251 [5]
Method	Regression, Logistic
Parameter estimate	Odds ratio (OR)
Point estimate	0.72
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.48
upper limit	1.09

Notes:

[5] - Based on logistic regression, adjusted for Baseline EDSS (<=5.5 or >=6) and/or T25FW and/or 9HPT (either hand).

Statistical analysis title	Statistical Analysis 6

Statistical analysis description:

Confirmed progressors on 9HPT (non-dominant hand)

Comparison groups	Placebo v Natalizumab 300 mg
Number of subjects included in analysis	887
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.0091 [6]
Method	Regression, Logistic
Parameter estimate	Odds ratio (OR)
Point estimate	0.58
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.39
upper limit	0.87

Notes:

[6] - Based on logistic regression, adjusted for Baseline EDSS (<=5.5 or >=6) and/or T25FW and/or 9HPT (either hand).

Primary: Number of Participants with Treatment-Emergent Adverse Events (AEs) and Serious Adverse Events (SAEs)

End point title	Number of Participants with Treatment-Emergent Adverse Events (AEs) and Serious Adverse Events (SAEs)[7]

End point description:

AE: any untoward medical occurrence that did not necessarily have a causal relationship with this treatment. SAE: any untoward medical occurrence that at any dose: resulted in death; in the view of the Investigator, placed the participant at immediate risk of death (a life-threatening event); required inpatient hospitalization or prolongation of existing hospitalization; resulted in persistent or significant disability/incapacity; resulted in a congenital anomaly/birth defect. An SAE may have also been any other medically important event in the opinion of the Investigator.

End point type	Primary

End point timeframe:

218 weeks

Notes:

[7] - No statistical analyses have been specified for this primary end point. It is expected there is at least one statistical analysis for each primary end point.
Justification: Descriptive statistics are presented, per protocol.

End point values	Placebo	Natalizumab 300 mg		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	274	291		
Units: participants				
Any event	250	245		
Moderate or severe event	157	158		
Severe event	28	27		
Related event	63	56		
Serious event	24	39		
Discontinuation of treatment due to event	12	5		
Withdrawal from study due to an event	11	3		

Statistical analyses

No statistical analyses for this end point

Secondary: Part 1: Percentage of Subjects With a T25FW Response

End point title	Part 1: Percentage of Subjects With a T25FW Response

End point description:

T25FW response is defined as any improvement from the best pre-dose T25FW in at least 75% of the scheduled on-treatment visits through Week 96. The T25FW is a quantitative mobility and leg function performance test based on a timed walk over 25 feet. The subject is directed to one end of a clearly marked 25-foot course and is instructed to walk 25 feet as quickly as possible, but safely. The time is calculated from the initiation of the instruction to start and ends when the subject has reached the 25-foot mark. The task is immediately administered again by having the subject walk back the same distance. The score for the T25FW is the average of the 2 completed trials. The 95% CI of the percentage is based on normal approximation.

End point type	Secondary

End point timeframe:

Up to 96 weeks

End point values	Placebo	Natalizumab 300 mg		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	363	383		
Units: percentage of subjects				
number (confidence interval 95%)	17 (12.7 to 20.3)	19 (14.6 to 22.4)		

Statistical analyses

Statistical analysis title	Statistical Analysis 1
Comparison groups	Placebo v Natalizumab 300 mg

Number of subjects included in analysis	746
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.4369 [8]
Method	Regression, Logistic
Parameter estimate	Odds ratio (OR)
Point estimate	1.16
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.8
upper limit	1.7

Notes:

[8] - Based on logistic regression, adjusted for baseline EDSS (<=5.5 or >=6) and T25FW.

Secondary: Part 1: Change from Baseline in the 12-Item MS Walking Scale (MSWS-12)

End point title	Part 1: Change from Baseline in the 12-Item MS Walking Scale (MSWS-12)

End point description:

MSWS-12 is a subject self-assessment of the walking limitations due to MS during the past 2 weeks. It contains 12 items that measure the impact of MS on walking. Items are summed to generate a total score and transformed to a scale with a range of 0 to 100, where higher scores indicate greater impact on walking. A negative number on change from BL value indicates an improvement in MSWS-12.

End point type	Secondary

End point timeframe:

Baseline and Week 96

End point values	Placebo	Natalizumab 300 mg		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	436	431		
Units: units on a scale				
arithmetic mean (standard deviation)	4.04 (± 21.061)	2.7 (± 22.11)		

Statistical analyses

Statistical analysis title	Statistical Analysis 1
Comparison groups	Placebo v Natalizumab 300 mg
Number of subjects included in analysis	867
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.5409 [9]
Method	ANCOVA

Notes:

[9] - p-value for comparison between the active and placebo groups at Week 96 is based on ANCOVA model, adjusted for BL EDSS (<=5.5 or >=6) and BL MSWS-12.

Secondary: Part 1: Change From Baseline in Manual Ability Score Based on the ABILHAND Questionnaire

End point title	Part 1: Change From Baseline in Manual Ability Score Based on the ABILHAND Questionnaire

End point description:

The ABILHAND Questionnaire measures the subject's perceived difficulty in performing everyday manual activities in the last 3 months. The subject completes a 56-item questionnaire by estimating their own difficulty or ease in performing each of 56 activities. Items are summed to generate a total score and transformed to a scale with a range of 0 to 100, where high scores indicate greater impact on manual ability. A positive number on change from baseline value indicates an improvement in ABILHAND.

End point type	Secondary

End point timeframe:

Baseline and Week 96

End point values	Placebo	Natalizumab 300 mg		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	437	431		
Units: units on a scale				
arithmetic mean (standard deviation)	-3.45 (± 14.739)	-2.44 (± 13.023)		

Statistical analyses

Statistical analysis title	Statistical Analysis 1
Comparison groups	Placebo v Natalizumab 300 mg
Number of subjects included in analysis	868
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.2586 [10]
Method	ANCOVA

Notes:

[10] - p-value for comparison between active and placebo groups at Week 96 is based on ANCOVA model, adjusted for BL EDSS (<=5.5 or >=6) and BL ABILHAND.

Secondary: Part 1: Change from Baseline in the Multiple Sclerosis Impact Scale-29 Physical (MSIS-29 Physical) Score

End point title	Part 1: Change from Baseline in the Multiple Sclerosis Impact Scale-29 Physical (MSIS-29 Physical) Score

End point description:

The 29-item MSIS-29 is a subject-reported outcome measure to assess the impact of MS on day-to-day life during the past 2 weeks from a subject's perspective; it measures 20 physical items and 9 psychological items. The physical score is generated by summing individual items and then transforming to a scale with a range of 0 to 100, where high scores indicate worse health. A negative number on change from baseline value indicates an improvement in MSIS-29.

End point type	Secondary

End point timeframe: Baseline and Week 96

End point values	Placebo	Natalizumab 300 mg		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	428	430		
Units: units on a scale				
arithmetic mean (standard deviation)	3.34 (± 20.947)	0.61 (± 19.885)		

Statistical analyses

Statistical analysis title	Statistical Analysis 1
Comparison groups	Placebo v Natalizumab 300 mg
Number of subjects included in analysis	858
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.1529 [11]
Method	ANCOVA

Notes:

[11] - p-value for comparison between active & placebo groups at Wk 96 based on ANCOVA model, adjusted for BL EDSS (≤5.5 or ≥6) & BL MSIS-29 physical score.

Secondary: Part 1: Percentage Change from Week 24 in Whole Brain Volume at Week 96

End point title	Part 1: Percentage Change from Week 24 in Whole Brain Volume at Week 96
End point description: Whole brain volume as measured by MRI.	
End point type	Secondary
End point timeframe: Week 24 and Week 96	

End point values	Placebo	Natalizumab 300 mg		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	265	287		
Units: percentage change				
arithmetic mean (standard deviation)	-0.72 (± 0.656)	-0.66 (± 0.596)		

Statistical analyses

Statistical analysis title	Statistical Analysis 1
Comparison groups	Placebo v Natalizumab 300 mg
Number of subjects included in analysis	552
Analysis specification	Pre-specified
Analysis type	superiority[12]
P-value	= 0.2424 [13]
Method	ANCOVA

Notes:

[12] - Only subjects with BL brain volume are included in the p-value calculation.

[13] - natalizumab subjects had a baseline after 6 months of treatment and the placebo-to-natalizumab group had a baseline of initiation of treatment

Secondary: Part 1: Percentage of Subjects Defined as Confirmed Progressors on EDSS Functional System Scores

End point title	Part 1: Percentage of Subjects Defined as Confirmed Progressors on EDSS Functional System Scores

End point description:

The EDSS measures disability status on a scale ranging from 0 to 10, with higher scores indicating more disability. Scoring is based on measures of impairment in eight functional systems on examination by a neurologist. Subjects with confirmed progression of disability in EDSS physical functional system scores were defined as those who met one of the following criteria: - an increase of ≥ 1 point from baseline system score of ≥ 1 or an increase of ≥ 2 points from baseline system score of 0 in at least 2 physical functional systems, or - an increase of ≥ 2 points from baseline system score of ≥ 1 or an increase of ≥ 3 points from baseline system score of 0 in any 1 physical functional system. A confirmed progressor was defined as a participant who met the criteria for disability progression at any given visit and at the 6-Month Confirmation Visit. The 95% CIs are based on normal approximation.

End point type	Secondary

End point timeframe:

Up to 96 weeks

End point values	Placebo	Natalizumab 300 mg		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	448	439		
Units: percentage of subjects				
number (confidence interval 95%)	29 (25.2 to 33.7)	25 (20.6 to 28.6)		

Statistical analyses

Statistical analysis title	Statistical Analysis 1
Comparison groups	Placebo v Natalizumab 300 mg
Number of subjects included in analysis	887
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.1052 [14]
Method	Regression, Logistic
Parameter estimate	Odds ratio (OR)
Point estimate	0.78

Confidence interval	
level	95 %
sides	2-sided
lower limit	0.58
upper limit	1.05

Notes:

[14] - Based on logistic regression, adjusted for baseline EDSS (<=5.5 or >=6).

Secondary: Part 2: Percentage of Subjects With Disability Worsening at 156 Weeks

End point title	Part 2: Percentage of Subjects With Disability Worsening at 156 Weeks

End point description:

Percentage of subjects with disability worsening at each scheduled efficacy visit in Part 2, defined as one or more of the following: • ≥ 20% worsening from Part 1 baseline in T25FW; • ≥ 20% worsening from Part 1 baseline in 9HPT; • Worsening from Part 1 baseline in EDSS (≥ 1 point increase if Part 1 baseline EDSS ≤ 5.5 or ≥ 0.5 point increase if Part 1 baseline EDSS > 5.5). The EDSS measures disability status on a scale ranging from 0 to 10, with higher scores indicating more disability. The T25FW is a quantitative mobility and leg function performance test where the subject is timed while walking for 25 feet. The 9HPT is a quantitative test of upper extremity function that measures the time it takes to place 9 pegs into 9 holes and then remove the pegs. 95% CIs of percentages are based on normal approximation.

End point type	Secondary

End point timeframe:

Week 156

End point values	Placebo	Natalizumab 300 mg		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	274	291		
Units: percentage of subjects				
number (confidence interval 95%)				
Confirmed on ≥1 of EDSS, T25FW, 9HPT at 156 weeks	61 (55.2 to 66.7)	52 (45.8 to 57.3)		
Confirmed on EDSS at 156 weeks	23 (18.3 to 28.4)	18 (13.8 to 22.6)		
Confirmed on T25FW at 156 weeks	46 (40.1 to 51.9)	41 (35.2 to 46.5)		
Confirmed on 9HPT (either hand) at 156 weeks	28 (23.1 to 33.8)	19 (14.4 to 23.4)		
Confirmed on 9HPT (dominant hand) at 156 weeks	18 (13 to 22)	12 (8 to 15.4)		
Confirmed on 9HPT (non-dominant hand) at 156 weeks	18 (13 to 22)	13 (9.2 to 16.9)		

Statistical analyses

Statistical analysis title	Statistical Analysis 1

Statistical analysis description:

Confirmed progressors on ≥ 1 of EDSS, T25FW, or 9HPT at 156 weeks

Comparison groups	Placebo v Natalizumab 300 mg

Number of subjects included in analysis	565
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.0205 [15]
Method	Regression, Logistic
Parameter estimate	Odds ratio (OR)
Point estimate	0.67
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.47
upper limit	0.94

Notes:

[15] - Based on logistic regression, adjusted for Baseline EDSS (<=5.5 or >=6) and/or T25FW and/or 9HPT (either hand).

Statistical analysis title	Statistical Analysis 2

Statistical analysis description:

Confirmed progressors on EDSS at 156 weeks

Comparison groups	Placebo v Natalizumab 300 mg
Number of subjects included in analysis	565
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.1305 [16]
Method	Regression, Logistic
Parameter estimate	Odds ratio (OR)
Point estimate	0.73
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.48
upper limit	1.1

Notes:

[16] - Based on logistic regression, adjusted for Baseline EDSS (<=5.5 or >=6) and/or T25FW and/or 9HPT (either hand).

Statistical analysis title	Statistical Analysis 3

Statistical analysis description:

Confirmed progressors on T25FW at 156 weeks

Comparison groups	Placebo v Natalizumab 300 mg
Number of subjects included in analysis	565
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.1988 [17]
Method	Regression, Logistic
Parameter estimate	Odds ratio (OR)
Point estimate	0.8
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.57
upper limit	1.12

Notes:

[17] - Based on logistic regression, adjusted for Baseline EDSS (<=5.5 or >=6) and/or T25FW and/or 9HPT (either hand).

Statistical analysis title	Statistical Analysis 4
Statistical analysis description:	
Confirmed progressors on 9HPT (either hand) at 156 weeks	
Comparison groups	Placebo v Natalizumab 300 mg
Number of subjects included in analysis	565
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.0093 [18]
Method	Regression, Logistic
Parameter estimate	Odds ratio (OR)
Point estimate	0.59
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.39
upper limit	0.88

Notes:

[18] - Based on logistic regression, adjusted for Baseline EDSS (<=5.5 or >=6) and/or T25FW and/or 9HPT (either hand).

Statistical analysis title	Statistical Analysis 5
Statistical analysis description:	
Confirmed progressors onm 9HPT (dominant hand) at 156 weeks	
Comparison groups	Placebo v Natalizumab 300 mg
Number of subjects included in analysis	565
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.054 [19]
Method	Regression, Logistic
Parameter estimate	Odds ratio (OR)
Point estimate	0.63
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.39
upper limit	1.01

Notes:

[19] - Based on logistic regression, adjusted for Baseline EDSS (<=5.5 or >=6) and/or T25FW and/or 9HPT (either hand).

Statistical analysis title	Statistical Analysis 6
Statistical analysis description:	
Confirmed progressors on 9HPT (non-dominant hand) at 156 weeks	
Comparison groups	Placebo v Natalizumab 300 mg

Number of subjects included in analysis	565
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.141 [20]
Method	Regression, Logistic
Parameter estimate	Odds ratio (OR)
Point estimate	0.7
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.44
upper limit	1.12

Notes:

[20] - Based on logistic regression, adjusted for Baseline EDSS (<=5.5 or >=6) and/or T25FW and/or 9HPT (either hand).

Secondary: Part 2: Absolute Change From Baseline (Part 1) in T25FW

End point title	Part 2: Absolute Change From Baseline (Part 1) in T25FW

End point description:

The T25FW is a quantitative mobility and leg function performance test based on a timed 25-foot walk. The subject is directed to one end of a clearly marked 25-foot course and is instructed to walk 25 feet as quickly as possible, but safely. The time is calculated from the initiation of the instruction to start and ends when the participant has reached the 25-foot mark. The task is immediately repeated; the score for the T25FW is the average of the two completed trials. Lower scores on time taken to reach 25 foot mark reflects a better outcome. Values are presented for the overall group, as well as the confirmed progressor (CP, defined in the primary endpoint description above) and non-progressor (NP) subgroups.

End point type	Secondary

End point timeframe:

Baseline (Part 1) and Weeks 156, 204

End point values	Placebo	Natalizumab 300 mg		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	255	264		
Units: seconds				
arithmetic mean (standard deviation)				
Overall: Change from BL to Week 156; n=255, 264	12.8 (± 35.111)	7.78 (± 21.251)		
Overall: Change from BL to Week 204; n=39, 38	25.01 (± 56.582)	9.01 (± 22.507)		
CP Group: Change from BL to Week 156; n=156, 135	21.67 (± 42.51)	16.26 (± 26.943)		
CP Group: Change from BL to Week 204; n=25, 18	40.06 (± 66.275)	20.89 (± 28.2)		
NP Group: Change from BL to Week 156; n=99, 129	-1.17 (± 3.804)	-1.09 (± 3.593)		
NP Group: Change from BL to Week 204; n=14, 20	-1.88 (± 5.917)	-1.67 (± 4.613)		

Statistical analyses

Statistical analysis title	Statistical Analysis 1

Statistical analysis description:

Week 156

Comparison groups	Placebo v Natalizumab 300 mg
Number of subjects included in analysis	519
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.0273 [21]
Method	ANCOVA

Notes:

[21] - p-value for comparison between active and placebo at Week 156 based on ANCOVA model, adjusted for BL EDSS (<=5.5 or>=6) and BL T25FW.

Secondary: Part 2: Percentage change from Baseline (Part 1) in T25FW

End point title	Part 2: Percentage change from Baseline (Part 1) in T25FW

End point description:

The T25FW is a quantitative mobility and leg function performance test based on a timed 25-foot walk. The subject is directed to one end of a clearly marked 25-foot course and is instructed to walk 25 feet as quickly as possible, but safely. The time is calculated from the initiation of the instruction to start and ends when the subject has reached the 25-foot mark. The task is immediately repeated; the score for the T25FW is the average of the two completed trials. Values are presented for the overall group, as well as the CP (defined in the primary endpoint description above) and NP subgroups.

End point type	Secondary

End point timeframe:

Baseline (Part 1) and Weeks 156, 204

End point values	Placebo	Natalizumab 300 mg		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	255	264		
Units: percentage change				
arithmetic mean (standard deviation)				
Overall: Change from BL at Week 156; n=255, 264	75.52 (± 166.191)	55.91 (± 130.286)		
Overall: Change from BL at Week 204; n=39, 38	130.72 (± 272.117)	71.09 (± 177.668)		
CP Group: Change from BL at Week 156; n=156, 135	127.05 (± 195.138)	113.51 (± 160.857)		
CP Group: Change from BL at Week 204; n=25, 18	206.78 (± 316.344)	158.91 (± 228.458)		
NP Group: Change from BL at Week 156; n=99, 129	-5.68 (± 21.708)	-4.37 (± 25.05)		
NP Group: Change from BL at Week 204; n=14, 20	-5.09 (± 26.591)	-7.94 (± 29.856)		

Statistical analyses

Statistical analysis title	Statistical Analysis 1

Statistical analysis description:

Overall: Week 156

Comparison groups	Placebo v Natalizumab 300 mg
Number of subjects included in analysis	519
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.096 [22]
Method	ANCOVA

Notes:

[22] - p-value for comparison between active and placebo at Week 156 based on ANCOVA model, adjusted for BL EDSS (<=5.5 or>=6) and BL T25FW.

Secondary: Part 2: Absolute Change From Baseline (Part 1) in 9HPT (Dominant Hand)

End point title	Part 2: Absolute Change From Baseline (Part 1) in 9HPT (Dominant Hand)

End point description:

The 9HPT is a brief, standardized, quantitative test of upper extremity function. The subject picks up 9 pegs, puts them in a block containing nine empty holes, and, once they are in the holes, removes them again as quickly as possible one at a time. The total time to complete the task is recorded. Two consecutive trials with the dominant hand are immediately followed by two consecutive trials with the non-dominant hand. The two trials for each hand are averaged. Values are presented for the overall group, as well as the CP (defined in the primary endpoint description above) and NP subgroups.

End point type	Secondary

End point timeframe:

Baseline (Part 1) and Weeks 156, 204

End point values	Placebo	Natalizumab 300 mg		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	257	271		
Units: seconds				
arithmetic mean (standard deviation)				
Overall: Change from BL to Week 156; n= 257, 271	5.22 (± 27.728)	2.12 (± 16.719)		
Overall: Change from BL to Week 204; n=39, 38	0.56 (± 7.923)	2.65 (± 16.001)		
CP Group: Change from BL to Week 156; n=158, 138	10.12 (± 33.675)	5.01 (± 20.625)		
CP Group: Change from BL to Week 204; n=24, 19	2.36 (± 9.187)	6.03 (± 21.994)		
NP Group: Change from BL to Week 156; n=99, 133	-2.6 (± 9.543)	-0.89 (± 10.602)		
NP Group: Change from BL to Week 204; n=15, 19	-2.32 (± 4.153)	-0.73 (± 4.292)		

Statistical analyses

Statistical analysis title	Statistical Analysis 1

Statistical analysis description:

Overall, Week 156

Comparison groups	Placebo v Natalizumab 300 mg

Number of subjects included in analysis	528
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.1119 [23]
Method	ANCOVA

Notes:

[23] - p-value for comparison between active & placebo groups at Week 156 based on ANCOVA model, adjusted for BL EDSS (≤5.5 or ≥6) & BL 9HPT (dominant hand).

Secondary: Part 2: Percentage Change From Baseline (Part 1) in 9HPT (Dominant Hand)

End point title	Part 2: Percentage Change From Baseline (Part 1) in 9HPT (Dominant Hand)

End point description:

The 9HPT is a brief, standardized, quantitative test of upper extremity function. The subject picks up 9 pegs, puts them in a block containing nine empty holes, and, once they are in the holes, removes them again as quickly as possible one at a time. The total time to complete the task is recorded. Two consecutive trials with the dominant hand are immediately followed by two consecutive trials with the non-dominant hand. The two trials for each hand are averaged. Values are presented for the overall group, as well as the CP (defined in the primary endpoint description above) and NP subgroups.

End point type	Secondary

End point timeframe:

Baseline (Part 1) and Weeks 156, 204

End point values	Placebo	Natalizumab 300 mg		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	257	271		
Units: percentage change				
arithmetic mean (standard deviation)				
Overall: Change from BL to Week 156; n=257, 271	14.32 (± 59.727)	5.25 (± 32.649)		
Overall: Change from BL to Week 204; n=39, 38	2.27 (± 19.193)	6.87 (± 32.333)		
CP Group: Change from BL to Week 156; n=158, 138	25.87 (± 72.621)	12.84 (± 40.232)		
CP Group: Change from BL to Week 204; n=24, 19	8.43 (± 20.247)	16.25 (± 41.317)		
NP Group: Change from BL to Week 156; n=99, 133	-4.1 (± 17.661)	-2.63 (± 19.436)		
NP Group: Change from BL to Week 204; n=15, 19	-7.57 (± 12.56)	-2.52 (± 15.998)		

Statistical analyses

Statistical analysis title	Statistical Analysis 1

Statistical analysis description:

Overall: Week 156

Comparison groups	Placebo v Natalizumab 300 mg

Number of subjects included in analysis	528
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.0261 [24]
Method	ANCOVA

Notes:

[24] - p-value for comparison between active & placebo groups at Week 156 based on ANCOVA model, adjusted for BL EDSS (≤5.5 or ≥6) & BL 9HPT (dominant hand).

Secondary: Part 2: Absolute Change From Baseline (Part 1) in 9HPT (Non-Dominant Hand)

End point title	Part 2: Absolute Change From Baseline (Part 1) in 9HPT (Non-Dominant Hand)

End point description:

The 9HPT is a brief, standardized, quantitative test of upper extremity function. The subject picks up 9 pegs, puts them in a block containing nine empty holes, and, once they are in the holes, removes them again as quickly as possible one at a time. The total time to complete the task is recorded. Two consecutive trials with the dominant hand are immediately followed by two consecutive trials with the non-dominant hand. The two trials for each hand are averaged. Values are presented for the overall group, as well as the CP (defined in the primary endpoint description above) and NP subgroups.

End point type	Secondary

End point timeframe:

Baseline (Part 1) and Weeks 156, 204

End point values	Placebo	Natalizumab 300 mg		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	254	269		
Units: seconds				
arithmetic mean (standard deviation)				
Overall: Change from BL to Week 156; n=254, 269	5.24 (± 32.91)	4.62 (± 30.333)		
Overall: Change from BL to Week 204; n=40, 40	1.41 (± 16.952)	4.91 (± 33.808)		
CP Group: Change from BL to Week 156; n=155, 137	11.25 (± 39.513)	11.25 (± 38.296)		
CP Group: Change from BL to Week 204; n=25, 20	5.87 (± 17.474)	17.2 (± 34.632)		
NP Group: Change from BL to Week 156; n=99, 132	-4.17 (± 13.999)	-2.26 (± 16.311)		
NP Group: Change from BL to Week 204; n=15, 20	-6.04 (± 13.491)	-7.39 (± 28.78)		

Statistical analyses

Statistical analysis title	Statistical Analysis 1

Statistical analysis description:

Overall: Week 156

Comparison groups	Placebo v Natalizumab 300 mg

Number of subjects included in analysis	523
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.723 [25]
Method	ANCOVA

Notes:

[25] - p-value for comparison between active & placebo groups at Week 156 based on ANCOVA, adjusted for BL EDSS (≤5.5 or ≥6) & BL 9HPT (non-dominant hand).

Secondary: Part 2: Percentage Change From Baseline (Part 1) in 9HPT (Non-Dominant Hand)

End point title	Part 2: Percentage Change From Baseline (Part 1) in 9HPT (Non-Dominant Hand)

End point description:

The 9HPT is a brief, standardized, quantitative test of upper extremity function. The subjec picks up 9 pegs, puts them in a block containing nine empty holes, and, once they are in the holes, removes them again as quickly as possible one at a time. The total time to complete the task is recorded. Two consecutive trials with the dominant hand are immediately followed by two consecutive trials with the non-dominant hand. The two trials for each hand are averaged. Values are presented for the overall group, as well as the CP (defined in the primary endpoint description above) and NP subgroups.

End point type	Secondary

End point timeframe:

Baseline (Part 1) and Weeks 156, 204

End point values	Placebo	Natalizumab 300 mg		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	254	269		
Units: percentage change				
arithmetic mean (standard deviation)				
Overall: Change from BL to Week 156; n=254, 269	13.87 (± 64.959)	11.04 (± 47.942)		
Overall: Change from BL to Week 204; n=40, 40	3.67 (± 28.755)	18.57 (± 62.537)		
CP Group: Change from BL to Week 156; n=155, 137	26.33 (± 79.957)	23.51 (± 60.074)		
CP Group: Change from BL to Week 204; n=25, 20	11.87 (± 31.05)	43.12 (± 80.639)		
NP Group: Change from BL to Week 156; n=99, 132	-5.63 (± 14.765)	-1.89 (± 24.987)		
NP Group: Change from BL to Week 204; n=15, 20	-9.98 (± 18.188)	-5.98 (± 16.005)		

Statistical analyses

Statistical analysis title	Statistical Analysis 1

Statistical analysis description:

Overall: Week 156

Comparison groups	Placebo v Natalizumab 300 mg

Number of subjects included in analysis	523
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.5051 [26]
Method	ANCOVA

Notes:

[26] - p-value for comparison between active & placebo groups at Week 156 based on ANCOVA, adjusted for BL EDSS (≤5.5 or ≥6) & BL 9HPT (non-dominant hand).

Secondary: Part 2: Absolute Change from Baseline (Part 1) in EDSS

End point title	Part 2: Absolute Change from Baseline (Part 1) in EDSS

End point description:

The EDSS measures disability status on a scale ranging from 0 to 10, with higher scores indicating more disability. Scoring is based on measures of impairment in eight functional systems on examination by a neurologist. Values are presented for the overall group, as well as the CP (defined in the primary endpoint description above) and NP subgroups.

End point type	Secondary

End point timeframe:

Baseline (Part 1) and Weeks 156, 204

End point values	Placebo	Natalizumab 300 mg		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	260	275		
Units: units on a scale				
arithmetic mean (standard deviation)				
Overall: Change from BL to Week 156; n=260, 275	0.11 (± 0.746)	0.06 (± 0.797)		
Overall: Change from BL to Week 204; n=40, 40	-0.01 (± 0.895)	0.15 (± 0.928)		
CP Group: Change from BL to Week 156; n=162, 141	0.38 (± 0.631)	0.36 (± 0.703)		
CP Group: Change from BL to Week 204; n=25, 20	0.28 (± 0.542)	0.68 (± 0.634)		
NP Group: Change from BL to Week 156; n=98, 134	-0.33 (± 0.718)	-0.25 (± 0.775)		
NP Group: Change from BL to Week 204; n=15, 20	-0.5 (± 1.15)	-0.38 (± 0.887)		

Statistical analyses

Statistical analysis title	Statistical Analysis 1

Statistical analysis description:

Overall: Week 156

Comparison groups	Placebo v Natalizumab 300 mg

Number of subjects included in analysis	535
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.433 [27]
Method	ANCOVA

Notes:

[27] - p-value for comparison between active & placebo groups at Week 156 based on ANCOVA, adjusted for BL EDSS (≤5.5 or ≥6).

Secondary: Part 2: Percentage Change From Baseline (Part 1) in EDSS

End point title	Part 2: Percentage Change From Baseline (Part 1) in EDSS

End point description:

The EDSS measures disability status on a scale ranging from 0 to 10, with higher scores indicating more disability. Scoring is based on measures of impairment in eight functional systems on examination by a neurologist. Values are presented for the overall group, as well as the CP (defined in the primary endpoint description above) and NP subgroups.

End point type	Secondary

End point timeframe:

Baseline (Part 1) and Weeks 156 and 204

End point values	Placebo	Natalizumab 300 mg		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	260	275		
Units: percentage change				
arithmetic mean (standard deviation)				
Overall: Change from BL to Week 156; n=260, 275	2.07 (± 15.188)	1.65 (± 16.53)		
Overall: Change from BL to Week 204; n=40, 40	-0.63 (± 17.889)	2.91 (± 18.656)		
CP Group Change from BL to Week 156; n=162, 141	7.23 (± 13.513)	7.3 (± 15.728)		
CP Group Change from BL to Week 204; n=25, 20	5.31 (± 10.711)	13.18 (± 13.957)		
NP Group Change from BL to Week 156; n=98, 134	-6.47 (± 13.951)	-4.29 (± 15.266)		
NP Group Change from BL to Week 204; n=15, 20	-10.53 (± 22.953)	-7.35 (± 17.26)		

Statistical analyses

Statistical analysis title	Statistical Analysis 1

Statistical analysis description:

Overall: Week 156

Comparison groups	Placebo v Natalizumab 300 mg

Number of subjects included in analysis	535
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.7225 [28]
Method	ANCOVA

Notes:

[28] - p-value for comparison between active & placebo groups at Week 156 based on ANCOVA, adjusted for BL EDSS (≤5.5 or ≥6).

Secondary: Part 2: Absolute change from Baseline (Part 1) in the 6-Minute Walk Test (6MWT)

End point title	Part 2: Absolute change from Baseline (Part 1) in the 6-Minute Walk Test (6MWT)

End point description:

The 6MWT measures the distance an individual is able to walk over a total of six minutes on a hard, flat surface. The goal is for the individual to walk as far as possible in six minutes.

End point type	Secondary

End point timeframe:

Baseline (Part 1) and Weeks 156 and 204

End point values	Placebo	Natalizumab 300 mg		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	272	290		
Units: meters				
arithmetic mean (standard deviation)				
Change from BL to Week 156; n=272, 289	-32.1 (± 117.55)	-40.4 (± 219.6)		
Change from BL to Week 204; n=272, 290	-33.3 (± 119.4)	-40.7 (± 219.58)		

Statistical analyses

No statistical analyses for this end point

Secondary: Part 2: Percentage Change from Baseline (Part 1) in the 6MWT

End point title	Part 2: Percentage Change from Baseline (Part 1) in the 6MWT

End point description:

The 6MWT measures the distance an individual is able to walk over a total of six minutes on a hard, flat surface. The goal is for the individual to walk as far as possible in six minutes.

End point type	Secondary

End point timeframe:

Baseline (Part 1) and Weeks 156, 204

End point values	Placebo	Natalizumab 300 mg		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	0[29]	0[30]		
Units: percentage change				

Notes:

[29] - Due to sparse data up to Week 204 the analysis was not done.

[30] - Due to sparse data up to Week 204 the analysis was not done.

Statistical analyses

No statistical analyses for this end point

Secondary: Part 2: Absolute Change From Baseline (Part 1) in the MSIS-29 Physical Score

End point title	Part 2: Absolute Change From Baseline (Part 1) in the MSIS-29 Physical Score

End point description:

The 29-item MSIS-29 is a subject-reported outcome measure to assess the impact of MS on day-to-day life during the past 2 weeks from a subject's perspective; it measures 20 physical items and 9 psychological items. The physical score is generated by summing individual items and then transforming to a scale with a range of 0 to 100, where high scores indicate worse health. A negative number on change from baseline value indicates an improvement in MSIS-29.

End point type	Secondary

End point timeframe:

Baseline (Part 1) and Weeks 156 and 204

End point values	Placebo	Natalizumab 300 mg		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	274	291		
Units: units on a scale				
arithmetic mean (standard deviation)				
Change from BL to Week 156	0.32 (± 20.943)	0.05 (± 20.843)		
Change to from BL Week 204	0.91 (± 21.018)	-0.28 (± 20.596)		

Statistical analyses

Statistical analysis title	Statistical Analysis 1
Comparison groups	Placebo v Natalizumab 300 mg
Number of subjects included in analysis	565
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.7084 [31]
Method	ANCOVA

Notes:

[31] - p-value for comparison between active & placebo at Week 156 based on ANCOVA model, adjusted for BL EDSS (≤5.5 or ≥6) & BL MSIS-29 physical score.

Secondary: Part 2: Percentage Change From Baseline (Part 1) in the MSIS-29 Physical Score

End point title	Part 2: Percentage Change From Baseline (Part 1) in the MSIS-29 Physical Score

End point description:

The 29-item MSIS-29 is a subject-reported outcome measure to assess the impact of MS on day-to-day life during the past 2 weeks from a subject's perspective; it measures 20 physical items and 9 psychological items. The physical score is generated by summing individual items and then transforming to a scale with a range of 0 to 100, where high scores indicate worse health. A negative number on change from baseline value indicates an improvement in MSIS-29.

End point type	Secondary

End point timeframe:

Baseline (Part 1) and Weeks 156, 204

End point values	Placebo	Natalizumab 300 mg		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	0[32]	0[33]		
Units: percentage change				

Notes:

[32] - Due to sparse data up to Week 204 the analysis was not done.

[33] - Due to sparse data up to Week 204 the analysis was not done.

Statistical analyses

No statistical analyses for this end point

Secondary: Part 2: Absolute Change from Baseline (Part 1) in the Symbol Digit Modalities Test (SDMT)

End point title	Part 2: Absolute Change from Baseline (Part 1) in the Symbol Digit Modalities Test (SDMT)

End point description:

SDMT is a screening test for cognitive impairment. Subjects are given 90 seconds in which to pair specific numbers with given geometric figures using a key. Scores range from 0 to 110 (best). Missing values were imputed using last observation carried forward.

End point type	Secondary

End point timeframe:

Baseline (Part 1) and every 4 weeks from Week 108 to Week 204

End point values	Placebo	Natalizumab 300 mg		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	273	291		
Units: units on a scale				
arithmetic mean (standard deviation)				
Change from BL to Week 108	13.6 (± 14.19)	15.5 (± 13.82)		

Change from BL to Week 112	14.4 (± 13.72)	15.1 (± 13.5)		
Change from BL to Week 116	14.1 (± 13.84)	15.3 (± 13.51)		
Change from BL to Week 120	14.3 (± 14.23)	15.3 (± 13.68)		
Change from BL to Week 124	14.4 (± 14.02)	15.7 (± 13.69)		
Change from BL to Week 128	15.1 (± 14.49)	15.7 (± 13.72)		
Change from BL to Week 132	15.1 (± 14.52)	15.6 (± 13.63)		
Change from BL to Week 136	14.8 (± 14.56)	16.3 (± 13.75)		
Change from BL to Week 140	15.4 (± 14.98)	16.4 (± 14.29)		
Change from BL to Week 144	15.7 (± 15.23)	16.2 (± 14.22)		
Change from BL to Week 148	15.5 (± 15.34)	16.3 (± 14.35)		
Change from BL to Week 152	15.5 (± 14.98)	16.3 (± 14.25)		
Change from BL to Week 156	11.2 (± 13.1)	12.3 (± 14.59)		
Change from BL to Week 160	15.2 (± 14.92)	16.2 (± 14.61)		
Change from BL to Week 164	15.6 (± 15.21)	16.3 (± 14.64)		
Change from BL to Week 168	15.8 (± 15.52)	16.4 (± 14.78)		
Change from BL to Week 172	15.6 (± 15.4)	16.3 (± 14.64)		
Change from BL to Week 176	15.5 (± 15.58)	16.3 (± 14.91)		
Change from BL to Week 180	15.5 (± 15.23)	16.4 (± 14.89)		
Change from BL to Week 184	15.6 (± 15.34)	16.3 (± 14.81)		
Change from BL to Week 188	15.6 (± 15.38)	16.4 (± 14.77)		
Change from BL to Week 192	15.6 (± 15.46)	16.3 (± 14.79)		
Change from BL to Week 196	15.7 (± 15.45)	16.3 (± 14.69)		
Change from BL to Week 200	15.7 (± 15.47)	16.3 (± 14.69)		
Change from BL to Week 204	15.7 (± 15.43)	16.3 (± 14.69)		

Statistical analyses

Statistical analysis title	Statistical Analysis 1

Statistical analysis description:

Week 156

Comparison groups	Placebo v Natalizumab 300 mg
Number of subjects included in analysis	564
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.3465 [34]
Method	ANCOVA

Notes:

[34] - p-value for comparison between active and placebo at Week 156 based on ANCOVA model, adjusted for BL EDSS (<=5.5 or>=6) and BL SDMT.

Secondary: Part 2: Percentage Change From Baseline (Part 1) in the SDMT

End point title	Part 2: Percentage Change From Baseline (Part 1) in the SDMT

End point description:

SDMT is a screening test for cognitive impairment. Subjects are given 90 seconds in which to pair specific numbers with given geometric figures using a key. Scores range from 0 to 110 (best).

End point type	Secondary

End point timeframe:

Baseline (Part 1) and every 4 weeks from Week 108 to Week 204

End point values	Placebo	Natalizumab 300 mg		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	0[35]	0[36]		
Units: percentage change				

Notes:

[35] - Due to sparse data up to Week 204 the analysis was not done.

[36] - Due to sparse data up to Week 204 the analysis was not done.

Statistical analyses

No statistical analyses for this end point

Secondary: Part 2: Absolute Change From Baseline (Part 2) in the Work Productivity and Activity Impairment – Multiple Sclerosis (WPAI-MS) Questionnaire

End point title	Part 2: Absolute Change From Baseline (Part 2) in the Work Productivity and Activity Impairment – Multiple Sclerosis (WPAI-MS) Questionnaire

End point description:

The WPAI questionnaire is a validated instrument to measure impairments in work and activities. The WPAI yields four types of scores: 1. Absenteeism (percentage of work time missed) 2. Presenteesism (percentage of impairment at work/reduced on-the-job effectiveness) 3. Work productivity loss (percentage of overall work impairment [absenteeism plus presenteeism]) 4. Activity Impairment (percentage of overall activity impairment). WPAI outcomes are expressed as impairment percentages, with higher numbers indicating greater impairment and less productivity.

End point type	Secondary

End point timeframe:

Part 2 Baseline (Week 108) and Weeks 156 and 204

End point values	Placebo	Natalizumab 300 mg		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	272	291		
Units: percentage of impairment				
arithmetic mean (standard deviation)				
Absenteeism: Week 108	2.6 (± 12.8)	1.4 (± 8.24)		
Absenteeism: Week 156	3 (± 14.61)	4.1 (± 17.36)		
Absenteeism: Week 204	3 (± 14.61)	4.2 (± 16.89)		
Presenteeism: Week 108	30.6 (± 12.1)	30.9 (± 11.71)		
Presenteeism: Week 156	30.8 (± 12.17)	33 (± 14.23)		
Presenteeism: Week 204	31 (± 12.29)	32.2 (± 13.78)		
Work Productivity Loss: Week 108	30.9 (± 12.36)	31.2 (± 11.7)		
Work Productivity Loss: Week 156	31.6 (± 13.54)	33.9 (± 15.75)		
Work Productivity Loss: Week 204	31.9 (± 13.66)	33.3 (± 15.61)		
Activity Impairment: Week 108	56.1 (± 24.78)	58 (± 24.84)		
Activity Impairment: Week 156	56.8 (± 26.49)	58.5 (± 24.08)		
Activity Impairment: Week 204	57.2 (± 25.15)	59.8 (± 23.6)		

Statistical analyses

No statistical analyses for this end point

Secondary: Part 2: Percentage Change From Baseline (Part 2) in the WPAI-MS Questionnaire

End point title	Part 2: Percentage Change From Baseline (Part 2) in the WPAI-MS Questionnaire

End point description:

The WPAI questionnaire is a validated instrument to measure impairments in work and activities. The WPAI yields four types of scores: 1. Absenteeism (percentage of work time missed) 2. Presenteesism (percentage of impairment at work/reduced on-the-job effectiveness) 3. Work productivity loss (WPL; percentage of overall work impairment [absenteeism plus presenteeism]) 4. Activity Impairment (AI; percentage of overall activity impairment). WPAI outcomes are expressed as impairment percentages, with higher numbers indicating greater impairment and less productivity.

End point type	Secondary

End point timeframe:

Part 2 Baseline (Week 108) and Weeks 156 and 204

End point values	Placebo	Natalizumab 300 mg		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	274	291		
Units: percentage change				
arithmetic mean (standard deviation)				
Absenteeism: Change at Week 156; n=18,17	-10.3 (± 116.81)	-7.4 (± 95.77)		
Absenteeism: Change at Week 204; n=18, 17	-6.6 (± 116.9)	151.5 (± 457.29)		
Presenteeism: Change at Week 156; n=264, 285	4 (± 50.08)	14.4 (± 90.39)		
Presenteeism: Change at Week 204; n=264, 285	5.3 (± 51.23)	7.4 (± 58.95)		
WPL: Change at Week 156; n=264,286	4.7 (± 51.73)	16.8 (± 95.43)		
WPL: Change at Week 204; n=264, 286	5.9 (± 53.44)	10.6 (± 69.34)		
AI: Change at Week 156; n=264, 284	16 (± 95.68)	15.7 (± 83.7)		
AI: Change at Week 204; n=264, 284	16.1 (± 88.56)	20.4 (± 99.54)		

Statistical analyses

No statistical analyses for this end point

Secondary: Part 2: Percentage Change From Week 24 (Part 1) in Whole Brain

Volume

End point title	Part 2: Percentage Change From Week 24 (Part 1) in Whole Brain Volume

End point description:

Whole brain volume as measured by MRI.

End point type	Secondary

End point timeframe:

Week 24 (Part 1) and Weeks 156 and 204

End point values	Placebo	Natalizumab 300 mg		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	274	291		
Units: percentage change				
arithmetic mean (standard deviation)				
Change from Week 24 to Week 156; n=155, 175	-1.164 (± 0.8228)	-0.948 (± 0.7193)		
Change from Week 24 to Week 204; n=28, 24	-1.687 (± 1.2872)	-1.517 (± 0.8412)		

Statistical analyses

No statistical analyses for this end point

Secondary: Part 2: Percentage Change from Baseline (Part 1) in Whole Gray Matter Brain Volume

End point title	Part 2: Percentage Change from Baseline (Part 1) in Whole Gray Matter Brain Volume

End point description:

Whole grey matter brain volume as measured by MRI.

End point type	Secondary

End point timeframe:

Baseline (Part 1) and Weeks 156 and 204

End point values	Placebo	Natalizumab 300 mg		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	274	291		
Units: percentage change				
arithmetic mean (standard deviation)				
Change from Baseline to Week 156; n=149, 170	-1.566 (± 0.9303)	-1.514 (± 0.8969)		
Change from Baseline to Week 204; n=26, 20	-1.883 (± 1.4222)	-2.086 (± 0.9068)		

Statistical analyses

No statistical analyses for this end point

Secondary: Part 2: Summary of New/Enlarging T2 Lesion Counts

End point title	Part 2: Summary of New/Enlarging T2 Lesion Counts

End point description:

New or enlarging T2 lesions as measured by MRI.

