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

Summary

EudraCT number	2015-004783-11
Trial protocol	ES DE GB
Global end of trial date	20 November 2017

Results information

Result version number	v1 (current)
This version publication date	14 November 2018
First version publication date	14 November 2018

Trial information

Trial identification

Sponsor protocol code	101SK202

Additional study identifiers

ISRCTN number	-
ClinicalTrials.gov id (NCT number)	NCT02730455
WHO universal trial number (UTN)	-

Notes:

Sponsors

Sponsor organisation name	Biogen
Sponsor organisation address	250 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	20 November 2017
Is this the analysis of the primary completion data?	No

Global end of trial reached?	Yes
Global end of trial date	20 November 2017
Was the trial ended prematurely?	No

Notes:

General information about the trial

Main objective of the trial:

The primary objective of the study was to assess the clinical effects of natalizumab versus placebo in acute ischemic stroke on clinical measures of functional independence and activities of daily living.

Protection of trial subjects:

Written informed consent was obtained from each subject prior to evaluations 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.

Background therapy: -

Evidence for comparator: -

Actual start date of recruitment	18 July 2016
Long term follow-up planned	Yes
Long term follow-up rationale	Safety, Efficacy
Long term follow-up duration	2 Months
Independent data monitoring committee (IDMC) involvement?	No

Notes:

Population of trial subjects

Subjects enrolled per country

Country: Number of subjects enrolled	United States: 83
Country: Number of subjects enrolled	United Kingdom: 24
Country: Number of subjects enrolled	Spain: 88
Country: Number of subjects enrolled	Germany: 82
Worldwide total number of subjects	277
EEA total number of subjects	194

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)	104
From 65 to 84 years	173
85 years and over	0

Subject disposition

Recruitment

Recruitment details:

Subjects were recruited from 19 sites in Germany, 4 sites in the United Kingdom (UK), 12 sites in Spain, and 18 sites in the United States (US).

Pre-assignment

Screening details:

A total of 277 subjects with acute ischemic stroke were randomised into the study (94 subjects in the placebo group, 91 subjects in the natalizumab 300 mg group, and 92 subjects in the natalizumab 600 mg group).

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, Carer, Assessor

Arms

Are arms mutually exclusive?	Yes
Arm title	Placebo

Arm description:

Single dose of matching placebo intravenous (IV) to natalizumab on Day 1 at one of two treatment windows, either within 9 hours or between 9-24 hours from when the subject was last known normal (LKN).

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:

Single IV dose of matching placebo to natalizumab on Day 1

Arm title	Natalizumab 300 mg IV

Arm description:

Single 300 mg natalizumab IV on Day 1 at one of two treatment windows, either within 9 hours or between 9-24 hours from when the subject was last known normal (LKN).

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

Dosage and administration details:

Single IV dose of 300 mg natalizumab on Day 1

Arm title	Natalizumab 600 mg IV

Arm description:

Single 600 mg natalizumab IV on Day 1 at one of two treatment windows, either within 9 hours or between 9-24 hours from when the subject was last known normal (LKN).

Arm type	Experimental

Investigational medicinal product name	Natalizumab
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Concentrate for solution for infusion
Routes of administration	Intravenous use

Dosage and administration details:

Single IV dose of 600 mg natalizumab on Day 1

Number of subjects in period 1	Placebo	Natalizumab 300 mg IV	Natalizumab 600 mg IV
Started	94	91	92
Safety population	91	90	89
Subjects dosed	91	88	91
Who received total volume of study drug	90	88	89
Completed	81	77	81
Not completed	13	14	11
Death	5	6	4
Other	1	1	2
Unknown	2	2	-
Lost to follow-up	3	1	4
Consent withdrawn	2	4	1

Baseline characteristics

Reporting groups	
Reporting group title	Placebo
Reporting group description:	
Single dose of matching placebo intravenous (IV) to natalizumab on Day 1 at one of two treatment windows, either within 9 hours or between 9-24 hours from when the subject was last known normal (LKN).	
Reporting group title	Natalizumab 300 mg IV
Reporting group description:	
Single 300 mg natalizumab IV on Day 1 at one of two treatment windows, either within 9 hours or between 9-24 hours from when the subject was last known normal (LKN).	
Reporting group title	Natalizumab 600 mg IV
Reporting group description:	
Single 600 mg natalizumab IV on Day 1 at one of two treatment windows, either within 9 hours or between 9-24 hours from when the subject was last known normal (LKN).	

Reporting group values	Placebo	Natalizumab 300 mg IV	Natalizumab 600 mg IV
Number of subjects	94	91	92
Age categorical			
Units: Subjects			
Age Continuous			
Units: years			
arithmetic mean	67.1	66.1	65.6
standard deviation	± 9.54	± 10.47	± 11.09
Sex: Female, Male			
Units: Subjects			
Female	29	36	37
Male	65	55	55
Ethnicity			
Units: Subjects			
Hispanic or Latino	2	2	3
Not Hispanic or Latino	28	24	24
Unknown or Not Reported	64	65	65
Race			
Units: Subjects			
Black or African American	2	1	1
White	27	25	25
Not Reported Due to Confidentiality Regulations	64	65	65
Missing	1	0	1

Reporting group values	Total		
Number of subjects	277		
Age categorical			
Units: Subjects			

Age Continuous Units: years arithmetic mean standard deviation	- 		
Sex: Female, Male Units: Subjects			
Female	102		
Male	175		
Ethnicity Units: Subjects			
Hispanic or Latino	7		
Not Hispanic or Latino	76		
Unknown or Not Reported	194		
Race Units: Subjects			
Black or African American	4		
White	77		
Not Reported Due to Confidentiality Regulations	194		
Missing	2		

End points

End points reporting groups

Reporting group title	Placebo
Reporting group description:	
Single dose of matching placebo intravenous (IV) to natalizumab on Day 1 at one of two treatment windows, either within 9 hours or between 9-24 hours from when the subject was last known normal (LKN).	
Reporting group title	Natalizumab 300 mg IV
Reporting group description:	
Single 300 mg natalizumab IV on Day 1 at one of two treatment windows, either within 9 hours or between 9-24 hours from when the subject was last known normal (LKN).	
Reporting group title	Natalizumab 600 mg IV
Reporting group description:	
Single 600 mg natalizumab IV on Day 1 at one of two treatment windows, either within 9 hours or between 9-24 hours from when the subject was last known normal (LKN).	

Primary: Percentage of Subjects With Composite Global Measure of Functional Disability Based at Day 90

End point title	Percentage of Subjects With Composite Global Measure of Functional Disability Based at Day 90
End point description:	
The composite global measure of functional disability excellent outcome was based on a score of 0 or 1 on the modified Rankin Scale (mRS) and a score of >=95 on the Barthel Index (BI). mRS measures independence, rather than neurological function, with specific tasks pre- and post-stroke. The scale consists of 7 grades, from 0 to 6, with 0 corresponding to no symptoms and 6 corresponding to death. BI consists of 10 items that measure a subject's daily functioning, specifically the activities of daily living and mobility. The items include feeding, moving from wheelchair to bed and returning, grooming, transferring to and from a toilet, bathing, walking on a level surface, going up and down stairs, dressing, and maintaining continence of bowels and bladder. Scores for each of the items are summed to create a total score of 0 to 100. Higher the score, more "independent" the subject is. Modified Intent-to-Treat (MITT) population. N=subjects evaluable with data available for analysis.	
End point type	Primary
End point timeframe:	
Day 90	

End point values	Placebo	Natalizumab 300 mg IV	Natalizumab 600 mg IV	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	90	88	89	
Units: percentage of subjects				
number (not applicable)	54.1	41.5	39.9	

Statistical analyses

Statistical analysis title	Placebo vs Natalizumab 300 mg IV
Statistical analysis description:	
Composite Measure: The global odds ratio was based on a linear logistic regression model with baseline	

National Institute of Health Stroke Scale (NIHSS) category (score 5-15, 16-23), age (<60, 60-69, 70-80), tissue plasminogen activator (tPA) use (yes/no), treatment window (<=9, >9 and <=24hours), thrombectomy (yes/no) and region (Spain, UK/Germany, United States of America [USA]) as covariates and unstructured working correlation structure

Comparison groups	Placebo v Natalizumab 300 mg IV
Number of subjects included in analysis	178
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.086
Method	Regression, Logistic
Parameter estimate	Odds ratio (OR)
Point estimate	0.64
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.38
upper limit	1.07

Statistical analysis title	Placebo vs Natalizumab 600 mg IV

Statistical analysis description:

Composite Measure: The global odds ratio was based on a linear logistic regression model with baseline NIHSS category (score 5-15, 16-23), age (<60, 60-69, 70-80), tPA use (yes/no), treatment window (<=9, >9 and <=24hours), thrombectomy (yes/no) and region (Spain, UK/Germany, USA) as covariates and unstructured working correlation structure

Comparison groups	Placebo v Natalizumab 600 mg IV
Number of subjects included in analysis	179
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.031
Method	Regression, Logistic
Parameter estimate	Odds ratio (OR)
Point estimate	0.57
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.34
upper limit	0.95

Secondary: Percentage of Subjects With Excellent Outcome in mRS Score at Day 90

End point title	Percentage of Subjects With Excellent Outcome in mRS Score at Day 90

End point description:

Excellent mRS is defined as mRS score of 0 or 1. mRS measures independence, rather than neurological function, with specific tasks pre- and poststroke. The scale consists of 7 grades, from 0 to 6, with 0 corresponding to no symptoms and 6 corresponding to death. MITT population: all randomised subjects who had received entire infusion of study treatment. Subjects who were accidentally enrolled based on conditions that mimicked stroke symptom at presentation were excluded from MITT population. Number of subject analysed is number of subjects with data available for analysis.

End point type	Secondary

End point timeframe:

Day 90

End point values	Placebo	Natalizumab 300 mg IV	Natalizumab 600 mg IV	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	86	83	82	
Units: percentage of subjects				
number (not applicable)	41	29	26	

Statistical analyses

Statistical analysis title	mRS Score: Placebo vs Natalizumab 300 mg IV

Statistical analysis description:

The odds ratio was based on a linear logistic regression model with baseline NIHSS category (score 5-15, 16-23), age (<60, 60-69, 70-80), tPA use (yes/no), treatment window (<=9, >9 and <=24hours), thrombectomy (yes/no) and region (Spain, UK/Germany, USA) as covariates and unstructured working correlation structure.

Comparison groups	Placebo v Natalizumab 300 mg IV
Number of subjects included in analysis	169
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.222
Method	Regression, Logistic
Parameter estimate	Odds ratio (OR)
Point estimate	0.67
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.35
upper limit	1.28

Statistical analysis title	mRS Score: Placebo vs Natalizumab 600 mg IV

Statistical analysis description:

The odds ratio was based on a linear logistic regression model with baseline NIHSS category (score 5-15, 16-23), age (<60, 60-69, 70-80), tPA use (yes/no), treatment window (<=9, >9 and <=24hours), thrombectomy (yes/no) and region (Spain, UK/Germany, USA) as covariates and unstructured working correlation structure.

Comparison groups	Placebo v Natalizumab 600 mg IV
Number of subjects included in analysis	168
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.073
Method	Regression, Logistic
Parameter estimate	Odds ratio (OR)
Point estimate	0.54

Confidence interval	
level	95 %
sides	2-sided
lower limit	0.28
upper limit	1.06

Secondary: Percentage of Subjects With Excellent Outcome in BI Score at Day 90

End point title	Percentage of Subjects With Excellent Outcome in BI Score at Day 90

End point description:

Excellent BI outcome is defined as a score of >=95. BI consists of 10 items that measure a subject's daily functioning, specifically the activities of daily living and mobility. The items include feeding, moving from wheelchair to bed and returning, grooming, transferring to and from a toilet, bathing, walking on a level surface, going up and down stairs, dressing, and maintaining continence of bowels and bladder. The scores for each of the items are summed to create a total score of 0 to 100. The higher the score, the more "independent" the subject is. MITT population: all randomised subjects who had received entire infusion of study treatment. Subjects who were accidentally enrolled based on conditions that mimicked stroke symptom at presentation were excluded from MITT population. Number of subject analysed is number of subjects with data available for analysis.

End point type	Secondary

End point timeframe:

Day 90

End point values	Placebo	Natalizumab 300 mg IV	Natalizumab 600 mg IV	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	86	81	81	
Units: percentage of subjects				
number (not applicable)	67	54	54	

Statistical analyses

Statistical analysis title	BI Score: Placebo vs Natalizumab 300 mg IV

Statistical analysis description:

The odds ratio was based on a linear logistic regression model with baseline NIHSS category (score 5-15, 16-23), age (<60, 60-69, 70-80), tPA use (yes/no), treatment window (<=9, >9 and <=24hours), thrombectomy (yes/no) and region (Spain, UK/Germany, USA) as covariates and unstructured working correlation structure.

Comparison groups	Placebo v Natalizumab 300 mg IV
Number of subjects included in analysis	167
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.085
Method	Regression, Logistic
Parameter estimate	Odds ratio (OR)
Point estimate	0.56

Confidence interval	
level	95 %
sides	2-sided
lower limit	0.29
upper limit	1.08

Statistical analysis title	BI Score: Placebo vs Natalizumab 600 mg IV

Statistical analysis description:

The odds ratio was based on a linear logistic regression model with baseline NIHSS category (score 5-15, 16-23), age (<60, 60-69, 70-80), tPA use (yes/no), treatment window (<=9, >9 and <=24hours), thrombectomy (yes/no) and region (Spain, UK/Germany, USA) as covariates and unstructured working correlation structure.

Comparison groups	Placebo v Natalizumab 600 mg IV
Number of subjects included in analysis	167
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.067
Method	Regression, Logistic
Parameter estimate	Odds ratio (OR)
Point estimate	0.54
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.28
upper limit	1.04

Secondary: Stroke Impact Scale-16 (SIS-16) Score Using a Repeated Measures Mixed Effects Model at Day 90

End point title	Stroke Impact Scale-16 (SIS-16) Score Using a Repeated Measures Mixed Effects Model at Day 90

End point description:

The SIS-16 is a 16-item physical dimension instrument that was developed as a brief, stand-alone tool for measuring the physical aspects of stroke recovery. The 16 physical aspects are rated on a 1 to 5 scale as follows: not difficult at all (5), a little difficult (4), somewhat difficult (3), very difficult (2), and could not do at all (1). Total score range is 16 to 80, with higher scores indicating higher levels of health-related quality of life and function. MITT population: all randomised subjects who had received entire infusion of study treatment. Subjects who were accidentally enrolled based on conditions that mimicked stroke symptom at presentation were excluded from MITT population. Number of subject analysed is number of subjects with data available for analysis.

End point type	Secondary

End point timeframe:

Day 90

End point values	Placebo	Natalizumab 300 mg IV	Natalizumab 600 mg IV	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	84	80	77	
Units: score on a scale				
arithmetic mean (standard deviation)	76.21 (± 30.783)	66.96 (± 35.493)	68.10 (± 31.461)	

Statistical analyses

Statistical analysis title	SIS-16 Score: Placebo vs Natalizumab 300 mg IV

Statistical analysis description:

Treatment and treatment by visit interaction were included in the model as explanatory variables. Baseline NIHSS category (score 5-15, 16-23), tPA use (yes/no), age (<60, 60-69, 70-80), thrombectomy (yes/no), region (Spain, UK/Germany, USA) and treatment window were considered as covariates. An unstructured variance-covariance matrix was used in the model.

Comparison groups	Placebo v Natalizumab 300 mg IV
Number of subjects included in analysis	164
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.106
Method	Mixed-effects model for repeated measure
Parameter estimate	Adjusted Mean Difference
Point estimate	-7.7
Confidence interval	
level	95 %
sides	2-sided
lower limit	-16.97
upper limit	1.64

Statistical analysis title	SIS-16 Score: Placebo vs Natalizumab 600 mg IV

Statistical analysis description:

Treatment and treatment by visit interaction were included in the model as explanatory variables. Baseline NIHSS category (score 5-15, 16-23), tPA use (yes/no), age (<60, 60-69, 70-80), thrombectomy (yes/no), region (Spain, UK/Germany, USA) and treatment window were considered as covariates. An unstructured variance-covariance matrix was used in the model.

Comparison groups	Placebo v Natalizumab 600 mg IV
Number of subjects included in analysis	161
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.202
Method	Mixed-effects model for repeated measure
Parameter estimate	Adjusted Mean Difference
Point estimate	-6.1
Confidence interval	
level	95 %
sides	2-sided
lower limit	-15.43
upper limit	3.27

Secondary: Montreal Cognitive Assessment (MoCA) Score at Day 90

End point title	Montreal Cognitive Assessment (MoCA) Score at Day 90

End point description:

The MoCA is a global cognitive screening test with favorable psychometric properties It screens 8 domains: visuospatial/executive, naming, memory, attention, language, abstraction, delayed recall, and orientation. Time to administer the MoCA is approximately 10 minutes. The total possible score is 0 to 30 points; a score of 26 or above is considered normal, <10 (severe cognitive impairment), 10-17 (moderate cognitive impairment) and >=18 (mild cognitive impairment). MITT population: all randomised subjects who had received entire infusion of study treatment. Subjects who were accidentally enrolled based on conditions that mimicked stroke symptom at presentation were excluded from MITT population. Number analysed is number of subjects with data available for analysis.

