Clinical trial results:
A Multicenter, Double-Blind, Placebo-Controlled, Randomized, Parallel-Group Study to Evaluate the Safety and Efficacy of Intravenous Natalizumab (BG00002) on Reducing Infarct Volume in Acute Ischemic Stroke

Summary

EudraCT number	2013-001514-15
Trial protocol	DE ES
Global end of trial date	09 April 2015

Results information

Result version number	v1 (current)
This version publication date	15 April 2016
First version publication date	15 April 2016

Trial information

Trial identification

Sponsor protocol code	101SK201

Additional study identifiers

ISRCTN number	-
ClinicalTrials.gov id (NCT number)	NCT01955707
WHO universal trial number (UTN)	-

Notes:

Sponsors

Sponsor organisation name	Biogen
Sponsor organisation address	225 Binney Street, Cambridge, United States, 02142
Public contact	Biogen Study Medical Director, Biogen, clinicaltrials@biogen.com
Scientific contact	Biogen Study Medical Director, Biogen, clinicaltrials@biogen.com

Notes:

Paediatric regulatory details

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

Notes:

Results analysis stage

Analysis stage	Final
Date of interim/final analysis	09 April 2015
Is this the analysis of the primary completion data?	No

Global end of trial reached?	Yes
Global end of trial date	09 April 2015
Was the trial ended prematurely?	No

Notes:

General information about the trial

Main objective of the trial:

The primary objective of the study is to determine whether one 300-mg dose of intravenous (IV) natalizumab reduces the change in infarct volume from Baseline to Day 5 on magnetic resonance imaging (MRI) in subjects with acute ischemic stroke when given at ≤ 6 hours or at > 6 to ≤ 9 hours from when they were last known normal (LKN).

The secondary objectives of this study in this study population are as follows: to assess the efficacy of natalizumab on change in infarct volume from Baseline to Day 30; to assess efficacy of natalizumab on change in infarct volume from 24 hours to Day 5 and Day 30; to assess the efficacy of natalizumab on clinical measures of stroke outcome; and to assess the safety of natalizumab in subjects with acute ischemic stroke.

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.

Subjects were observed for 1 hour after the study treatment infusion to allow monitoring for hypersensitivity reactions.

Background therapy: -

Evidence for comparator: -

Actual start date of recruitment	28 January 2014
Long term follow-up planned	No
Independent data monitoring committee (IDMC) involvement?	No

Notes:

Population of trial subjects

Subjects enrolled per country

Country: Number of subjects enrolled	Spain: 62
Country: Number of subjects enrolled	Germany: 57
Country: Number of subjects enrolled	United States: 42
Worldwide total number of subjects	161
EEA total number of subjects	119

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)	37
From 65 to 84 years	118
85 years and over	6

Subject disposition

Recruitment

Recruitment details: -

Pre-assignment

Screening details:

Subject eligibility for the study was determined at the time of acute ischemic stroke diagnosis.

Period 1

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

Blinding implementation details:

This was a randomized, double-blind, placebo-controlled study. Subjects and all study staff, including the Pharmacist, were blinded to the subject treatment assignments.

Arms

Are arms mutually exclusive?	Yes
Arm title	Placebo

Arm description:

A single IV injection of placebo

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:

All subjects with acute ischemic stroke will receive an infusion of blinded study treatment at ≤ 6 hours or at > 6 to ≤ 9 hours from when they were LKN.

Arm title	Natalizumab

Arm description:

300-mg single IV injection of natalizumab

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:

All subjects with acute ischemic stroke will receive an infusion of blinded study treatment at ≤ 6 hours or at > 6 to ≤ 9 hours from when they were LKN.

Number of subjects in period 1	Placebo	Natalizumab
Started	82	79
Withdrew Prior to Dosing	0 [1]	1 [2]
Dosed	82	78
Received Total Volume of Study Drug	82	77
Completed	62	57
Not completed	20	22
Consent withdrawn by subject	-	3
Death	13	14
Not specified	4	2
Adverse event	1	2
Lost to follow-up	2	1

Notes:

[1] - 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 follow the correct flow of subjects through the study.

[2] - 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 follow the correct flow of subjects through the study.

Baseline characteristics

Reporting groups	
Reporting group title	Placebo
Reporting group description: A single IV injection of placebo	
Reporting group title	Natalizumab
Reporting group description: 300-mg single IV injection of natalizumab	

Reporting group values	Placebo	Natalizumab	Total
Number of subjects	82	79	161
Age categorical Units: Subjects			
</= 39 years	2	3	5
40 to 59 years	13	11	24
60 to 79 years	41	45	86
>/= 80 years	26	20	46
Age continuous Units: years			
arithmetic mean	71.6	70.3	
standard deviation	± 11.83	± 13.34	-
Gender categorical Units: Subjects			
Female	34	38	72
Male	48	41	89

End points

End points reporting groups

Reporting group title	Placebo
Reporting group description: A single IV injection of placebo	
Reporting group title	Natalizumab
Reporting group description: 300-mg single IV injection of natalizumab	
Subject analysis set title	Modified intention to treat: Placebo
Subject analysis set type	Intention-to-treat
Subject analysis set description: All subjects who were randomized to placebo and received the entire infusion of study treatment.	
Subject analysis set title	Modified intention to treat: Natalizumab
Subject analysis set type	Intention-to-treat
Subject analysis set description: All subjects who were randomized to natalizumab and received the entire infusion of study treatment.	
Subject analysis set title	Safety population: Placebo
Subject analysis set type	Safety analysis
Subject analysis set description: All subjects who were randomized to placebo and received any portion of the infusion of study treatment.	
Subject analysis set title	Safety population: Natalizumab
Subject analysis set type	Safety analysis
Subject analysis set description: All subjects who were randomized to natalizumab and received any portion of the infusion of study treatment.	

Primary: Change in Infarct Volume From Baseline (Diffusion-Weighted Imaging [DWI]) to Day 5 (Fluid-Attenuated Inversion Recovery [FLAIR])

End point title	Change in Infarct Volume From Baseline (Diffusion-Weighted Imaging [DWI]) to Day 5 (Fluid-Attenuated Inversion Recovery [FLAIR])
End point description: Relative growth of infarct volume from Baseline (relative growth = FLAIR at Day 5 divided by Baseline DWI). Geometric mean calculated as the exponential of the mean log relative growth.	
End point type	Primary
End point timeframe: Baseline, Day 5	

End point values	Modified intention to treat: Placebo	Modified intention to treat: Natalizumab		
Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed	73	69		
Units: mL				
geometric mean (inter-quartile range (Q1-Q3))	2.17 (1.6 to 3.17)	2.37 (1.51 to 2.91)		

Statistical analyses

Statistical analysis title	Statistical Analysis 1

Statistical analysis description:

Treatment contrasts derived from a repeated measures mixed effects model modeling log relative growth relative to baseline using an autoregressive variance-covariance matrix structure. The model adjusts for treatment, time, treatment by time, log baseline DWI volume, treatment time window, and tissue plasminogen activator (tPA) use.

Comparison groups	Modified intention to treat: Placebo v Modified intention to treat: Natalizumab
Number of subjects included in analysis	142
Analysis specification	Pre-specified
Analysis type	superiority
Parameter estimate	adjusted mean difference (log-scale)
Point estimate	0.08
Confidence interval	
level	90 %
sides	2-sided
lower limit	-0.09
upper limit	0.26

Statistical analysis title	Statistical Analysis 2

Statistical analysis description:

Adjusted mean (log-scale) back-transformed to the original scale as the estimated ratio of natalizumab to placebo. 90% confidence interval (log-scale) back-transformed to the original scale and reflect the interval around the ratio.

Comparison groups	Modified intention to treat: Placebo v Modified intention to treat: Natalizumab
Number of subjects included in analysis	142
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.779 [1]
Method	repeated measures mixed effects model
Parameter estimate	ratio of relative growth
Point estimate	1.09
Confidence interval	
level	90 %
sides	2-sided
lower limit	0.91
upper limit	1.3

Notes:

[1] - one-sided p-value

Secondary: Change in Infarct Volume From Baseline (DWI) to 24 Hours (FLAIR)

End point title	Change in Infarct Volume From Baseline (DWI) to 24 Hours (FLAIR)

End point description:

Relative growth of infarct volume from Baseline (relative growth = FLAIR at 24 hours divided by Baseline DWI). Geometric mean calculated as the exponential of the mean log relative growth.

End point type	Secondary

End point timeframe:

Baseline, 24 hrs

End point values	Modified intention to treat: Placebo	Modified intention to treat: Natalizumab		
Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed	74[2]	69[3]		
Units: mL				
geometric mean (inter-quartile range (Q1-Q3))	1.73 (1.33 to 2.15)	1.95 (1.36 to 2.2)		

Notes:

[2] - subjects with assessments at both time points

[3] - subjects with assessments at both time points

Statistical analyses

Statistical analysis title	Statistical Analysis 1

Statistical analysis description:

Treatment contrasts derived from a repeated measures mixed effects model modeling log relative growth relative to baseline using an autoregressive variance-covariance matrix structure. The model adjusts for treatment, time, treatment by time, log baseline DWI volume, treatment time window, and tPA use.

Comparison groups	Modified intention to treat: Placebo v Modified intention to treat: Natalizumab
Number of subjects included in analysis	143
Analysis specification	Pre-specified
Analysis type	superiority
Parameter estimate	adjusted mean difference (log-scale)
Point estimate	0.09
Confidence interval	
level	90 %
sides	2-sided
lower limit	-0.09
upper limit	0.27

Statistical analysis title	Statistical Analysis 2

Statistical analysis description:

Adjusted mean (log-scale) back-transformed to the original scale as the estimated ratio of natalizumab to placebo. 90% confidence interval (log-scale) back-transformed to the original scale and reflect the interval around the ratio.

Comparison groups	Modified intention to treat: Placebo v Modified intention to treat: Natalizumab

Number of subjects included in analysis	143
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.797 [4]
Method	repeated measures mixed effects model
Parameter estimate	ratio of relative growth
Point estimate	1.09
Confidence interval	
level	90 %
sides	2-sided
lower limit	0.92
upper limit	1.31

Notes:

[4] - one-sided p-value

Secondary: Change in Infarct Volume From Baseline (DWI) to Day 30 (FLAIR)

End point title	Change in Infarct Volume From Baseline (DWI) to Day 30 (FLAIR)

End point description:

Relative growth of infarct volume from Baseline (relative growth = FLAIR at Day 30 divided by Baseline DWI). Geometric mean calculated as the exponential of the mean log relative growth.

End point type	Secondary

End point timeframe:

Baseline, Day 30

End point values	Modified intention to treat: Placebo	Modified intention to treat: Natalizumab		
Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed	66[5]	55[6]		
Units: mL				
geometric mean (inter-quartile range (Q1-Q3))	1.27 (0.9 to 1.88)	1.25 (0.78 to 1.93)		

Notes:

[5] - subjects with assessments at both time points.

[6] - subjects with assessments at both time points.

Statistical analyses

Statistical analysis title	Statistical Analysis 1

Statistical analysis description:

Treatment contrasts derived from a repeated measures mixed effects model modeling log relative growth relative to baseline using an autoregressive variance-covariance matrix structure. The model adjusts for treatment, time, treatment by time, log baseline DWI volume, treatment time window, and tPA use.

Comparison groups	Modified intention to treat: Placebo v Modified intention to treat: Natalizumab

Number of subjects included in analysis	121
Analysis specification	Pre-specified
Analysis type	superiority
Parameter estimate	adjusted mean difference (log-scale)
Point estimate	0.05
Confidence interval	
level	90 %
sides	2-sided
lower limit	-0.13
upper limit	0.24

Statistical analysis title	Statistical Analysis 2

Statistical analysis description:

Adjusted mean (log-scale) back-transformed to the original scale as the estimated ratio of natalizumab to placebo. 90% confidence interval (log-scale) back-transformed to the original scale and reflect the interval around the ratio.

Comparison groups	Modified intention to treat: Placebo v Modified intention to treat: Natalizumab
Number of subjects included in analysis	121
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.684 [7]
Method	repeated measures mixed effects model
Parameter estimate	ratio of relative growth
Point estimate	1.05
Confidence interval	
level	90 %
sides	2-sided
lower limit	0.88
upper limit	1.27

Notes:

[7] - one-sided p-value

Secondary: Change in Infarct Volume From 24 Hours (FLAIR) to Day 5 (FLAIR)

End point title	Change in Infarct Volume From 24 Hours (FLAIR) to Day 5 (FLAIR)

End point description:

Relative growth of infarct volume from 24 hours (relative growth = FLAIR at Day 5 divided by FLAIR at 24 hours). Geometric mean calculated as the exponential of the mean log relative growth.

End point type	Secondary

End point timeframe:

24 hours, Day 5

End point values	Modified intention to treat: Placebo	Modified intention to treat: Natalizumab		
Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed	70[8]	65[9]		
Units: mL				
geometric mean (inter-quartile range (Q1-Q3))	1.27 (1.11 to 1.37)	1.25 (1.11 to 1.42)		

Notes:

[8] - subjects with assessments at both time points.

[9] - subjects with assessments at both time points.

Statistical analyses

Statistical analysis title	Statistical Analysis 1

Statistical analysis description:

Treatment contrasts derived from a repeated measures mixed effects model modeling log relative growth relative to 24 hours using an autoregressive variance-covariance matrix structure. The model adjusts for treatment, time, treatment by time, log baseline DWI volume, treatment time window, and tPA use.

Comparison groups	Modified intention to treat: Placebo v Modified intention to treat: Natalizumab
Number of subjects included in analysis	135
Analysis specification	Pre-specified
Analysis type	superiority
Parameter estimate	adjusted mean difference (log-scale)
Point estimate	0
Confidence interval	
level	90 %
sides	2-sided
lower limit	-0.12
upper limit	0.11

Statistical analysis title	Statistical Analysis 2

Statistical analysis description:

Adjusted mean (log-scale) back-transformed to the original scale as the estimated ratio of natalizumab to placebo. 90% confidence interval (log-scale) back-transformed to the original scale and reflect the interval around the ratio.

Comparison groups	Modified intention to treat: Placebo v Modified intention to treat: Natalizumab
Number of subjects included in analysis	135
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.487 [10]
Method	repeated measures mixed effects model
Parameter estimate	ratio of relative growth
Point estimate	1
Confidence interval	
level	90 %
sides	2-sided
lower limit	0.89
upper limit	1.12

Notes:

[10] - one-sided p-value

Secondary: Change in Infarct Volume From 24 Hours (FLAIR) to Day 30 (FLAIR)

End point title	Change in Infarct Volume From 24 Hours (FLAIR) to Day 30 (FLAIR)

End point description:

Relative growth in infarct volume from 24 hours (relative growth = FLAIR Day 30 divided by FLAIR at 24 hours). Geometric mean calculated as the exponential of the mean log relative growth.

End point type	Secondary

End point timeframe:

24 hours, Day 30

End point values	Modified intention to treat: Placebo	Modified intention to treat: Natalizumab		
Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed	62[11]	53[12]		
Units: mL				
geometric mean (inter-quartile range (Q1-Q3))	0.75 (0.62 to 1.03)	0.72 (0.56 to 1.09)		

Notes:

[11] - Subjects with assessments at both time points.

[12] - Subjects with assessments at both time points.

Statistical analyses

Statistical analysis title	Statistical Analysis 1

Statistical analysis description:

Treatment contrasts derived from a repeated measures mixed effects model modeling log relative growth relative to 24 hours using an autoregressive variance-covariance matrix structure. The model adjusts for treatment, time, treatment by time, log baseline DWI volume, treatment time window, and tPA use.

Comparison groups	Modified intention to treat: Placebo v Modified intention to treat: Natalizumab
Number of subjects included in analysis	115
Analysis specification	Pre-specified
Analysis type	superiority
Parameter estimate	adjusted mean difference (log-scale)
Point estimate	-0.02
Confidence interval	
level	90 %
sides	2-sided
lower limit	-0.14
upper limit	0.1

Statistical analysis title	Statistical Analysis 2

Statistical analysis description:

Adjusted mean (log-scale) back-transformed to the original scale as the estimated ratio of natalizumab to placebo. 90% confidence interval (log-scale) back-transformed to the original scale and reflect the interval around the ratio.

Comparison groups	Modified intention to treat: Placebo v Modified intention to treat: Natalizumab
Number of subjects included in analysis	115
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.402 [13]
Method	repeated measures mixed effects model
Parameter estimate	ratio of relative growth
Point estimate	0.98
Confidence interval	
level	90 %
sides	2-sided
lower limit	0.87
upper limit	1.11

Notes:

[13] - one-sided p-value

Secondary: Change in Infarct Volume From Day 5 (FLAIR) to Day 30 (FLAIR)

End point title	Change in Infarct Volume From Day 5 (FLAIR) to Day 30 (FLAIR)

End point description:

Relative growth of infarct volume from Day 5 (relative growth = FLAIR at Day 30 divided by FLAIR at Day 5). Geometric mean calculated as the exponential of the mean log relative growth.

End point type	Secondary

End point timeframe:

Day 5. Day 30

End point values	Modified intention to treat: Placebo	Modified intention to treat: Natalizumab		
Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed	64[14]	54[15]		
Units: mL				
geometric mean (inter-quartile range (Q1-Q3))	0.6 (0.52 to 0.79)	0.59 (0.42 to 0.81)		

Notes:

[14] - Subjects with assessments at both time points.

[15] - Subjects with assessments at both time points.

Statistical analyses

Statistical analysis title	Statistical Analysis 1

Statistical analysis description:

Treatment contrasts derived from a repeated measures mixed effects model modeling log relative growth relative to Day 5 using an autoregressive variance-covariance matrix structure. The model adjusts for for treatment, log baseline DWI volume, treatment time window, and tPA use.

Comparison groups	Modified intention to treat: Placebo v Modified intention to

	treat: Natalizumab
Number of subjects included in analysis	118
Analysis specification	Pre-specified
Analysis type	superiority
Parameter estimate	adjusted mean difference (log-scale)
Point estimate	-0.02
Confidence interval	
level	90 %
sides	2-sided
lower limit	-0.18
upper limit	0.13

Statistical analysis title	Statistical Analysis 2

Statistical analysis description:

Adjusted mean (log-scale) back-transformed to the original scale as the estimated ratio of natalizumab to placebo. 90% confidence interval (log-scale) back-transformed to the original scale and reflect the interval around the ratio.

Comparison groups	Modified intention to treat: Placebo v Modified intention to treat: Natalizumab
Number of subjects included in analysis	118
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.394 [16]
Method	repeated measures mixed effects model
Parameter estimate	ratio of relative growth
Point estimate	0.98
Confidence interval	
level	90 %
sides	2-sided
lower limit	0.84
upper limit	1.14

Notes:

[16] - one-sided p-value

Secondary: Change in National Institute of Health Stroke Scale (NIHSS) Score From Baseline to 24 Hours, Day 5, Day 30, and Day 90

End point title	Change in National Institute of Health Stroke Scale (NIHSS) Score From Baseline to 24 Hours, Day 5, Day 30, and Day 90

End point description:

The NIHSS is a systematic assessment tool that provides a quantitative measure of stroke-related neurologic deficit. Scores for the NIHSS range from 0 to 42, with 0 representing no symptoms and 42 representing death.

End point type	Secondary

End point timeframe:

Baseline, 24 hours, Day 5, Day 30, Day 90

End point values	Modified intention to treat: Placebo	Modified intention to treat: Natalizumab		
Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed	82[17]	77[18]		
Units: units on a scale				
arithmetic mean (standard deviation)				
Change at 24 hours; n=82, 77	-1.5 (± 3.96)	-1.5 (± 5.1)		
Change at Day 5; n=79, 72	-3.3 (± 5.31)	-2.1 (± 6.24)		
Change at Day 30; n=73, 62	-5.7 (± 5.22)	-4.9 (± 5.73)		
Change at Day 90; n=62, 56	-7.3 (± 3.95)	-6.8 (± 5.78)		

Notes:

[17] - n=subjects with assessments at Baseline and given time point.

[18] - n=subjects with assessments at Baseline and given time point.

Attachments (see zip file)	NIHSS Statistical Analyses/Statistical Analyses NIHSS Score

Statistical analyses

No statistical analyses for this end point

Secondary: Modified Rankin Scale (mRS) Distribution at Day 5, Day 30, and Day 90

End point title	Modified Rankin Scale (mRS) Distribution at Day 5, Day 30, and Day 90

End point description:

The mRS measures independence, rather than neurologic function, with specific tasks pre- and post-stroke, respectively. The scale consists of 7 grades, from 0 to 6, with 0 corresponding to no symptoms and 6 corresponding to death. The distribution of mRS scores was summarized at each timepoint. An excellent outcome on the mRS was defined as a score of 0 or 1, while a good outcome was defined as a score of 0, 1, or 2.

End point type	Secondary

End point timeframe:

Day 5, Day 30, and Day 90

End point values	Modified intention to treat: Placebo	Modified intention to treat: Natalizumab		
Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed	82[19]	77[20]		
Units: subjects				
Day 5: Score 0; n=82, 76	0	2		
Day 5: Score 1; n=82, 76	3	2		
Day 5: Score 2; n=82, 76	10	11		
Day 5: Score 3; n=82, 76	13	11		
Day 5: Score 4; n=82, 76	25	16		
Day 5: Score 5; n=82, 76	29	31		
Day 5: Score 6; n=82, 76	2	3		
Day 30: Score 0; n=81, 72	0	5		
Day 30: Score 1; n=81, 72	7	8		
Day 30: Score 2; n=81, 72	14	8		

Day 30: Score 3; n=81, 72	17	17		
Day 30: Score 4; n=81, 72	22	14		
Day 30: Score 5; n=81, 72	13	11		
Day 30: Score 6; n=81, 72	8	9		
Day 90: Score 0; n=78, 72	4	8		
Day 90: Score 1; n=78, 72	12	10		
Day 90: Score 2; n=78, 72	12	10		
Day 90: Score 3; n=78, 72	15	13		
Day 90: Score 4; n=78, 72	14	11		
Day 90: Score 5; n=78, 72	8	6		
Day 90: Score 6; n=78, 72	13	14		

Notes:

[19] - imputed data; n=number of subjects with an assessment at given time point.

[20] - imputed data; n=number of subjects with an assessment at given time point.

Attachments (see zip file)	Statistical Analyses mRS Day 5.pdf Statistical Analyses mRS Day 30.pdf Statistical Analyses mRS Day 90.pdf

Statistical analyses

No statistical analyses for this end point

Secondary: Barthel Index at Day 5, Day 30, and Day 90

End point title	Barthel Index at Day 5, Day 30, and Day 90

End point description:

The Barthel Index consists of 10 items that measure a person’s daily functioning, specifically the activities of daily living and mobility, and can be used to determine a baseline level of functioning and to monitor change in activities of daily living over time. The scores for each of the items are summed to create a total score up to a potential of 100, with higher scores representing a greater level of independence.

End point type	Secondary

End point timeframe:

Day 5, Day 30, and Day 90

End point values	Modified intention to treat: Placebo	Modified intention to treat: Natalizumab		
Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed	82[21]	77[22]		
Units: units on a scale				
median (full range (min-max))				
Day 5; n=78, 73	35 (0 to 100)	30 (0 to 100)		
Day 30; n=73, 60	70 (0 to 100)	80 (0 to 100)		
Day 90; n=61, 55	80 (0 to 100)	95 (0 to 100)		

Notes:

[21] - n=subjects with assessment at given time point.

[22] - n=subjects with assessment at given time point.

Attachments (see zip file)	Statistical Analyses Barthel Index.pdf

Statistical analyses

No statistical analyses for this end point

Secondary: Number of Subjects Who Experience Adverse Events (AEs) and Serious Adverse Events (SAEs)

End point title	Number of Subjects Who Experience Adverse Events (AEs) and Serious Adverse Events (SAEs)

End point description:

AE: any untoward medical occurrence that does not necessarily have a causal relationship with this treatment. SAE: any untoward medical occurrence that at any dose: results in death; in the view of the Investigator, places the subject at immediate risk of death (a life-threatening event); requires inpatient hospitalization or prolongation of existing hospitalization; results in persistent or significant disability/incapacity; results in a congenital anomaly/birth defect; any other medically important event that, in the opinion of the Investigator, may jeopardize the subject or may require intervention to prevent one of the other outcomes listed in the definition above. Events were categorized as severe, moderate, or mild, and related or not related to study treatment.

End point type	Secondary

End point timeframe:

Up to Day 90 ± 5 days

End point values	Safety population: Placebo	Safety population: Natalizumab		
Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed	82	78		
Units: subjects				
Subjects with an event	81	77		
Subjects with a moderate or severe event	60	53		
Subjects with a severe event	27	22		
Subjects with a related event	7	6		
Subjects with a serious event	38	36		
Subjects discontinuing due to an event	0	0		
Subjects withdrawing from study due to event	2	1		

Statistical analyses

No statistical analyses for this end point

Adverse events

Adverse events information

Timeframe for reporting adverse events:

From informed consent (SAE) or initiation of study drug (AE) until Final Visit Day 90 ± 5 days or early termination follow-up.

Assessment type	Systematic

Dictionary used

Dictionary name	MedDRA
Dictionary version	17.1

Reporting groups

Reporting group title	Natalizumab

Reporting group description:

300 mg single IV injection of natalizumab

Reporting group title	Placebo

Reporting group description:

A single IV injection of placebo

Serious adverse events	Natalizumab	Placebo	
Total subjects affected by serious adverse events			
subjects affected / exposed	36 / 78 (46.15%)	38 / 82 (46.34%)	
number of deaths (all causes)	14	13	
number of deaths resulting from adverse events			
Neoplasms benign, malignant and unspecified (incl cysts and polyps)			
Cholangiocarcinoma			
subjects affected / exposed	1 / 78 (1.28%)	0 / 82 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 1	0 / 0	
Glioma			
subjects affected / exposed	0 / 78 (0.00%)	1 / 82 (1.22%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 1	
Vascular disorders			
Peripheral embolism			
subjects affected / exposed	0 / 78 (0.00%)	1 / 82 (1.22%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 1	
Peripheral ischaemia			

subjects affected / exposed	0 / 78 (0.00%)	1 / 82 (1.22%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Surgical and medical procedures			
Endarterectomy			
subjects affected / exposed	0 / 78 (0.00%)	1 / 82 (1.22%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
General disorders and administration site conditions			
Death			
subjects affected / exposed	1 / 78 (1.28%)	0 / 82 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 1	0 / 0	
Device dislocation			
subjects affected / exposed	1 / 78 (1.28%)	0 / 82 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Multi-organ failure			
subjects affected / exposed	2 / 78 (2.56%)	0 / 82 (0.00%)	
occurrences causally related to treatment / all	1 / 2	0 / 0	
deaths causally related to treatment / all	1 / 2	0 / 0	
Respiratory, thoracic and mediastinal disorders			
Acute respiratory failure			
subjects affected / exposed	1 / 78 (1.28%)	1 / 82 (1.22%)	
occurrences causally related to treatment / all	0 / 2	0 / 1	
deaths causally related to treatment / all	0 / 2	0 / 1	
Pneumonia aspiration			
subjects affected / exposed	1 / 78 (1.28%)	1 / 82 (1.22%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	0 / 1	0 / 0	
Respiratory distress			

subjects affected / exposed	0 / 78 (0.00%)	1 / 82 (1.22%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 1	
Respiratory failure			
subjects affected / exposed	2 / 78 (2.56%)	0 / 82 (0.00%)	
occurrences causally related to treatment / all	0 / 2	0 / 0	
deaths causally related to treatment / all	0 / 2	0 / 0	
Psychiatric disorders			
Aggression			
subjects affected / exposed	0 / 78 (0.00%)	1 / 82 (1.22%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Delirium			
subjects affected / exposed	0 / 78 (0.00%)	2 / 82 (2.44%)	
occurrences causally related to treatment / all	0 / 0	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Injury, poisoning and procedural complications			
Avulsion fracture			
subjects affected / exposed	1 / 78 (1.28%)	0 / 82 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Brain herniation			
subjects affected / exposed	1 / 78 (1.28%)	1 / 82 (1.22%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	0 / 1	0 / 1	
Fall			
subjects affected / exposed	0 / 78 (0.00%)	1 / 82 (1.22%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Femur fracture			
subjects affected / exposed	0 / 78 (0.00%)	2 / 82 (2.44%)	
occurrences causally related to treatment / all	0 / 0	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	

Hip fracture			
subjects affected / exposed	1 / 78 (1.28%)	0 / 82 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cardiac disorders			
Acute myocardial infarction			
subjects affected / exposed	0 / 78 (0.00%)	1 / 82 (1.22%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Atrial fibrillation			
subjects affected / exposed	1 / 78 (1.28%)	0 / 82 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cardiac arrest			
subjects affected / exposed	1 / 78 (1.28%)	0 / 82 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 1	0 / 0	
Cardiac failure			
subjects affected / exposed	0 / 78 (0.00%)	2 / 82 (2.44%)	
occurrences causally related to treatment / all	0 / 0	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 1	
Cardiac failure chronic			
subjects affected / exposed	0 / 78 (0.00%)	1 / 82 (1.22%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Intracardiac thrombus			
subjects affected / exposed	1 / 78 (1.28%)	0 / 82 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Myocardial infarction			
subjects affected / exposed	0 / 78 (0.00%)	2 / 82 (2.44%)	
occurrences causally related to treatment / all	0 / 0	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 1	
Pulseless electrical activity			

subjects affected / exposed	0 / 78 (0.00%)	1 / 82 (1.22%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 1	
Ventricular tachycardia			
subjects affected / exposed	1 / 78 (1.28%)	0 / 82 (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			
Basilar artery thrombosis			
subjects affected / exposed	0 / 78 (0.00%)	1 / 82 (1.22%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 1	
Brain midline shift			
subjects affected / exposed	1 / 78 (1.28%)	1 / 82 (1.22%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Brain oedema			
subjects affected / exposed	1 / 78 (1.28%)	2 / 82 (2.44%)	
occurrences causally related to treatment / all	0 / 1	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Carotid artery stenosis			
subjects affected / exposed	3 / 78 (3.85%)	1 / 82 (1.22%)	
occurrences causally related to treatment / all	0 / 3	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cerebral infarction			
subjects affected / exposed	4 / 78 (5.13%)	2 / 82 (2.44%)	
occurrences causally related to treatment / all	0 / 4	0 / 2	
deaths causally related to treatment / all	0 / 1	0 / 1	
Cerebral ischaemia			
subjects affected / exposed	1 / 78 (1.28%)	1 / 82 (1.22%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cerebrovascular accident			

subjects affected / exposed	2 / 78 (2.56%)	2 / 82 (2.44%)	
occurrences causally related to treatment / all	1 / 2	0 / 2	
deaths causally related to treatment / all	0 / 1	0 / 1	
Convulsion			
subjects affected / exposed	2 / 78 (2.56%)	0 / 82 (0.00%)	
occurrences causally related to treatment / all	0 / 2	0 / 0	
deaths causally related to treatment / all	0 / 2	0 / 0	
Dementia			
subjects affected / exposed	1 / 78 (1.28%)	0 / 82 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Dementia alzheimer's type			
subjects affected / exposed	0 / 78 (0.00%)	1 / 82 (1.22%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Encephalopathy			
subjects affected / exposed	1 / 78 (1.28%)	0 / 82 (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 / 78 (1.28%)	0 / 82 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Generalised non-convulsive epilepsy			
subjects affected / exposed	1 / 78 (1.28%)	0 / 82 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Haemorrhage intracranial			
subjects affected / exposed	1 / 78 (1.28%)	0 / 82 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Haemorrhagic transformation stroke			

subjects affected / exposed	4 / 78 (5.13%)	3 / 82 (3.66%)	
occurrences causally related to treatment / all	0 / 6	0 / 4	
deaths causally related to treatment / all	0 / 0	0 / 0	
Headache			
subjects affected / exposed	0 / 78 (0.00%)	1 / 82 (1.22%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Intracranial pressure increased			
subjects affected / exposed	1 / 78 (1.28%)	0 / 82 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 1	0 / 0	
Ischaemic stroke			
subjects affected / exposed	1 / 78 (1.28%)	1 / 82 (1.22%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	0 / 1	0 / 0	
Nervous system disorder			
subjects affected / exposed	1 / 78 (1.28%)	0 / 82 (0.00%)	
occurrences causally related to treatment / all	0 / 2	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Neurological decompensation			
subjects affected / exposed	1 / 78 (1.28%)	2 / 82 (2.44%)	
occurrences causally related to treatment / all	0 / 1	0 / 2	
deaths causally related to treatment / all	0 / 1	0 / 1	
Partial seizures			
subjects affected / exposed	0 / 78 (0.00%)	1 / 82 (1.22%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Stroke in evolution			
subjects affected / exposed	2 / 78 (2.56%)	0 / 82 (0.00%)	
occurrences causally related to treatment / all	0 / 2	0 / 0	
deaths causally related to treatment / all	0 / 1	0 / 0	
Subdural hygroma			

subjects affected / exposed	0 / 78 (0.00%)	1 / 82 (1.22%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Vocal cord paralysis			
subjects affected / exposed	0 / 78 (0.00%)	1 / 82 (1.22%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Blood and lymphatic system disorders			
Splenic haemorrhage			
subjects affected / exposed	1 / 78 (1.28%)	0 / 82 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hepatobiliary disorders			
Cholecystitis acute			
subjects affected / exposed	0 / 78 (0.00%)	1 / 82 (1.22%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 1	
Renal and urinary disorders			
Renal failure			
subjects affected / exposed	0 / 78 (0.00%)	1 / 82 (1.22%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 1	
Renal failure chronic			
subjects affected / exposed	0 / 78 (0.00%)	1 / 82 (1.22%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Endocrine disorders			
Toxic nodular goitre			
subjects affected / exposed	0 / 78 (0.00%)	1 / 82 (1.22%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Infections and infestations			
Diverticulitis			

subjects affected / exposed	0 / 78 (0.00%)	1 / 82 (1.22%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Endocarditis			
subjects affected / exposed	0 / 78 (0.00%)	1 / 82 (1.22%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 1	
Gastroenteritis			
subjects affected / exposed	1 / 78 (1.28%)	0 / 82 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Influenza			
subjects affected / exposed	1 / 78 (1.28%)	0 / 82 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 1	0 / 0	
Pneumonia			
subjects affected / exposed	3 / 78 (3.85%)	2 / 82 (2.44%)	
occurrences causally related to treatment / all	2 / 4	0 / 2	
deaths causally related to treatment / all	1 / 3	0 / 0	
Respiratory tract infection			
subjects affected / exposed	1 / 78 (1.28%)	1 / 82 (1.22%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	0 / 1	0 / 0	
Septic shock			
subjects affected / exposed	1 / 78 (1.28%)	0 / 82 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	1 / 1	0 / 0	
Urinary tract infection			
subjects affected / exposed	0 / 78 (0.00%)	2 / 82 (2.44%)	
occurrences causally related to treatment / all	0 / 0	1 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Urinary tract infection pseudomonal			

subjects affected / exposed	0 / 78 (0.00%)	1 / 82 (1.22%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Metabolism and nutrition disorders			
Dehydration			
subjects affected / exposed	0 / 78 (0.00%)	1 / 82 (1.22%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hyponatraemia			
subjects affected / exposed	0 / 78 (0.00%)	1 / 82 (1.22%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	

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

Non-serious adverse events	Natalizumab	Placebo	
Total subjects affected by non-serious adverse events			
subjects affected / exposed	68 / 78 (87.18%)	75 / 82 (91.46%)	
Vascular disorders			
Hypertension			
subjects affected / exposed	15 / 78 (19.23%)	10 / 82 (12.20%)	
occurrences (all)	16	11	
Hypotension			
subjects affected / exposed	2 / 78 (2.56%)	12 / 82 (14.63%)	
occurrences (all)	3	13	
General disorders and administration site conditions			
Pain			
subjects affected / exposed	9 / 78 (11.54%)	6 / 82 (7.32%)	
occurrences (all)	9	6	
Pyrexia			
subjects affected / exposed	32 / 78 (41.03%)	26 / 82 (31.71%)	
occurrences (all)	34	30	
Psychiatric disorders			
Agitation			

subjects affected / exposed	11 / 78 (14.10%)	3 / 82 (3.66%)	
occurrences (all)	12	4	
Anxiety			
subjects affected / exposed	6 / 78 (7.69%)	1 / 82 (1.22%)	
occurrences (all)	6	1	
Depression			
subjects affected / exposed	5 / 78 (6.41%)	13 / 82 (15.85%)	
occurrences (all)	5	14	
Insomnia			
subjects affected / exposed	7 / 78 (8.97%)	13 / 82 (15.85%)	
occurrences (all)	7	13	
Post stroke depression			
subjects affected / exposed	4 / 78 (5.13%)	2 / 82 (2.44%)	
occurrences (all)	4	2	
Sleep disorder			
subjects affected / exposed	8 / 78 (10.26%)	7 / 82 (8.54%)	
occurrences (all)	10	7	
Investigations			
Alanine aminotransferase increased			
subjects affected / exposed	5 / 78 (6.41%)	1 / 82 (1.22%)	
occurrences (all)	5	1	
Aspartate aminotransferase increased			
subjects affected / exposed	4 / 78 (5.13%)	2 / 82 (2.44%)	
occurrences (all)	4	2	
Gamma-glutamyltransferase increased			
subjects affected / exposed	4 / 78 (5.13%)	5 / 82 (6.10%)	
occurrences (all)	4	5	
Injury, poisoning and procedural complications			
Fall			
subjects affected / exposed	8 / 78 (10.26%)	4 / 82 (4.88%)	
occurrences (all)	9	4	
Cardiac disorders			
Atrial fibrillation			
subjects affected / exposed	7 / 78 (8.97%)	10 / 82 (12.20%)	
occurrences (all)	7	10	

Bradycardia			
subjects affected / exposed	1 / 78 (1.28%)	5 / 82 (6.10%)	
occurrences (all)	1	6	
Tachycardia			
subjects affected / exposed	3 / 78 (3.85%)	5 / 82 (6.10%)	
occurrences (all)	3	5	
Nervous system disorders			
Brain oedema			
subjects affected / exposed	6 / 78 (7.69%)	3 / 82 (3.66%)	
occurrences (all)	6	3	
Cerebral haemorrhage			
subjects affected / exposed	4 / 78 (5.13%)	0 / 82 (0.00%)	
occurrences (all)	4	0	
Haemorrhagic transformation stroke			
subjects affected / exposed	18 / 78 (23.08%)	21 / 82 (25.61%)	
occurrences (all)	18	21	
Headache			
subjects affected / exposed	13 / 78 (16.67%)	19 / 82 (23.17%)	
occurrences (all)	13	21	
Neurological decompensation			
subjects affected / exposed	4 / 78 (5.13%)	2 / 82 (2.44%)	
occurrences (all)	4	2	
Somnolence			
subjects affected / exposed	4 / 78 (5.13%)	3 / 82 (3.66%)	
occurrences (all)	4	3	
Blood and lymphatic system disorders			
Anaemia			
subjects affected / exposed	8 / 78 (10.26%)	4 / 82 (4.88%)	
occurrences (all)	9	5	
Gastrointestinal disorders			
Constipation			
subjects affected / exposed	24 / 78 (30.77%)	23 / 82 (28.05%)	
occurrences (all)	29	23	
Nausea			
subjects affected / exposed	9 / 78 (11.54%)	11 / 82 (13.41%)	
occurrences (all)	9	11	
Vomiting			

subjects affected / exposed	5 / 78 (6.41%)	15 / 82 (18.29%)	
occurrences (all)	5	15	
Renal and urinary disorders			
Urinary retention			
subjects affected / exposed	5 / 78 (6.41%)	6 / 82 (7.32%)	
occurrences (all)	5	6	
Musculoskeletal and connective tissue disorders			
Back pain			
subjects affected / exposed	4 / 78 (5.13%)	6 / 82 (7.32%)	
occurrences (all)	5	6	
Pain in extremity			
subjects affected / exposed	4 / 78 (5.13%)	4 / 82 (4.88%)	
occurrences (all)	4	4	
Infections and infestations			
Pneumonia			
subjects affected / exposed	10 / 78 (12.82%)	6 / 82 (7.32%)	
occurrences (all)	11	6	
Respiratory tract infection			
subjects affected / exposed	4 / 78 (5.13%)	9 / 82 (10.98%)	
occurrences (all)	4	9	
Urinary tract infection			
subjects affected / exposed	19 / 78 (24.36%)	13 / 82 (15.85%)	
occurrences (all)	24	16	
Metabolism and nutrition disorders			
Diabetes mellitus			
subjects affected / exposed	4 / 78 (5.13%)	2 / 82 (2.44%)	
occurrences (all)	4	2	
Hypercholesterolaemia			
subjects affected / exposed	6 / 78 (7.69%)	3 / 82 (3.66%)	
occurrences (all)	6	3	
Hyperglycaemia			
subjects affected / exposed	9 / 78 (11.54%)	3 / 82 (3.66%)	
occurrences (all)	9	5	
Hypokalaemia			
subjects affected / exposed	10 / 78 (12.82%)	10 / 82 (12.20%)	
occurrences (all)	10	10	

Hyponatraemia subjects affected / exposed occurrences (all)	3 / 78 (3.85%) 3	5 / 82 (6.10%) 5	

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? No

Interruptions (globally)

Were there any global interruptions to the trial? No

Limitations and caveats

None reported