End point type	Secondary

End point timeframe:

Baseline (Part 1) up to Week 204

End point values	Placebo	Natalizumab 300 mg		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	274	291		
Units: lesions				
arithmetic mean (standard deviation)				
At Week 24 compared to BL; n=272, 287	2.1 (± 4.24)	0.6 (± 3.27)		
At Week 48 compared to Week 24; n=272, 289	1.8 (± 4.47)	0 (± 0.37)		
At Week 72 compared to Week 48; n=271, 287	1.6 (± 3.76)	0 (± 0.19)		
At Week 96 compared to Week 72; n=269, 284	1.8 (± 4.33)	0 (± 0)		
At Week 108 compared to Week 96; n=269, 288	1.2 (± 3.38)	0 (± 0.13)		
At Week 156 compared to Week 108; n=245, 258	0.2 (± 0.79)	0 (± 0.2)		
At Week 204 compared to Week 156; n=50, 47	0 (± 0.2)	0 (± 0.15)		
Cumulative count from BL to Week 204; n=274, 291	8.6 (± 16.04)	0.7 (± 3.53)		

Statistical analyses

No statistical analyses for this end point

Secondary: Part 2: Percentage Change From Baseline (Part 1) in Number of New/Enlarging T2 Lesions

End point title	Part 2: Percentage Change From Baseline (Part 1) in Number of New/Enlarging T2 Lesions

End point description:

New or enlarging T2 lesions as measured by MRI.

End point type	Secondary

End point timeframe:

Baseline (Part 1) and Weeks 156 and 204

End point values	Placebo	Natalizumab 300 mg		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	0[37]	0[38]		
Units: percentage change				
arithmetic mean (standard deviation)	()	()		

Notes:

[37] - Due to sparse data up to Week 204 the analysis was not done.

[38] - Due to sparse data up to Week 204 the analysis was not done.

Statistical analyses

No statistical analyses for this end point

Adverse events

Adverse events information

Timeframe for reporting adverse events:

Adverse events are captured through the last study visit; subjects were followed through Week 228, or 24 weeks following last dose of study treatment, or premature withdrawal.

Assessment type	Systematic

Dictionary used

Dictionary name	MedDRA
Dictionary version	18.0

Reporting groups

Reporting group title	Natalizumab 300 mg
Reporting group description: -	
Reporting group title	Placebo

Reporting group description: -

Serious adverse events	Natalizumab 300 mg	Placebo	
Total subjects affected by serious adverse events			
subjects affected / exposed	90 / 439 (20.50%)	100 / 449 (22.27%)	
number of deaths (all causes)	1	0	
number of deaths resulting from adverse events			
Neoplasms benign, malignant and unspecified (incl cysts and polyps)			
Basal cell carcinoma			
subjects affected / exposed	0 / 439 (0.00%)	1 / 449 (0.22%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Breast cancer			
subjects affected / exposed	0 / 439 (0.00%)	1 / 449 (0.22%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cholesteatoma			
subjects affected / exposed	1 / 439 (0.23%)	0 / 449 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Colon adenoma			

subjects affected / exposed	0 / 439 (0.00%)	1 / 449 (0.22%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Lipoma			
subjects affected / exposed	0 / 439 (0.00%)	1 / 449 (0.22%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Lung neoplasm malignant			
subjects affected / exposed	1 / 439 (0.23%)	0 / 449 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pancreatic carcinoma			
subjects affected / exposed	1 / 439 (0.23%)	0 / 449 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Papillary cystadenoma lymphomatosum			
subjects affected / exposed	1 / 439 (0.23%)	0 / 449 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Renal cell carcinoma			
subjects affected / exposed	1 / 439 (0.23%)	0 / 449 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Signet-ring cell carcinoma			
subjects affected / exposed	1 / 439 (0.23%)	0 / 449 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 1	0 / 0	
Tonsil cancer			
subjects affected / exposed	1 / 439 (0.23%)	0 / 449 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Uterine leiomyoma			

subjects affected / exposed	0 / 439 (0.00%)	1 / 449 (0.22%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Vascular disorders			
Deep vein thrombosis			
subjects affected / exposed	2 / 439 (0.46%)	0 / 449 (0.00%)	
occurrences causally related to treatment / all	0 / 2	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hypotension			
subjects affected / exposed	1 / 439 (0.23%)	0 / 449 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Surgical and medical procedures			
Joint surgery			
subjects affected / exposed	1 / 439 (0.23%)	0 / 449 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Limb operation			
subjects affected / exposed	1 / 439 (0.23%)	0 / 449 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Meniscus operation			
subjects affected / exposed	1 / 439 (0.23%)	0 / 449 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Nephrectomy			
subjects affected / exposed	1 / 439 (0.23%)	0 / 449 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
General disorders and administration site conditions			
Asthenia			
subjects affected / exposed	2 / 439 (0.46%)	0 / 449 (0.00%)	
occurrences causally related to treatment / all	0 / 2	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	

Catheter site haemorrhage			
subjects affected / exposed	0 / 439 (0.00%)	1 / 449 (0.22%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Gait disturbance			
subjects affected / exposed	2 / 439 (0.46%)	1 / 449 (0.22%)	
occurrences causally related to treatment / all	0 / 2	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Influenza like illness			
subjects affected / exposed	0 / 439 (0.00%)	1 / 449 (0.22%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pyrexia			
subjects affected / exposed	1 / 439 (0.23%)	1 / 449 (0.22%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Immune system disorders			
Anaphylactic reaction			
subjects affected / exposed	3 / 439 (0.68%)	0 / 449 (0.00%)	
occurrences causally related to treatment / all	2 / 3	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Anaphylactic shock			
subjects affected / exposed	0 / 439 (0.00%)	2 / 449 (0.45%)	
occurrences causally related to treatment / all	0 / 0	2 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hypersensitivity			
subjects affected / exposed	1 / 439 (0.23%)	0 / 449 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Reproductive system and breast disorders			
Cervical dysplasia			
subjects affected / exposed	1 / 439 (0.23%)	0 / 449 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	

Metrorrhagia			
subjects affected / exposed	1 / 439 (0.23%)	0 / 449 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Ovarian cyst			
subjects affected / exposed	0 / 439 (0.00%)	1 / 449 (0.22%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Respiratory, thoracic and mediastinal disorders			
Asthma			
subjects affected / exposed	0 / 439 (0.00%)	1 / 449 (0.22%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pulmonary oedema			
subjects affected / exposed	0 / 439 (0.00%)	1 / 449 (0.22%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Sinus polyp			
subjects affected / exposed	0 / 439 (0.00%)	1 / 449 (0.22%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Psychiatric disorders			
Abnormal behaviour			
subjects affected / exposed	1 / 439 (0.23%)	0 / 449 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Acute psychosis			
subjects affected / exposed	0 / 439 (0.00%)	1 / 449 (0.22%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Mood disorder due to a general medical condition			

subjects affected / exposed	1 / 439 (0.23%)	0 / 449 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Substance-induced psychotic disorder			
subjects affected / exposed	0 / 439 (0.00%)	1 / 449 (0.22%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Investigations			
Weight decreased			
subjects affected / exposed	1 / 439 (0.23%)	1 / 449 (0.22%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Injury, poisoning and procedural complications			
Ankle fracture			
subjects affected / exposed	0 / 439 (0.00%)	2 / 449 (0.45%)	
occurrences causally related to treatment / all	0 / 0	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Brain contusion			
subjects affected / exposed	1 / 439 (0.23%)	0 / 449 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Comminuted fracture			
subjects affected / exposed	0 / 439 (0.00%)	1 / 449 (0.22%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Concussion			
subjects affected / exposed	1 / 439 (0.23%)	0 / 449 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Contusion			
subjects affected / exposed	0 / 439 (0.00%)	1 / 449 (0.22%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	

Ear injury			
subjects affected / exposed	1 / 439 (0.23%)	0 / 449 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Extradural haematoma			
subjects affected / exposed	1 / 439 (0.23%)	1 / 449 (0.22%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Fall			
subjects affected / exposed	6 / 439 (1.37%)	3 / 449 (0.67%)	
occurrences causally related to treatment / all	0 / 6	0 / 3	
deaths causally related to treatment / all	0 / 0	0 / 0	
Femoral neck fracture			
subjects affected / exposed	1 / 439 (0.23%)	0 / 449 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Femur fracture			
subjects affected / exposed	1 / 439 (0.23%)	1 / 449 (0.22%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Fibula fracture			
subjects affected / exposed	0 / 439 (0.00%)	2 / 449 (0.45%)	
occurrences causally related to treatment / all	0 / 0	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Foot fracture			
subjects affected / exposed	1 / 439 (0.23%)	1 / 449 (0.22%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Fractured sacrum			
subjects affected / exposed	1 / 439 (0.23%)	0 / 449 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Head injury			

subjects affected / exposed	1 / 439 (0.23%)	0 / 449 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hip fracture			
subjects affected / exposed	1 / 439 (0.23%)	0 / 449 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Infusion related reaction			
subjects affected / exposed	1 / 439 (0.23%)	0 / 449 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Ligament sprain			
subjects affected / exposed	0 / 439 (0.00%)	1 / 449 (0.22%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Multiple fractures			
subjects affected / exposed	1 / 439 (0.23%)	0 / 449 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Overdose			
subjects affected / exposed	1 / 439 (0.23%)	0 / 449 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Postoperative ileus			
subjects affected / exposed	1 / 439 (0.23%)	0 / 449 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Radius fracture			
subjects affected / exposed	0 / 439 (0.00%)	1 / 449 (0.22%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Road traffic accident			

subjects affected / exposed	1 / 439 (0.23%)	0 / 449 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Soft tissue injury			
subjects affected / exposed	1 / 439 (0.23%)	0 / 449 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Stab wound			
subjects affected / exposed	0 / 439 (0.00%)	1 / 449 (0.22%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Subdural haematoma			
subjects affected / exposed	0 / 439 (0.00%)	1 / 449 (0.22%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Thermal burn			
subjects affected / exposed	0 / 439 (0.00%)	1 / 449 (0.22%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Wrist fracture			
subjects affected / exposed	1 / 439 (0.23%)	0 / 449 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Congenital, familial and genetic disorders			
Pelvic kidney			
subjects affected / exposed	0 / 439 (0.00%)	1 / 449 (0.22%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cardiac disorders			
Acute myocardial infarction			
subjects affected / exposed	1 / 439 (0.23%)	2 / 449 (0.45%)	
occurrences causally related to treatment / all	0 / 1	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	

Atrial fibrillation			
subjects affected / exposed	0 / 439 (0.00%)	2 / 449 (0.45%)	
occurrences causally related to treatment / all	0 / 0	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Coronary artery disease			
subjects affected / exposed	1 / 439 (0.23%)	1 / 449 (0.22%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Tachycardia			
subjects affected / exposed	1 / 439 (0.23%)	0 / 449 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Nervous system disorders			
Cerebral venous thrombosis			
subjects affected / exposed	1 / 439 (0.23%)	0 / 449 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cervical myelopathy			
subjects affected / exposed	1 / 439 (0.23%)	0 / 449 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Epilepsy			
subjects affected / exposed	1 / 439 (0.23%)	0 / 449 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Generalised tonic-clonic seizure			
subjects affected / exposed	1 / 439 (0.23%)	0 / 449 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Multiple sclerosis			
subjects affected / exposed	0 / 439 (0.00%)	5 / 449 (1.11%)	
occurrences causally related to treatment / all	0 / 0	0 / 5	
deaths causally related to treatment / all	0 / 0	0 / 0	
Multiple sclerosis relapse			

subjects affected / exposed	21 / 439 (4.78%)	28 / 449 (6.24%)	
occurrences causally related to treatment / all	1 / 23	0 / 37	
deaths causally related to treatment / all	0 / 0	0 / 0	
Muscle spasticity			
subjects affected / exposed	2 / 439 (0.46%)	0 / 449 (0.00%)	
occurrences causally related to treatment / all	0 / 2	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Optic neuritis			
subjects affected / exposed	0 / 439 (0.00%)	2 / 449 (0.45%)	
occurrences causally related to treatment / all	0 / 0	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Quadriparesis			
subjects affected / exposed	0 / 439 (0.00%)	1 / 449 (0.22%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Secondary progressive multiple sclerosis			
subjects affected / exposed	0 / 439 (0.00%)	1 / 449 (0.22%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Seizure			
subjects affected / exposed	0 / 439 (0.00%)	1 / 449 (0.22%)	
occurrences causally related to treatment / all	0 / 0	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Syncope			
subjects affected / exposed	0 / 439 (0.00%)	1 / 449 (0.22%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Tonic convulsion			
subjects affected / exposed	1 / 439 (0.23%)	0 / 449 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Transient global amnesia			

subjects affected / exposed	0 / 439 (0.00%)	1 / 449 (0.22%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Transient ischaemic attack			
subjects affected / exposed	0 / 439 (0.00%)	1 / 449 (0.22%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Uhthoff's phenomenon			
subjects affected / exposed	1 / 439 (0.23%)	3 / 449 (0.67%)	
occurrences causally related to treatment / all	0 / 1	1 / 3	
deaths causally related to treatment / all	0 / 0	0 / 0	
Blood and lymphatic system disorders			
Anaemia			
subjects affected / exposed	1 / 439 (0.23%)	0 / 449 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Ear and labyrinth disorders			
Vertigo positional			
subjects affected / exposed	0 / 439 (0.00%)	1 / 449 (0.22%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Eye disorders			
Uveitis			
subjects affected / exposed	0 / 439 (0.00%)	1 / 449 (0.22%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Gastrointestinal disorders			
Abdominal hernia			
subjects affected / exposed	0 / 439 (0.00%)	1 / 449 (0.22%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Colitis			

subjects affected / exposed	1 / 439 (0.23%)	0 / 449 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Constipation			
subjects affected / exposed	0 / 439 (0.00%)	1 / 449 (0.22%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Duodenal ulcer			
subjects affected / exposed	0 / 439 (0.00%)	1 / 449 (0.22%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Enteritis			
subjects affected / exposed	0 / 439 (0.00%)	1 / 449 (0.22%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Gastritis			
subjects affected / exposed	1 / 439 (0.23%)	1 / 449 (0.22%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Haematemesis			
subjects affected / exposed	1 / 439 (0.23%)	0 / 449 (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	1 / 439 (0.23%)	0 / 449 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Inguinal hernia			
subjects affected / exposed	0 / 439 (0.00%)	1 / 449 (0.22%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Oesophageal food impaction			

subjects affected / exposed	0 / 439 (0.00%)	1 / 449 (0.22%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Small intestinal stenosis			
subjects affected / exposed	0 / 439 (0.00%)	1 / 449 (0.22%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Upper gastrointestinal haemorrhage			
subjects affected / exposed	1 / 439 (0.23%)	0 / 449 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Vomiting			
subjects affected / exposed	0 / 439 (0.00%)	1 / 449 (0.22%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hepatobiliary disorders			
Cholecystitis acute			
subjects affected / exposed	0 / 439 (0.00%)	1 / 449 (0.22%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cholelithiasis			
subjects affected / exposed	1 / 439 (0.23%)	0 / 449 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Drug-induced liver injury			
subjects affected / exposed	1 / 439 (0.23%)	0 / 449 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Skin and subcutaneous tissue disorders			
Erythema multiforme			
subjects affected / exposed	1 / 439 (0.23%)	0 / 449 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Rash			

subjects affected / exposed	0 / 439 (0.00%)	1 / 449 (0.22%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Renal and urinary disorders			
Acute kidney injury			
subjects affected / exposed	0 / 439 (0.00%)	1 / 449 (0.22%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Calculus ureteric			
subjects affected / exposed	0 / 439 (0.00%)	1 / 449 (0.22%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Nephrolithiasis			
subjects affected / exposed	1 / 439 (0.23%)	0 / 449 (0.00%)	
occurrences causally related to treatment / all	0 / 2	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Neurogenic bladder			
subjects affected / exposed	1 / 439 (0.23%)	0 / 449 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Tubulointerstitial nephritis			
subjects affected / exposed	0 / 439 (0.00%)	1 / 449 (0.22%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Urge incontinence			
subjects affected / exposed	1 / 439 (0.23%)	0 / 449 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Urinary incontinence			
subjects affected / exposed	0 / 439 (0.00%)	1 / 449 (0.22%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Urinary retention			

subjects affected / exposed	1 / 439 (0.23%)	0 / 449 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Endocrine disorders			
Toxic nodular goitre			
subjects affected / exposed	1 / 439 (0.23%)	0 / 449 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Musculoskeletal and connective tissue disorders			
Back pain			
subjects affected / exposed	1 / 439 (0.23%)	1 / 449 (0.22%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Foot deformity			
subjects affected / exposed	0 / 439 (0.00%)	1 / 449 (0.22%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Fracture nonunion			
subjects affected / exposed	0 / 439 (0.00%)	1 / 449 (0.22%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Intervertebral disc protrusion			
subjects affected / exposed	1 / 439 (0.23%)	0 / 449 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Myalgia			
subjects affected / exposed	1 / 439 (0.23%)	0 / 449 (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	1 / 439 (0.23%)	0 / 449 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	