End point type	Secondary

End point timeframe:

Day 90

End point values	Placebo	Natalizumab 300 mg IV	Natalizumab 600 mg IV	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	69	74	69	
Units: scores on a scale				
arithmetic mean (standard deviation)	21.23 (± 8.412)	20.73 (± 8.141)	20.90 (± 8.223)	

Statistical analyses

Statistical analysis title	MoCA: Palcebo vs Natalizumab 300 mg IV

Statistical analysis description:

Treatment and treatment by visit interaction were included in the model as explanatory variables. Baseline NIHSS category (score 5-15, 16-23), tPA use (yes/no), age (<60, 60-69, 70-80), thrombectomy (yes/no), region (Spain, UK/Germany, USA) and treatment window were considered as covariates. An unstructured variance-covariance matrix was used in the model.

Comparison groups	Placebo v Natalizumab 300 mg IV
Number of subjects included in analysis	143
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.78
Method	Mixed-effects model for repeated measure
Parameter estimate	Adjusted Mean Difference
Point estimate	-0.3
Confidence interval	
level	95 %
sides	2-sided
lower limit	-2.64
upper limit	1.99

Statistical analysis title	MoCA: Placebo vs Natalizumab 600 mg IV

Statistical analysis description:

Treatment and treatment by visit interaction were included in the model as explanatory variables. Baseline NIHSS category (score 5-15, 16-23), tPA use (yes/no), age (<60, 60-69, 70-80), thrombectomy (yes/no), region (Spain, UK/Germany, USA) and treatment window were considered as covariates. An unstructured variance-covariance matrix was used in the model.

Comparison groups	Placebo v Natalizumab 600 mg IV
Number of subjects included in analysis	138
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.622
Method	Mixed-effects model for repeated measure
Parameter estimate	Adjusted Mean Difference
Point estimate	-0.6
Confidence interval	
level	95 %
sides	2-sided
lower limit	-2.89
upper limit	1.73

Secondary: Change From Baseline in National Institute of Health Stroke Scale (NIHSS) Score at Day 90

End point title	Change From Baseline in National Institute of Health Stroke Scale (NIHSS) Score at Day 90

End point description:

The NIHSS is a reliable tool for rapidly evaluating the effects of acute cerebral infarction. A trained observer rates the subject's ability to answer questions and perform activities relating to level of consciousness, language, visual-field loss, extraocular movement, motor strength, ataxia, dysarthria, sensory loss, and extinction and inattention (formerly neglect). There are 15 items. Total score ranges from 0 as normal to a maximum possible total severity score of 42 for all items. Higher the score, more the severity. A negative change from Baseline indicates improvement. MITT population: all randomised subjects who had received entire infusion of study treatment. Subjects who were accidentally enrolled based on conditions that mimicked stroke symptom at presentation were excluded from MITT population. Number of subject analysed is number of subjects with data available for analysis.

End point type	Secondary

End point timeframe:

Baseline, Day 90

End point values	Placebo	Natalizumab 300 mg IV	Natalizumab 600 mg IV	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	77	76	71	
Units: score on a scale				
arithmetic mean (standard deviation)	-6.14 (± 6.920)	-5.17 (± 7.937)	-6.28 (± 6.510)	

Statistical analyses

Statistical analysis title	Placebo vs Natalizumab 300 mg IV

Statistical analysis description:

Treatment and treatment by visit interaction were included in the model as explanatory variables. Baseline NIHSS category (score 5-15, 16-23), tPA use (yes/no), age (<60, 60-69, 70-80), thrombectomy (yes/no), region (Spain, UK/Germany, USA) and treatment window were considered as covariates. An unstructured variance-covariance matrix was used in the model.

Comparison groups	Placebo v Natalizumab 300 mg IV
Number of subjects included in analysis	153
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.315
Method	Mixed-effects model for repeated measure
Parameter estimate	Adjusted Mean Difference
Point estimate	1.2
Confidence interval	
level	95 %
sides	2-sided
lower limit	-1.1
upper limit	3.4

Statistical analysis title	Placebo vs Natalizumab 600 mg IV

Statistical analysis description:

Treatment and treatment by visit interaction were included in the model as explanatory variables. Baseline NIHSS category (score 5-15, 16-23), tPA use (yes/no), age (<60, 60-69, 70-80), thrombectomy (yes/no), region (Spain, UK/Germany, USA) and treatment window were considered as covariates. An unstructured variance-covariance matrix was used in the model.

Comparison groups	Placebo v Natalizumab 600 mg IV
Number of subjects included in analysis	148
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.542
Method	Mixed-effects model for repeated measure
Parameter estimate	Adjusted Mean Difference
Point estimate	-0.7
Confidence interval	
level	95 %
sides	2-sided
lower limit	-2.96
upper limit	1.56

Secondary: Number of Subjects Experiencing Adverse Events (AE)

End point title	Number of Subjects Experiencing Adverse Events (AE)

End point description:

An AE is any untoward medical occurrence in a subject or clinical investigation subject administered a pharmaceutical product and that does not necessarily have a causal relationship with this treatment. An AE can therefore be any unfavorable and unintended sign (including an abnormal laboratory finding), symptom, or disease temporally associated with the use of a medicinal (investigational) product, whether or not related to the medicinal (investigational) product. The safety population was defined as subjects who had received any study treatment, including cases of complete or incomplete infusion.

End point type	Secondary

End point timeframe:

Baseline up to Day 90

End point values	Placebo	Natalizumab 300 mg IV	Natalizumab 600 mg IV	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	91	90	89	
Units: subjects	84	81	82	

Statistical analyses

No statistical analyses for this end point

Secondary: Number of Subjects Experiencing Serious Adverse Events (SAE)

End point title	Number of Subjects Experiencing Serious Adverse Events (SAE)

End point description:

A SAE is any untoward medical occurrence that at any dose results in death, is a life-threatening event, requires inpatient hospitalization, results in a significant disability/incapacity or congenital anomaly. The safety population was defined as subjects who had received any study treatment, including cases of complete or incomplete infusion.

End point type	Secondary

End point timeframe:

Baseline up to Day 90

End point values	Placebo	Natalizumab 300 mg IV	Natalizumab 600 mg IV	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	91	90	89	
Units: subjects	19	23	29	

Statistical analyses

No statistical analyses for this end point

Secondary: Percentage of Subjects With Dose Response at Day 90

End point title	Percentage of Subjects With Dose Response at Day 90

End point description:

Percentage of subjects with dose response was evaluated in proportion of excellent outcome on mRS and BI. MITT population: all randomised subjects who had received entire infusion of study treatment. Subjects who were accidentally enrolled based on conditions that mimicked stroke symptom at presentation were excluded from MITT population. n specifies number of subjects evaluate for specific categories.

End point type	Secondary

End point timeframe:

Day 90

End point values	Placebo	Natalizumab 300 mg IV	Natalizumab 600 mg IV	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	90	88	89	
Units: percentage of subjects				
number (not applicable)				
mRS (0, 1), n= 86, 83, 82	41	29	26	
BI (>=95), n= 86, 81, 81	67	54	54	

Statistical analyses

Statistical analysis title	Dose response in proportion of mRS

Statistical analysis description:

mRS: The Cochran-Armitage trend test of a monotonically increasing dose response in a proportion of excellent outcome. Dose levels are log transformed.

Comparison groups	Placebo v Natalizumab 300 mg IV v Natalizumab 600 mg IV
Number of subjects included in analysis	267
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.028
Method	Cochran-Armitage trend test

Statistical analysis title	Dose response in proportion of BI

Statistical analysis description:

BI: The Cochran-Armitage trend test of a monotonically increasing dose response in a proportion of excellent outcome. Dose levels are log transformed

Comparison groups	Placebo v Natalizumab 300 mg IV v Natalizumab 600 mg IV
Number of subjects included in analysis	267
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.049
Method	Cochran-Armitage trend test

Adverse events

Adverse events information

Timeframe for reporting adverse events:

Baseline up to Day 90

Adverse event reporting additional description:

The safety population was defined as subjects who had received any study treatment, including cases of complete or incomplete infusion.

Assessment type	Systematic

Dictionary used

Dictionary name	MedDRA
Dictionary version	20.1

Reporting groups

Reporting group title	Placebo

Reporting group description:

Single dose of matching placebo intravenous (IV) to natalizumab on Day 1 at one of two treatment windows, either within 9 hours of last known normal (LKN) or between 9-24 hours after LKN.

Reporting group title	Natalizumab 600 mg IV

Reporting group description:

Single 600 mg natalizumab IV on Day 1 at one of two treatment windows, either within 9 hours of LKN or between 9-24 hours after LKN.

Reporting group title	Natalizumab 300 mg IV

Reporting group description:

Single 300 milligram (mg) natalizumab IV on Day 1 at one of two treatment windows, either within 9 hours of LKN or between 9-24 hours after LKN.

Serious adverse events	Placebo	Natalizumab 600 mg IV	Natalizumab 300 mg IV
Total subjects affected by serious adverse events			
subjects affected / exposed	19 / 91 (20.88%)	29 / 89 (32.58%)	23 / 90 (25.56%)
number of deaths (all causes)	5	4	6
number of deaths resulting from adverse events			
Neoplasms benign, malignant and unspecified (incl cysts and polyps)			
Pancreatic carcinoma stage IV			
subjects affected / exposed	0 / 91 (0.00%)	1 / 89 (1.12%)	0 / 90 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 1	0 / 0
Vascular disorders			
Aortic embolus			
subjects affected / exposed	0 / 91 (0.00%)	1 / 89 (1.12%)	0 / 90 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Deep vein thrombosis			

subjects affected / exposed	1 / 91 (1.10%)	0 / 89 (0.00%)	0 / 90 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Orthostatic hypotension			
subjects affected / exposed	1 / 91 (1.10%)	0 / 89 (0.00%)	0 / 90 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Peripheral artery occlusion			
subjects affected / exposed	0 / 91 (0.00%)	1 / 89 (1.12%)	0 / 90 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
General disorders and administration site conditions			
Death			
subjects affected / exposed	1 / 91 (1.10%)	0 / 89 (0.00%)	0 / 90 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 1	0 / 0	0 / 0
Gait disturbance			
subjects affected / exposed	0 / 91 (0.00%)	0 / 89 (0.00%)	1 / 90 (1.11%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Multiple organ dysfunction syndrome			
subjects affected / exposed	1 / 91 (1.10%)	0 / 89 (0.00%)	1 / 90 (1.11%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 1	0 / 0	0 / 1
Respiratory, thoracic and mediastinal disorders			
Acute respiratory failure			
subjects affected / exposed	1 / 91 (1.10%)	2 / 89 (2.25%)	0 / 90 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 2	0 / 0
deaths causally related to treatment / all	0 / 1	0 / 1	0 / 0
Asthma			
subjects affected / exposed	0 / 91 (0.00%)	1 / 89 (1.12%)	0 / 90 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0

Haemothorax			
subjects affected / exposed	0 / 91 (0.00%)	1 / 89 (1.12%)	0 / 90 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Pneumonia aspiration			
subjects affected / exposed	1 / 91 (1.10%)	1 / 89 (1.12%)	2 / 90 (2.22%)
occurrences causally related to treatment / all	0 / 1	0 / 1	1 / 2
deaths causally related to treatment / all	0 / 1	0 / 0	1 / 2
Pneumothorax			
subjects affected / exposed	0 / 91 (0.00%)	0 / 89 (0.00%)	1 / 90 (1.11%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 1
Pulmonary embolism			
subjects affected / exposed	0 / 91 (0.00%)	3 / 89 (3.37%)	3 / 90 (3.33%)
occurrences causally related to treatment / all	0 / 0	0 / 3	0 / 3
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 1
Respiratory failure			
subjects affected / exposed	1 / 91 (1.10%)	2 / 89 (2.25%)	1 / 90 (1.11%)
occurrences causally related to treatment / all	0 / 1	0 / 2	1 / 1
deaths causally related to treatment / all	0 / 1	0 / 0	1 / 1
Investigations			
Escherichia test positive			
subjects affected / exposed	0 / 91 (0.00%)	1 / 89 (1.12%)	0 / 90 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Injury, poisoning and procedural complications			
Aortic restenosis			
subjects affected / exposed	0 / 91 (0.00%)	1 / 89 (1.12%)	0 / 90 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Brain herniation			
subjects affected / exposed	0 / 91 (0.00%)	0 / 89 (0.00%)	1 / 90 (1.11%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 1

Fall			
subjects affected / exposed	1 / 91 (1.10%)	1 / 89 (1.12%)	1 / 90 (1.11%)
occurrences causally related to treatment / all	0 / 1	0 / 1	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Ilium fracture			
subjects affected / exposed	0 / 91 (0.00%)	1 / 89 (1.12%)	0 / 90 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Periprocedural myocardial infarction			
subjects affected / exposed	0 / 91 (0.00%)	0 / 89 (0.00%)	1 / 90 (1.11%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 1
Post procedural complication			
subjects affected / exposed	0 / 91 (0.00%)	0 / 89 (0.00%)	1 / 90 (1.11%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 1
Wound dehiscence			
subjects affected / exposed	0 / 91 (0.00%)	0 / 89 (0.00%)	1 / 90 (1.11%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Cardiac disorders			
Acute myocardial infarction			
subjects affected / exposed	0 / 91 (0.00%)	0 / 89 (0.00%)	1 / 90 (1.11%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Atrial fibrillation			
subjects affected / exposed	1 / 91 (1.10%)	0 / 89 (0.00%)	0 / 90 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Cardiac arrest			
subjects affected / exposed	1 / 91 (1.10%)	2 / 89 (2.25%)	1 / 90 (1.11%)
occurrences causally related to treatment / all	0 / 1	0 / 2	0 / 1
deaths causally related to treatment / all	0 / 1	0 / 2	0 / 1
Cardiac failure congestive			

subjects affected / exposed	1 / 91 (1.10%)	1 / 89 (1.12%)	0 / 90 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Cardiogenic shock			
subjects affected / exposed	0 / 91 (0.00%)	0 / 89 (0.00%)	1 / 90 (1.11%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 1
Coronary artery disease			
subjects affected / exposed	0 / 91 (0.00%)	0 / 89 (0.00%)	1 / 90 (1.11%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Coronary artery stenosis			
subjects affected / exposed	0 / 91 (0.00%)	1 / 89 (1.12%)	0 / 90 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Sinus node dysfunction			
subjects affected / exposed	1 / 91 (1.10%)	1 / 89 (1.12%)	1 / 90 (1.11%)
occurrences causally related to treatment / all	0 / 1	0 / 1	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Supraventricular tachycardia			
subjects affected / exposed	0 / 91 (0.00%)	0 / 89 (0.00%)	1 / 90 (1.11%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Nervous system disorders			
Carotid artery stenosis			
subjects affected / exposed	0 / 91 (0.00%)	1 / 89 (1.12%)	0 / 90 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Cerebral artery occlusion			
subjects affected / exposed	0 / 91 (0.00%)	2 / 89 (2.25%)	0 / 90 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 2	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Cerebral haemorrhage			

subjects affected / exposed	0 / 91 (0.00%)	1 / 89 (1.12%)	3 / 90 (3.33%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 3
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 1
Cerebral infarction			
subjects affected / exposed	1 / 91 (1.10%)	2 / 89 (2.25%)	0 / 90 (0.00%)
occurrences causally related to treatment / all	0 / 2	0 / 2	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 2	0 / 0
Cerebral reperfusion injury			
subjects affected / exposed	1 / 91 (1.10%)	0 / 89 (0.00%)	0 / 90 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 1	0 / 0	0 / 0
Cerebrovascular accident			
subjects affected / exposed	2 / 91 (2.20%)	3 / 89 (3.37%)	0 / 90 (0.00%)
occurrences causally related to treatment / all	0 / 2	0 / 3	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Cytotoxic oedema			
subjects affected / exposed	0 / 91 (0.00%)	0 / 89 (0.00%)	1 / 90 (1.11%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Embolic cerebral infarction			
subjects affected / exposed	0 / 91 (0.00%)	0 / 89 (0.00%)	1 / 90 (1.11%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 1
Generalised tonic-clonic seizure			
subjects affected / exposed	0 / 91 (0.00%)	0 / 89 (0.00%)	1 / 90 (1.11%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Haemorrhagic transformation stroke			
subjects affected / exposed	1 / 91 (1.10%)	1 / 89 (1.12%)	1 / 90 (1.11%)
occurrences causally related to treatment / all	0 / 1	0 / 1	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Headache			

subjects affected / exposed	0 / 91 (0.00%)	0 / 89 (0.00%)	1 / 90 (1.11%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Hydrocephalus			
subjects affected / exposed	0 / 91 (0.00%)	0 / 89 (0.00%)	1 / 90 (1.11%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Ischaemic stroke			
subjects affected / exposed	0 / 91 (0.00%)	2 / 89 (2.25%)	3 / 90 (3.33%)
occurrences causally related to treatment / all	0 / 0	0 / 2	0 / 3
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 1
Lacunar infarction			
subjects affected / exposed	0 / 91 (0.00%)	1 / 89 (1.12%)	0 / 90 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Neurological decompensation			
subjects affected / exposed	1 / 91 (1.10%)	1 / 89 (1.12%)	1 / 90 (1.11%)
occurrences causally related to treatment / all	0 / 1	0 / 1	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Partial seizures			
subjects affected / exposed	0 / 91 (0.00%)	0 / 89 (0.00%)	1 / 90 (1.11%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Seizure			
subjects affected / exposed	0 / 91 (0.00%)	1 / 89 (1.12%)	0 / 90 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Stroke in evolution			
subjects affected / exposed	1 / 91 (1.10%)	1 / 89 (1.12%)	2 / 90 (2.22%)
occurrences causally related to treatment / all	0 / 1	0 / 1	0 / 2
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Eye disorders			
Retinal detachment			

subjects affected / exposed	0 / 91 (0.00%)	1 / 89 (1.12%)	0 / 90 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Gastrointestinal disorders			
Constipation			
subjects affected / exposed	0 / 91 (0.00%)	0 / 89 (0.00%)	1 / 90 (1.11%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Ileus paralytic			
subjects affected / exposed	0 / 91 (0.00%)	0 / 89 (0.00%)	1 / 90 (1.11%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Large intestine perforation			
subjects affected / exposed	0 / 91 (0.00%)	0 / 89 (0.00%)	1 / 90 (1.11%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Oesophageal ulcer haemorrhage			
subjects affected / exposed	0 / 91 (0.00%)	1 / 89 (1.12%)	0 / 90 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Retroperitoneal haematoma			
subjects affected / exposed	0 / 91 (0.00%)	0 / 89 (0.00%)	1 / 90 (1.11%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 1
Hepatobiliary disorders			
Ischaemic hepatitis			
subjects affected / exposed	0 / 91 (0.00%)	0 / 89 (0.00%)	1 / 90 (1.11%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 1
Skin and subcutaneous tissue disorders			
Idiopathic angioedema			
subjects affected / exposed	0 / 91 (0.00%)	0 / 89 (0.00%)	1 / 90 (1.11%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0

Renal and urinary disorders			
Haematuria			
subjects affected / exposed	0 / 91 (0.00%)	2 / 89 (2.25%)	0 / 90 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 2	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Ureteric rupture			
subjects affected / exposed	1 / 91 (1.10%)	0 / 89 (0.00%)	0 / 90 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Urinary retention			
subjects affected / exposed	0 / 91 (0.00%)	0 / 89 (0.00%)	1 / 90 (1.11%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Infections and infestations			
Endocarditis			
subjects affected / exposed	0 / 91 (0.00%)	1 / 89 (1.12%)	0 / 90 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Endocarditis bacterial			
subjects affected / exposed	0 / 91 (0.00%)	1 / 89 (1.12%)	0 / 90 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 1	0 / 0
Enterococcal sepsis			
subjects affected / exposed	0 / 91 (0.00%)	1 / 89 (1.12%)	0 / 90 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 1	0 / 0
Febrile infection			
subjects affected / exposed	0 / 91 (0.00%)	1 / 89 (1.12%)	0 / 90 (0.00%)
occurrences causally related to treatment / all	0 / 0	1 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Gastroenteritis			
subjects affected / exposed	1 / 91 (1.10%)	0 / 89 (0.00%)	0 / 90 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0

Gastroenteritis viral			
subjects affected / exposed	1 / 91 (1.10%)	0 / 89 (0.00%)	0 / 90 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Haemophilus infection			
subjects affected / exposed	0 / 91 (0.00%)	0 / 89 (0.00%)	1 / 90 (1.11%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Peritonitis			
subjects affected / exposed	0 / 91 (0.00%)	0 / 89 (0.00%)	1 / 90 (1.11%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Pneumonia			
subjects affected / exposed	2 / 91 (2.20%)	1 / 89 (1.12%)	0 / 90 (0.00%)
occurrences causally related to treatment / all	1 / 2	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Pneumonia acinetobacter			
subjects affected / exposed	1 / 91 (1.10%)	0 / 89 (0.00%)	0 / 90 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 1	0 / 0	0 / 0
Respiratory tract infection			
subjects affected / exposed	1 / 91 (1.10%)	0 / 89 (0.00%)	0 / 90 (0.00%)
occurrences causally related to treatment / all	1 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Sepsis			
subjects affected / exposed	2 / 91 (2.20%)	0 / 89 (0.00%)	1 / 90 (1.11%)
occurrences causally related to treatment / all	1 / 2	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 1	0 / 0	0 / 1
Septic encephalopathy			
subjects affected / exposed	0 / 91 (0.00%)	1 / 89 (1.12%)	0 / 90 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Septic shock			

subjects affected / exposed	1 / 91 (1.10%)	1 / 89 (1.12%)	0 / 90 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 1	0 / 0	0 / 0
Splenic abscess			
subjects affected / exposed	0 / 91 (0.00%)	1 / 89 (1.12%)	0 / 90 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 1	0 / 0
Urinary tract infection			
subjects affected / exposed	1 / 91 (1.10%)	1 / 89 (1.12%)	0 / 90 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Urosepsis			
subjects affected / exposed	1 / 91 (1.10%)	0 / 89 (0.00%)	0 / 90 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Wound infection staphylococcal			
subjects affected / exposed	1 / 91 (1.10%)	0 / 89 (0.00%)	0 / 90 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Metabolism and nutrition disorders			
Gout			
subjects affected / exposed	0 / 91 (0.00%)	1 / 89 (1.12%)	0 / 90 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Hyperglycaemic hyperosmolar nonketotic syndrome			
subjects affected / exposed	0 / 91 (0.00%)	0 / 89 (0.00%)	1 / 90 (1.11%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 1

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

Non-serious adverse events	Placebo	Natalizumab 600 mg IV	Natalizumab 300 mg IV
Total subjects affected by non-serious adverse events			
subjects affected / exposed	67 / 91 (73.63%)	65 / 89 (73.03%)	69 / 90 (76.67%)
Vascular disorders			
Hypertension			
subjects affected / exposed	6 / 91 (6.59%)	8 / 89 (8.99%)	7 / 90 (7.78%)
occurrences (all)	6	9	7
Hypotension			
subjects affected / exposed	5 / 91 (5.49%)	7 / 89 (7.87%)	4 / 90 (4.44%)
occurrences (all)	5	7	4
General disorders and administration site conditions			
Fatigue			
subjects affected / exposed	5 / 91 (5.49%)	1 / 89 (1.12%)	1 / 90 (1.11%)
occurrences (all)	5	1	1
Pain			
subjects affected / exposed	3 / 91 (3.30%)	2 / 89 (2.25%)	7 / 90 (7.78%)
occurrences (all)	3	3	8
Pyrexia			
subjects affected / exposed	11 / 91 (12.09%)	14 / 89 (15.73%)	19 / 90 (21.11%)
occurrences (all)	11	21	24
Respiratory, thoracic and mediastinal disorders			
Pneumonia aspiration			
subjects affected / exposed	5 / 91 (5.49%)	1 / 89 (1.12%)	5 / 90 (5.56%)
occurrences (all)	5	1	5
Psychiatric disorders			
Agitation			
subjects affected / exposed	8 / 91 (8.79%)	0 / 89 (0.00%)	5 / 90 (5.56%)
occurrences (all)	8	0	5
Anxiety			
subjects affected / exposed	4 / 91 (4.40%)	7 / 89 (7.87%)	2 / 90 (2.22%)
occurrences (all)	4	7	2
Depression			
subjects affected / exposed	16 / 91 (17.58%)	10 / 89 (11.24%)	13 / 90 (14.44%)
occurrences (all)	16	10	13
Insomnia			

subjects affected / exposed	4 / 91 (4.40%)	10 / 89 (11.24%)	11 / 90 (12.22%)
occurrences (all)	4	11	11
Injury, poisoning and procedural complications			
Fall			
subjects affected / exposed	5 / 91 (5.49%)	5 / 89 (5.62%)	7 / 90 (7.78%)
occurrences (all)	5	5	7
Cardiac disorders			
Atrial fibrillation			
subjects affected / exposed	8 / 91 (8.79%)	7 / 89 (7.87%)	6 / 90 (6.67%)
occurrences (all)	8	8	6
Nervous system disorders			
Haemorrhagic transformation stroke			
subjects affected / exposed	4 / 91 (4.40%)	5 / 89 (5.62%)	4 / 90 (4.44%)
occurrences (all)	4	5	4
Headache			
subjects affected / exposed	15 / 91 (16.48%)	20 / 89 (22.47%)	16 / 90 (17.78%)
occurrences (all)	18	22	17
Blood and lymphatic system disorders			
Anaemia			
subjects affected / exposed	3 / 91 (3.30%)	5 / 89 (5.62%)	3 / 90 (3.33%)
occurrences (all)	3	6	3
Gastrointestinal disorders			
Abdominal pain			
subjects affected / exposed	1 / 91 (1.10%)	1 / 89 (1.12%)	5 / 90 (5.56%)
occurrences (all)	1	1	5
Constipation			
subjects affected / exposed	18 / 91 (19.78%)	23 / 89 (25.84%)	19 / 90 (21.11%)
occurrences (all)	21	30	22
Diarrhoea			
subjects affected / exposed	4 / 91 (4.40%)	3 / 89 (3.37%)	5 / 90 (5.56%)
occurrences (all)	5	3	5
Dysphagia			
subjects affected / exposed	1 / 91 (1.10%)	2 / 89 (2.25%)	6 / 90 (6.67%)
occurrences (all)	1	2	6
Nausea			

subjects affected / exposed	4 / 91 (4.40%)	6 / 89 (6.74%)	7 / 90 (7.78%)
occurrences (all)	5	7	7
Vomiting			
subjects affected / exposed	3 / 91 (3.30%)	1 / 89 (1.12%)	7 / 90 (7.78%)
occurrences (all)	3	1	8
Renal and urinary disorders			
Haematuria			
subjects affected / exposed	5 / 91 (5.49%)	3 / 89 (3.37%)	3 / 90 (3.33%)
occurrences (all)	5	3	3
Urinary retention			
subjects affected / exposed	6 / 91 (6.59%)	3 / 89 (3.37%)	4 / 90 (4.44%)
occurrences (all)	6	3	4
Musculoskeletal and connective tissue disorders			
Arthralgia			
subjects affected / exposed	0 / 91 (0.00%)	5 / 89 (5.62%)	1 / 90 (1.11%)
occurrences (all)	0	6	1
Pain in extremity			
subjects affected / exposed	2 / 91 (2.20%)	2 / 89 (2.25%)	5 / 90 (5.56%)
occurrences (all)	2	2	8
Infections and infestations			
Pneumonia			
subjects affected / exposed	3 / 91 (3.30%)	8 / 89 (8.99%)	2 / 90 (2.22%)
occurrences (all)	3	9	2
Urinary tract infection			
subjects affected / exposed	11 / 91 (12.09%)	15 / 89 (16.85%)	14 / 90 (15.56%)
occurrences (all)	13	18	16
Metabolism and nutrition disorders			
Hypokalaemia			
subjects affected / exposed	6 / 91 (6.59%)	6 / 89 (6.74%)	12 / 90 (13.33%)
occurrences (all)	6	7	13

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

Date	Amendment
15 December 2016	• The protocol was amended to remove unnecessary study procedures (i.e., 0 hour blood draw and the Functional Independence Measure at Day 5) and to add an expanded treatment window (>9 to ≤24 hours) in which subjects would be eligible for inclusion in the study. • An NIHSS screening score for eligibility was added to the inclusion criteria for the >9 to ≤24 hour treatment window, and NIHSS eligibility was to be confirmed within 60 minutes prior to randomization. • Exclusion criteria were updated to clarify that the subjects with rapidly improving or minor stroke symptoms, or with petechial hemorrhages ≤1 centimeter (cm) were no longer excluded from the study. • The statement regarding performing brain Magnetic resonance imaging (MRI) to assess subject eligibility was removed from the exclusion criteria, and the types of exclusionary strokes were clarified. • The exclusion criteria regarding hepatitis infections and bacterial, fungal, or viral infections were simplified. • It was clarified that thrombolytic treatments/procedures would be recorded as concomitant regardless of whether they were given before or after informed consent. • Contraception language was updated so that all subjects were instructed to use highly effective methods of contraception and so that the methods of highly effective contraception were defined consistently with the Clinical Trial Facilitation Group's recommendations. • The sample size was increased from 225 to 270 to account for the addition of a new treatment window (>9 to ≤24 hours from LKN).
03 May 2017	• The protocol was amended to correct an error in the pharmacokinetic (PK)/pharmacodynamic (PD) sampling times. It was clarified that the blood samples for PK/PD assessments, as well as vital sign measurements, were taken within 1 hour after the infusion had stopped.

Notes:

Interruptions (globally)

Were there any global interruptions to the trial? No

Limitations and caveats

None reported