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

## Summary

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

**Results information**

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

## Trial information

**Trial identification**

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

**Additional study identifiers**

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

Notes:

**Sponsors**

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

Notes:

**Paediatric regulatory details**

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

Notes:

## Results analysis stage

| | |
|---|---|
| Analysis stage | Final |
| Date of interim/final analysis | 24 July 2023 |
| Is this the analysis of the primary completion data? | No |

| | |
|---|---|
| Global end of trial reached? | Yes |
| Global end of trial date | 24 July 2023 |
| Was the trial ended prematurely? | No |

Notes:

## General information about the trial

Main objective of the trial:

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

Protection of trial subjects:

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

Background therapy:

N/A

Evidence for comparator:

N/A

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

Notes:

## Population of trial subjects

### Subjects enrolled per country

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

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

Notes:

**Subjects enrolled per age group**

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

## Subject disposition

### Recruitment

Recruitment details:

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

### Pre-assignment

Screening details:

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

### Period 1

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

### Arms

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

Arm description:

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

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

Dosage and administration details:

Administered as specified in the treatment arm.

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

Arm description:

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

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

Dosage and administration details:

Administered as specified in the treatment arm.

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

Notes:

[1] - The number of subjects reported to be in the baseline period are not the same as the worldwide number enrolled in the trial. It is expected that these numbers will be the same.
Justification: 585 participants were enrolled in the study, out of which 499 participants were randomised in Part 1.

## Period 2

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

## Arms

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

Arm description:

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

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

Dosage and administration details:

Administered as specified in the treatment arm.

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

## Period 3

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

## Arms

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

Arm description:

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

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

Dosage and administration details:

Administered as specified in the treatment arm.

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

Arm description:

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

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

Dosage and administration details:

Administered as specified in the treatment arm.

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

## Baseline characteristics

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

| Reporting group values | Part 1: IV Q4W | Part 1: IV Q6W | Total |
|---|---|---|---|
| Number of subjects | 248 | 251 | 499 |
| Age Categorical<br>Units: Subjects | | | |
| Age continuous | | | |
| Part 1: All randomised population included all the randomised participants in Part 1 of the study. Part 2: Included all the newly enrolled randomised participants in the crossover period of Part 2 of the study. | | | |
| Units: years | | | |
| arithmetic mean | 40.5 | 41.0 | |
| standard deviation | ± 10.03 | ± 9.66 | - |
| Gender categorical<br>Units: Subjects | | | |
| Male | 67 | 73 | 140 |
| Female | 181 | 178 | 359 |
| Ethnicity<br>Units: Subjects | | | |
| Hispanic or Latino | 10 | 9 | 19 |
| Not Hispanic or Latino | 223 | 224 | 447 |
| Unknown or Not Reported | 15 | 18 | 33 |
| Race<br>Units: Subjects | | | |
| American Indian or Alaska Native | 1 | 1 | 2 |
| Asian | 1 | 4 | 5 |
| Black or African American | 23 | 14 | 37 |
| White | 211 | 211 | 422 |
| Not reported due to confidentiality regulations | 11 | 15 | 26 |
| Other | 1 | 6 | 7 |

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

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

| **Reporting group values** | Part 2: Crossover Period | Part 2: Crossover Period: IV Q6W | Part 2: Crossover Period: SC Q6W |
|---|---|---|---|
| Number of subjects | 86 | 153 | 153 |
| Age Categorical<br>Units: Subjects | | | |
| Age continuous | | | |
| Part 1: All randomised population included all the randomised participants in Part 1 of the study. Part 2: Included all the newly enrolled randomised participants in the crossover period of Part 2 of the study. | | | |
| Units: years | | | |
| arithmetic mean | 37.6 | 0 | 0 |
| standard deviation | ± 9.85 | ± 0 | ± 0 |
| Gender categorical<br>Units: Subjects | | | |
| Male | 28 | 0 | 0 |
| Female | 58 | 0 | 0 |
| Ethnicity<br>Units: Subjects | | | |
| Hispanic or Latino | 1 | 0 | 0 |
| Not Hispanic or Latino | 67 | 0 | 0 |
| Unknown or Not Reported | 18 | 0 | 0 |
| Race<br>Units: Subjects | | | |
| American Indian or Alaska Native | 0 | 0 | 0 |
| Asian | 0 | 0 | 0 |
| Black or African American | 0 | 0 | 0 |
| White | 71 | 0 | 0 |
| Not reported due to confidentiality regulations | 14 | 0 | 0 |
| Other | 1 | 0 | 0 |

## End points

### End points reporting groups

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

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

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

End point timeframe:

Week 72

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

### Statistical analyses

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

Notes:

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

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

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

End point description:

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

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

End point timeframe:

Week 150

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

**Statistical analyses**

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

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

| End point title | Part 1: Time to First Relapse as Adjudicated by an Independent Neurology Evaluation Committee (INEC) |
|---|---|

End point description:

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

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

End point timeframe:

Up to Week 72

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

### Statistical analyses

No statistical analyses for this end point

### Secondary: Part 1: Annualised Relapse Rate at Week 72

| End point title | Part 1: Annualised Relapse Rate at Week 72 |
|---|---|

End point description:

Annualised relapse rate is calculated as the total number of INEC-confirmed relapses that occurred during the treatment period divided by the total number of participant-years followed in the period. mITT population included all randomised participants who received at least one dose of study treatment and had at least 1 postbaseline result in Part 1.

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

End point timeframe:

Week 72

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

### Statistical analyses

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

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

Notes:

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

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

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

End point description:

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

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

End point timeframe:

Up to Week 72

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

### Statistical analyses

No statistical analyses for this end point

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

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

End point description:

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

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

End point timeframe:

Weeks 24, 48, and 72

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

### Statistical analyses

No statistical analyses for this end point

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

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

End point description:

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

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

End point timeframe:

Weeks 24 and 48

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

### Statistical analyses

No statistical analyses for this end point

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

## Weeks 24, 48, and 72

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

End point description:

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

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

End point timeframe:

Weeks 24, 48, and 72

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

### Statistical analyses

No statistical analyses for this end point

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

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

End point description:

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

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

End point timeframe:

Baseline up to Week 96

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

### Statistical analyses

No statistical analyses for this end point

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

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

End point description:

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

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

End point timeframe:

Part 2 Baseline (Week 108) up to Week 156

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

### Statistical analyses

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

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

Notes:

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

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

| | |
|---|---|
| End point title | Part 2: Mean Time for Drug Preparation and Drug Administration During the Crossover Period |

End point description:

FAS included all randomised participants who received at least one dose of study treatment during at least one study period and had at least one baseline assessment in Part 2.

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

End point timeframe:

Week 108 up to Week 156

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

## Statistical analyses

No statistical analyses for this end point

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

| | |
|---|---|
| End point title | Part 2: Percentage of Participants With Treatment-Emergent Adverse Events (TEAEs) |

End point description:

An AE is any untoward medical occurrence in a participant or clinical investigation participant administered a pharmaceutical product and that does not necessarily have a causal relationship with this

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

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

End point timeframe:

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

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

**Statistical analyses**

No statistical analyses for this end point

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

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

End point description:

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

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

End point timeframe:

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

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

**Statistical analyses**

No statistical analyses for this end point

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

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

End point description:

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

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

End point timeframe:

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

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

### Statistical analyses

No statistical analyses for this end point

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

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

End point description:

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

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

End point timeframe:

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

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

### Statistical analyses

No statistical analyses for this end point

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

| End point title | Part 2: Annualized Relapse Rate During the Crossover Period |
|---|---|

End point description:

Annualised relapse rate is calculated as the total number of relapses that occurred during the treatment period divided by the total number of participant-years followed in the period.

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

End point timeframe:

Part 2 Baseline (Week 108) up to Week 156

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

Notes:

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

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

### Statistical analyses

No statistical analyses for this end point

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

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

End point description:

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

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

End point timeframe:

Part 2 Baseline (Week 108) up to Week 156

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

**Statistical analyses**

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

Notes:

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

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

| End point title | Part 2: Mean Number of New Gd Enhancing Lesions During the Crossover Period |
|---|---|

End point description:

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

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

End point timeframe:

Week 108 up to Week 156

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

### Statistical analyses

No statistical analyses for this end point

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

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

End point description:

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

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

End point timeframe:

Week 108 up to Week 156

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

### Statistical analyses

No statistical analyses for this end point

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

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

| | |
|---|---|
| | Volume During the Crossover Period |

End point description:

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

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

End point timeframe:

Part 2 Baseline (Week 108) up to Week 156

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

## Statistical analyses

No statistical analyses for this end point

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

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

End point description:

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

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

End point timeframe:

Part 2 Baseline (Week 108) up to Week 156

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

## Statistical analyses

No statistical analyses for this end point

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

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

End point description:

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

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

End point timeframe:

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

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

## Statistical analyses

No statistical analyses for this end point

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

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

End point description:

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

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

End point timeframe:

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

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

## Statistical analyses

No statistical analyses for this end point

## Adverse events

| Adverse events information | |
|---|---|
| Timeframe for reporting adverse events: | |
| From first dose of study drug up to Week 180 | |
| Adverse event reporting additional description: | |
| Safety population included all randomised participants who received at least one dose of study treatment. MedDRA version 24.0 applied for Part 1 and MedDRA version 26.0 applied for Part 2. | |
| Assessment type | Systematic |

| Dictionary used | |
|---|---|
| Dictionary name | MedDRA |
| Dictionary version | 24.0, 26.0 |

| Reporting groups | |
|---|---|
| Reporting group title | Part 1: IV Q4W |
| Reporting group description: | |
| Participants received natalizumab 300 mg IV infusion Q4W up to Week 72. | |
| Reporting group title | Part 2: Crossover Period: SC Q6W |
| Reporting group description: | |
| Participants received natalizumab 300 mg SC injection Q6W for 24 weeks. | |
| Reporting group title | Part 2: Crossover Period: IV Q6W |
| Reporting group description: | |
| Participants received natalizumab 300 mg IV infusion Q6W for 24 weeks. | |
| Reporting group title | Part 1: IV Q6W |
| Reporting group description: | |
| Participants received natalizumab 300 mg IV infusion Q6W up to Week 72. | |
| Reporting group title | Part 2: Run-in period: IV Q6W |
| Reporting group description: | |
| Participants who completed Part 1 or were newly enrolled in Part 2 received natalizumab 300 mg IV infusion Q6W from Week 72 through Week 102. | |

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

## More information

## Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

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

Notes:

## Interruptions (globally)

Were there any global interruptions to the trial? No

## Limitations and caveats

None reported