Rotator cuff syndrome			
subjects affected / exposed	0 / 439 (0.00%)	1 / 449 (0.22%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Infections and infestations			
Bacterial sepsis			
subjects affected / exposed	0 / 439 (0.00%)	1 / 449 (0.22%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Brain abscess			
subjects affected / exposed	0 / 439 (0.00%)	1 / 449 (0.22%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Bronchitis			
subjects affected / exposed	1 / 439 (0.23%)	1 / 449 (0.22%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cellulitis			
subjects affected / exposed	3 / 439 (0.68%)	2 / 449 (0.45%)	
occurrences causally related to treatment / all	1 / 3	1 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Clostridium difficile colitis			
subjects affected / exposed	1 / 439 (0.23%)	0 / 449 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cystitis			
subjects affected / exposed	1 / 439 (0.23%)	1 / 449 (0.22%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Enteritis infectious			
subjects affected / exposed	0 / 439 (0.00%)	1 / 449 (0.22%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Gastroenteritis			

subjects affected / exposed	3 / 439 (0.68%)	0 / 449 (0.00%)	
occurrences causally related to treatment / all	0 / 3	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
H1n1 influenza			
subjects affected / exposed	0 / 439 (0.00%)	1 / 449 (0.22%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Herpes virus infection			
subjects affected / exposed	1 / 439 (0.23%)	0 / 449 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Infected dermal cyst			
subjects affected / exposed	1 / 439 (0.23%)	0 / 449 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Infected skin ulcer			
subjects affected / exposed	0 / 439 (0.00%)	1 / 449 (0.22%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Influenza			
subjects affected / exposed	1 / 439 (0.23%)	1 / 449 (0.22%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Localised infection			
subjects affected / exposed	0 / 439 (0.00%)	1 / 449 (0.22%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Lower respiratory tract infection			
subjects affected / exposed	0 / 439 (0.00%)	2 / 449 (0.45%)	
occurrences causally related to treatment / all	0 / 0	0 / 3	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pneumonia			

subjects affected / exposed	2 / 439 (0.46%)	5 / 449 (1.11%)	
occurrences causally related to treatment / all	1 / 2	1 / 5	
deaths causally related to treatment / all	0 / 0	0 / 0	
Prostatic abscess			
subjects affected / exposed	1 / 439 (0.23%)	0 / 449 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pyelonephritis			
subjects affected / exposed	0 / 439 (0.00%)	1 / 449 (0.22%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pyelonephritis acute			
subjects affected / exposed	0 / 439 (0.00%)	1 / 449 (0.22%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Sepsis			
subjects affected / exposed	1 / 439 (0.23%)	1 / 449 (0.22%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Sinusitis			
subjects affected / exposed	1 / 439 (0.23%)	0 / 449 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Urinary tract infection			
subjects affected / exposed	5 / 439 (1.14%)	12 / 449 (2.67%)	
occurrences causally related to treatment / all	2 / 6	0 / 13	
deaths causally related to treatment / all	0 / 0	0 / 0	
Urinary tract infection enterococcal			
subjects affected / exposed	0 / 439 (0.00%)	1 / 449 (0.22%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Urosepsis			

subjects affected / exposed	3 / 439 (0.68%)	1 / 449 (0.22%)	
occurrences causally related to treatment / all	1 / 3	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Metabolism and nutrition disorders			
Diabetic ketoacidosis			
subjects affected / exposed	1 / 439 (0.23%)	0 / 449 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Insulin-requiring type 2 diabetes mellitus			
subjects affected / exposed	1 / 439 (0.23%)	0 / 449 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Obesity			
subjects affected / exposed	0 / 439 (0.00%)	1 / 449 (0.22%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Type 1 diabetes mellitus			
subjects affected / exposed	1 / 439 (0.23%)	0 / 449 (0.00%)	
occurrences causally related to treatment / all	1 / 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	Natalizumab 300 mg	Placebo	
Total subjects affected by non-serious adverse events			
subjects affected / exposed	325 / 439 (74.03%)	347 / 449 (77.28%)	
Injury, poisoning and procedural complications			
Contusion			
subjects affected / exposed	26 / 439 (5.92%)	17 / 449 (3.79%)	
occurrences (all)	36	19	
Fall			
subjects affected / exposed	82 / 439 (18.68%)	85 / 449 (18.93%)	
occurrences (all)	198	212	
Nervous system disorders			

Dizziness			
subjects affected / exposed	22 / 439 (5.01%)	35 / 449 (7.80%)	
occurrences (all)	28	43	
Headache			
subjects affected / exposed	66 / 439 (15.03%)	50 / 449 (11.14%)	
occurrences (all)	126	92	
Multiple sclerosis relapse			
subjects affected / exposed	68 / 439 (15.49%)	116 / 449 (25.84%)	
occurrences (all)	79	166	
Muscle spasticity			
subjects affected / exposed	17 / 439 (3.87%)	27 / 449 (6.01%)	
occurrences (all)	20	27	
Paraesthesia			
subjects affected / exposed	22 / 439 (5.01%)	13 / 449 (2.90%)	
occurrences (all)	26	16	
General disorders and administration site conditions			
Fatigue			
subjects affected / exposed	59 / 439 (13.44%)	53 / 449 (11.80%)	
occurrences (all)	91	61	
Gastrointestinal disorders			
Constipation			
subjects affected / exposed	21 / 439 (4.78%)	26 / 449 (5.79%)	
occurrences (all)	22	31	
Diarrhoea			
subjects affected / exposed	33 / 439 (7.52%)	31 / 449 (6.90%)	
occurrences (all)	38	55	
Nausea			
subjects affected / exposed	34 / 439 (7.74%)	23 / 449 (5.12%)	
occurrences (all)	42	30	
Respiratory, thoracic and mediastinal disorders			
Cough			
subjects affected / exposed	24 / 439 (5.47%)	20 / 449 (4.45%)	
occurrences (all)	26	23	
Musculoskeletal and connective tissue disorders			

Arthralgia			
subjects affected / exposed	43 / 439 (9.79%)	40 / 449 (8.91%)	
occurrences (all)	48	55	
Back pain			
subjects affected / exposed	45 / 439 (10.25%)	50 / 449 (11.14%)	
occurrences (all)	56	63	
Muscle spasms			
subjects affected / exposed	23 / 439 (5.24%)	21 / 449 (4.68%)	
occurrences (all)	29	26	
Muscular weakness			
subjects affected / exposed	28 / 439 (6.38%)	39 / 449 (8.69%)	
occurrences (all)	41	48	
Pain in extremity			
subjects affected / exposed	42 / 439 (9.57%)	42 / 449 (9.35%)	
occurrences (all)	82	52	
Infections and infestations			
Cystitis			
subjects affected / exposed	22 / 439 (5.01%)	16 / 449 (3.56%)	
occurrences (all)	35	19	
Influenza			
subjects affected / exposed	32 / 439 (7.29%)	33 / 449 (7.35%)	
occurrences (all)	38	38	
Nasopharyngitis			
subjects affected / exposed	98 / 439 (22.32%)	73 / 449 (16.26%)	
occurrences (all)	157	136	
Upper respiratory tract infection			
subjects affected / exposed	48 / 439 (10.93%)	30 / 449 (6.68%)	
occurrences (all)	63	37	
Urinary tract infection			
subjects affected / exposed	100 / 439 (22.78%)	103 / 449 (22.94%)	
occurrences (all)	226	216	

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

Date	Amendment
29 June 2011	Per the original protocol, subjects were to be randomized in a ratio of 1:1 to 1 of the double-blind treatment regimens: natalizumab 300 mg q4wk IV or placebo q4wk IV. The primary reason for amendment 1 was the addition of stratification by EDSS score for subjects with scores ranging from 3.0 to 5.5 and those ranging from 6.0 to 6.5 during randomization to the double-blind treatment regimens at enrollment to ensure treatment balance across EDSS strata.
27 October 2011	The primary reason for this amendment was to provide additional confirmation of progressor status at Week 96 (or at the last available study visit) in order to further reduce the potential variability of the data.
15 February 2012	The primary reason for this amendment was to describe the sensitivity analyses for the first secondary endpoint, the proportion of subjects with consistent improvement in T25FW. These analyses were planned to evaluate the robustness of data, including the impact on T25FW analysis of the exclusion of randomized subjects who discontinued the study within the first year.
27 February 2013	The primary reason for this amendment to Protocol 101MS326 was to change the frequency of anti-JCV antibody testing from every 48 weeks to every 24 weeks and to add an approximately 2-year open-label Extension Phase (Part 2) for subjects who complete the Placebo-controlled Phase (Part 1), are eligible, and choose to participate.
16 September 2014	The primary reason for this amendment to Protocol 101MS326 was to clarify the following aspects of the protocol: specify the timing of the Premature Withdrawal Visit (i.e., 4 weeks after the last dose of study treatment); specify the timing of a follow-up visit via phone (i.e., after the Premature Withdrawal Visit, 12 weeks after the last dose of study treatment); and add the requirement that a subject not miss 2 or more consecutive infusions in Part 1 of the study in order to qualify for inclusion in Part 2 of the study.

Notes:

Interruptions (globally)

Were there any global interruptions to the trial? No

Limitations and caveats

Limitations of the trial such as small numbers of subjects analysed or technical problems leading to unreliable data.

The ASCEND Study did not achieve statistical significance on the primary or secondary endpoints and was terminated early.

Notes: