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

## Summary

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

### Results information

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

## Trial information

### Trial identification

| | |
|---|---|
| Sponsor protocol code | 101MS326 |

### Additional study identifiers

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

Notes:

### Sponsors

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

Notes:

### Paediatric regulatory details

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

Notes:

## Results analysis stage

| | |
|---|---|
| Analysis stage | Final |
| Date of interim/final analysis | 13 April 2016 |
| Is this the analysis of the primary completion data? | No |

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

Notes:

## General information about the trial

Main objective of the trial:

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

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

Protection of trial subjects:

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

Background therapy: -

Evidence for comparator: -

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

Notes:

## Population of trial subjects

### Subjects enrolled per country

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

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

Notes:

**Subjects enrolled per age group**

| | |
|---|---|
| In utero | 0 |
| Preterm newborn - gestational age < 37 wk | 0 |
| Newborns (0-27 days) | 0 |
| Infants and toddlers (28 days-23 months) | 0 |
| Children (2-11 years) | 0 |
| Adolescents (12-17 years) | 0 |
| Adults (18-64 years) | 889 |
| From 65 to 84 years | 0 |
| 85 years and over | 0 |

## Subject disposition

### Recruitment

Recruitment details: -

### Pre-assignment

Screening details:

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

### Period 1

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

Blinding implementation details:

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

### Arms

| | |
|---|---|
| Are arms mutually exclusive? | Yes |
| **Arm title** | Placebo |

Arm description:

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

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

Dosage and administration details:

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

| | |
|---|---|
| **Arm title** | Natalizumab 300 mg |

Arm description:

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

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

Dosage and administration details:

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

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

Notes:

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

## Period 2

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

## Arms

| | |
|---|---|
| Are arms mutually exclusive? | Yes |
| **Arm title** | Placebo |

Arm description:

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

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

Dosage and administration details:

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

| | |
|---|---|
| **Arm title** | Natalizumab 300 mg |

Arm description:

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

| | |
|---|---|
| Arm type | Experimental |

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

Dosage and administration details:

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

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

Notes:

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

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

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

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

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

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

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

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

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

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

## Baseline characteristics

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

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

## End points

### End points reporting groups

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

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

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

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

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

**Statistical analyses**

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

Notes:

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

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

Notes:

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

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

Notes:

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

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

Notes:

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

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

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

Notes:

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

| **Statistical analysis title** | Statistical Analysis 6 |
|---|---|

Statistical analysis description:

Confirmed progressors on 9HPT (non-dominant hand)

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

Notes:

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

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

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

End point description:

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

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

End point timeframe:

218 weeks

Notes:

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

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

### Statistical analyses

No statistical analyses for this end point

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

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

End point description:

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

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

End point timeframe:

Up to 96 weeks

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

### Statistical analyses

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

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

Notes:

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

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

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

End point description:

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

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

End point timeframe:

Baseline and Week 96

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

### Statistical analyses

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

Notes:

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

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

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

End point description:

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

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

End point timeframe:

Baseline and Week 96

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

### Statistical analyses

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

Notes:

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

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

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

End point description:

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

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

| End point timeframe:<br>Baseline and Week 96 |
|---|

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

**Statistical analyses**

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

Notes:

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

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

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

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

**Statistical analyses**

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

Notes:

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

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

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

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

End point description:

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

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

End point timeframe:

Up to 96 weeks

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

### Statistical analyses

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

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

Notes:

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

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

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

End point description:

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

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

End point timeframe:

Week 156

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

### Statistical analyses

| Statistical analysis title | Statistical Analysis 1 |
|---|---|

Statistical analysis description:

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

| Comparison groups | Placebo v Natalizumab 300 mg |
|---|---|

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

Notes:

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

| **Statistical analysis title** | Statistical Analysis 2 |
|---|---|

Statistical analysis description:

Confirmed progressors on EDSS at 156 weeks

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

Notes:

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

| **Statistical analysis title** | Statistical Analysis 3 |
|---|---|

Statistical analysis description:

Confirmed progressors on T25FW at 156 weeks

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

Notes:

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

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

Notes:

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

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

Notes:

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

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

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

Notes:

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

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

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

End point description:

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

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

End point timeframe:

Baseline (Part 1) and Weeks 156, 204

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

## Statistical analyses

| Statistical analysis title | Statistical Analysis 1 |
|---|---|

Statistical analysis description:

Week 156

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

Notes:

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

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

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

End point description:

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

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

End point timeframe:

Baseline (Part 1) and Weeks 156, 204

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

## Statistical analyses

| Statistical analysis title | Statistical Analysis 1 |
|---|---|

Statistical analysis description:

Overall: Week 156

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

Notes:

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

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

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

End point description:

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

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

End point timeframe:

Baseline (Part 1) and Weeks 156, 204

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

### Statistical analyses

| | |
|---|---|
| **Statistical analysis title** | Statistical Analysis 1 |

Statistical analysis description:

Overall, Week 156

| | |
|---|---|
| Comparison groups | Placebo v Natalizumab 300 mg |

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

Notes:

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

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

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

End point description:

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

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

End point timeframe:

Baseline (Part 1) and Weeks 156, 204

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

### Statistical analyses

| Statistical analysis title | Statistical Analysis 1 |
|---|---|

Statistical analysis description:

Overall: Week 156

| | |
|---|---|
| Comparison groups | Placebo v Natalizumab 300 mg |

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

Notes:

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

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

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

End point description:

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

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

End point timeframe:

Baseline (Part 1) and Weeks 156, 204

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

### Statistical analyses

| Statistical analysis title | Statistical Analysis 1 |
|---|---|

Statistical analysis description:

Overall: Week 156

| | |
|---|---|
| Comparison groups | Placebo v Natalizumab 300 mg |

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

Notes:

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

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

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

End point description:

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

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

End point timeframe:

Baseline (Part 1) and Weeks 156, 204

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

### Statistical analyses

| **Statistical analysis title** | Statistical Analysis 1 |
|---|---|

Statistical analysis description:

Overall: Week 156

| | |
|---|---|
| Comparison groups | Placebo v Natalizumab 300 mg |

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

Notes:

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

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

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

End point description:

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

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

End point timeframe:

Baseline (Part 1) and Weeks 156, 204

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

### Statistical analyses

| Statistical analysis title | Statistical Analysis 1 |
|---|---|

Statistical analysis description:

Overall: Week 156

| | |
|---|---|
| Comparison groups | Placebo v Natalizumab 300 mg |

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

Notes:

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

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

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

End point description:

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

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

End point timeframe:

Baseline (Part 1) and Weeks 156 and 204

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

### Statistical analyses

| Statistical analysis title | Statistical Analysis 1 |
|---|---|

Statistical analysis description:

Overall: Week 156

| | |
|---|---|
| Comparison groups | Placebo v Natalizumab 300 mg |

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

Notes:

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

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

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

End point description:

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

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

End point timeframe:

Baseline (Part 1) and Weeks 156 and 204

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

### Statistical analyses

No statistical analyses for this end point

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

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

End point description:

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

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

End point timeframe:

Baseline (Part 1) and Weeks 156, 204

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

Notes:

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

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

### Statistical analyses

No statistical analyses for this end point

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

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

End point description:

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

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

End point timeframe:

Baseline (Part 1) and Weeks 156 and 204

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

### Statistical analyses

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

Notes:

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

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

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

End point description:

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

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

End point timeframe:

Baseline (Part 1) and Weeks 156, 204

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

Notes:

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

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

### Statistical analyses

No statistical analyses for this end point

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

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

End point description:

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

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

End point timeframe:

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

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

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

**Statistical analyses**

| **Statistical analysis title** | Statistical Analysis 1 |
|---|---|

Statistical analysis description:

Week 156

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

Notes:

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

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

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

End point description:

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

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

End point timeframe:

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

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

Notes:

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

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

### Statistical analyses

No statistical analyses for this end point

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

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

End point description:

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

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

End point timeframe:

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

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

## Statistical analyses

No statistical analyses for this end point

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

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

End point description:

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

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

End point timeframe:

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

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

## Statistical analyses

No statistical analyses for this end point

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

## Volume

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

End point description:

Whole brain volume as measured by MRI.

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

End point timeframe:

Week 24 (Part 1) and Weeks 156 and 204

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

### Statistical analyses

No statistical analyses for this end point

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

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

End point description:

Whole grey matter brain volume as measured by MRI.

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

End point timeframe:

Baseline (Part 1) and Weeks 156 and 204

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

### Statistical analyses

No statistical analyses for this end point

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

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

End point description:

New or enlarging T2 lesions as measured by MRI.

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

End point timeframe:

Baseline (Part 1) up to Week 204

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

### Statistical analyses

No statistical analyses for this end point

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

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

End point description:

New or enlarging T2 lesions as measured by MRI.

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

End point timeframe:

Baseline (Part 1) and Weeks 156 and 204

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

Notes:

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

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

## Statistical analyses

No statistical analyses for this end point

## Adverse events

### Adverse events information

Timeframe for reporting adverse events:

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

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

### Dictionary used

| | |
|---|---|
| Dictionary name | MedDRA |
| Dictionary version | 18.0 |

### Reporting groups

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

Reporting group description: -

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

| | | | |
|---|---|---|---|
| subjects affected / exposed | 3 / 439 (0.68%) | 1 / 449 (0.22%) | |
| occurrences causally related to treatment / all | 1 / 3 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Metabolism and nutrition disorders | | | |
| Diabetic ketoacidosis | | | |
| subjects affected / exposed | 1 / 439 (0.23%) | 0 / 449 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Insulin-requiring type 2 diabetes mellitus | | | |
| subjects affected / exposed | 1 / 439 (0.23%) | 0 / 449 (0.00%) | |
| occurrences causally related to treatment / all | 1 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Obesity | | | |
| subjects affected / exposed | 0 / 439 (0.00%) | 1 / 449 (0.22%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Type 1 diabetes mellitus | | | |
| subjects affected / exposed | 1 / 439 (0.23%) | 0 / 449 (0.00%) | |
| occurrences causally related to treatment / all | 1 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |

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

| **Non-serious adverse events** | Natalizumab 300 mg | Placebo | |
|---|---|---|---|
| Total subjects affected by non-serious adverse events | | | |
| subjects affected / exposed | 325 / 439 (74.03%) | 347 / 449 (77.28%) | |
| Injury, poisoning and procedural complications | | | |
| Contusion | | | |
| subjects affected / exposed | 26 / 439 (5.92%) | 17 / 449 (3.79%) | |
| occurrences (all) | 36 | 19 | |
| Fall | | | |
| subjects affected / exposed | 82 / 439 (18.68%) | 85 / 449 (18.93%) | |
| occurrences (all) | 198 | 212 | |
| Nervous system disorders | | | |

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

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

## More information

## Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

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

Notes:

## Interruptions (globally)

Were there any global interruptions to the trial? No

## Limitations and caveats

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

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

Notes: