# Clinical trial results:
# A Multi-centre and Prospective Trial to Evaluate the Effects on Multiple Sclerosis Related Fatigue During Treatment With Tysabri® in Patients With Relapsing Remitting Multiple Sclerosis Over the Course of 12 Months

## Summary

| | |
|---|---|
| EudraCT number | 2008-008065-35 |
| Trial protocol | SE |
| Global end of trial date | 30 June 2011 |

### Results information

| | |
|---|---|
| Result version number | v1 (current) |
| This version publication date | 08 February 2019 |
| First version publication date | 08 February 2019 |

## Trial information

### Trial identification

| | |
|---|---|
| Sponsor protocol code | TYNERGY |

### Additional study identifiers

| | |
|---|---|
| ISRCTN number | - |
| ClinicalTrials.gov id (NCT number) | NCT00884481 |
| WHO universal trial number (UTN) | - |

Notes:

### Sponsors

| | |
|---|---|
| Sponsor organisation name | Biogen |
| Sponsor organisation address | 250 Binney Street, Cambridge, Massachusetts, United States, 02142 |
| Public contact | Study Medical Director, Biogen, clinicaltrials@biogen.com |
| Scientific contact | 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 | 30 June 2011 |
| Is this the analysis of the primary completion data? | No |

| | |
|---|---|
| Global end of trial reached? | Yes |
| Global end of trial date | 30 June 2011 |
| Was the trial ended prematurely? | No |

Notes:

## General information about the trial

Main objective of the trial:

To investigate the multiple sclerosis (MS) related fatigue during treatment with natalizumab as measured by changes on the fatigue scale for motor and cognitive functions (FSMC) over the course of 12 months.

Protection of trial subjects:

Subjects were treated according to clinical practice; protection of subjects was ensured by health care professional (HCP) as per clinical practice.

Background therapy: -

Evidence for comparator: -

| | |
|---|---|
| Actual start date of recruitment | 23 March 2009 |
| 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 | Denmark: 23 |
| Country: Number of subjects enrolled | Sweden: 83 |
| Country: Number of subjects enrolled | Austria: 29 |
| Country: Number of subjects enrolled | Norway: 60 |
| Worldwide total number of subjects | 195 |
| EEA total number of subjects | 195 |

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) | 195 |
| From 65 to 84 years | 0 |

| | |
|---|---|
| 85 years and over | 0 |

## Subject disposition

### Recruitment

Recruitment details:

The study was conducted in 4 countries- Sweden, Denmark, Norway and Austria.

### Pre-assignment

Screening details:

A total of 205 subjects were screened, 10 subjects were considered screening failures. Total 195 subjects were enrolled in the study and started treatment of Natalizumab.

### Period 1

| | |
|---|---|
| Period 1 title | Overall Study (overall period) |
| Is this the baseline period? | Yes |
| Allocation method | Not applicable |
| Blinding used | Not blinded |

### Arms

| | |
|---|---|
| **Arm title** | Natalizumab |

Arm description:

Subjects with MS-related fatigue received Natalizumab infusion as per the summary of product characteristics (SmPC).

| | |
|---|---|
| Arm type | Experimental |
| Investigational medicinal product name | Natalizumab |
| Investigational medicinal product code | |
| Other name | Tysabri® |
| Pharmaceutical forms | Infusion |
| Routes of administration | Intravenous use |

Dosage and administration details:

Natalizumab infusion as per the SmPC.

| **Number of subjects in period 1** | Natalizumab |
|---|---|
| Started | 195 |
| Completed | 164 |
| Not completed | 31 |
| Moved/Long Travel Distance | 6 |
| Informed Consent Withdrawn | 3 |
| Other | 8 |
| Non-fulfillment of in/exclusion criteria | 1 |
| Antibodies Against Tysabri | 3 |
| Due to Adverse Event | 8 |
| Pregnancy/pregnancy wish | 2 |

## Baseline characteristics

| Reporting groups | |
|---|---|
| Reporting group title | Natalizumab |
| Reporting group description: | |
| Subjects with MS-related fatigue received Natalizumab infusion as per the summary of product characteristics (SmPC). | |

| Reporting group values | Natalizumab | Total | |
|---|---|---|---|
| Number of subjects | 195 | 195 | |
| Age Categorical | | | |
| Units: Subjects | | | |

| | | | |
|---|---|---|---|
| Age Continuous | | | |
| Units: years | | | |
| arithmetic mean | 39.7 | | |
| standard deviation | ± 9.2 | - | |
| Gender Categorical | | | |
| Units: Subjects | | | |
| Female | 139 | 139 | |
| Male | 56 | 56 | |

## End points

### End points reporting groups

| Reporting group title | Natalizumab |
|---|---|

Reporting group description:

Subjects with MS-related fatigue received Natalizumab infusion as per the summary of product characteristics (SmPC).

### Primary: Change From Baseline in Total Fatigue Scale for Motor and Cognitive Functions (FSMC) Score at Month 12

| End point title | Change From Baseline in Total Fatigue Scale for Motor and Cognitive Functions (FSMC) Score at Month 12[1] |
|---|---|

End point description:

FSMC is a 20-item questionnaire (Ten questions relate to motor fatigue and ten to cognitive fatigue) and produces a score between 1 and 5 for each scored question (ranging from "does not apply at all" to "applies completely"). Items are summed to generate a total score and transformed to a scale with a range of 20 to 100, where higher scores indicate higher levels of fatigue. A negative change from baseline indicates improvement. Intention to treat (ITT) population included all subjects who were enrolled and treated with Natalizumab.

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

End point timeframe:

Baseline, Month 12

Notes:

[1] - 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: Only descriptive statistics were planned to be reported for this endpoint.

| End point values | Natalizumab | | | |
|---|---|---|---|---|
| Subject group type | Reporting group | | | |
| Number of subjects analysed | 162[2] | | | |
| Units: score on a scale | | | | |
| least squares mean (standard error) | -9.00 (± 1.10) | | | |

Notes:

[2] - Number of subjects analysed signifies those subjects who were evaluable for this endpoint.

### Statistical analyses

No statistical analyses for this end point

### Secondary: Change From Baseline in Total FSMC Fatigue Score at Month 3, 6, and 9

| End point title | Change From Baseline in Total FSMC Fatigue Score at Month 3, 6, and 9 |
|---|---|

End point description:

FSMC is a 20-item questionnaire (Ten questions relate to motor fatigue and ten to cognitive fatigue) and produces a score between 1 and 5 for each scored question (ranging from "does not apply at all" to "applies completely"). Items are summed to generate a total score and transformed to a scale with a range of 20 to 100, where higher scores indicate higher levels of fatigue. A negative change from baseline indicates improvement. ITT population included all subjects who were enrolled and treated with Natalizumab. Here ‘n’ signifies the number of subjects who were evaluated at specified timepoints.

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

End point timeframe:

Baseline, Month 3, 6, and 9

| End point values | Natalizumab | | | |
|---|---|---|---|---|
| Subject group type | Reporting group | | | |
| Number of subjects analysed | 195 | | | |
| Units: score on a scale | | | | |
| least squares mean (standard error) | | | | |
| Baseline (n =195) | -0.21 (± 0.06) | | | |
| Change at Month 3 (n =180) | -5.09 (± 0.81) | | | |
| Change at Month 6 (n =173) | -7.03 (± 0.94) | | | |
| Change at Month 9 (n =161) | -8.58 (± 1.01) | | | |

## Statistical analyses

No statistical analyses for this end point

## Secondary: Change From Baseline in FSMC Motor Score at Month 3, 6 and 9

| End point title | Change From Baseline in FSMC Motor Score at Month 3, 6 and 9 |
|---|---|

End point description:

FSMC is a 20-item questionnaire that includes 10 questions related to motor fatigue and produces a score between 1 and 5 for each scored question (ranging from "does not apply at all" to "applies completely"). Items are summed to generate a total score and transformed to a scale with a range of 10 to 50, where higher scores indicate higher levels of motor fatigue. A negative change from baseline indicates improvement. ITT population included all subjects who were enrolled and treated with Natalizumab. Here, 'n' signifies those subjects who were evaluable at specified timepoint.

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

End point timeframe:

Baseline, Month 3, 6 and 9

| End point values | Natalizumab | | | |
|---|---|---|---|---|
| Subject group type | Reporting group | | | |
| Number of subjects analysed | 195 | | | |
| Units: score on a Scale | | | | |
| least squares mean (standard error) | | | | |
| Baseline (n =195) | -0.25 (± 0.06) | | | |
| Change at Month 3 (n =180) | -2.80 (± 0.44) | | | |
| Change at Month 6 (n =172) | -3.74 (± 0.50) | | | |
| Change at Month 9 (n =161) | -4.71 (± 0.54) | | | |

## Statistical analyses

No statistical analyses for this end point

## Secondary: Change From Baseline in FSMC Cognitive Scores at Month 3, 6 and 9

| End point title | Change From Baseline in FSMC Cognitive Scores at Month 3, 6 and 9 |
|---|---|

End point description:

FSMC is a 20-item questionnaire that includes 10 questions relate to cognitive fatigue and produces a score between 1 and 5 for each scored question (ranging from "does not apply at all" to "applies completely"). Items are summed to generate a total score and transformed to a scale with a range of 10 to 50, where higher scores indicate higher levels of cognitive fatigue. A negative change from baseline indicates improvement. ITT population included all subjects who were enrolled and treated with Natalizumab. Here, 'n' signifies those subjects who were evaluable at specified timepoint.

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

End point timeframe:

Baseline, Month 3, 6 and 9

| End point values | Natalizumab | | | |
|---|---|---|---|---|
| Subject group type | Reporting group | | | |
| Number of subjects analysed | 195 | | | |
| Units: score on a scale | | | | |
| least squares mean (standard error) | | | | |
| Baseline (n =195) | -0.20 (± 0.05) | | | |
| Change at Month 3 (n =180) | -2.29 (± 0.42) | | | |
| Change at Month 6 (n =173) | -3.29 (± 0.50) | | | |
| Change at Month 9 (n =161) | -3.89 (± 0.53) | | | |

### Statistical analyses

No statistical analyses for this end point

## Secondary: Change From Baseline in Capacity for Work Questionnaire (CWQ) Score at Month 6 and 12

| End point title | Change From Baseline in Capacity for Work Questionnaire (CWQ) Score at Month 6 and 12 |
|---|---|

End point description:

The CWQ contained several different questions to measure subjects' Capacity for Work. Only one question – Question 1 – could be analysed across countries. CWQ Question 1 was used to analyse whether the subjects increased their number of weekly working hours. The question 'How many hours per week are you working?' was divided into 6 categories 0, 1- 10, 11-20, 21-30, 31-40 and 'Other'. Subjects with more working hours showed improvement. ITT population included all subjects who were enrolled and treated with Natalizumab. Here, measure type 'number' indicates odds ratio for Question 1. An odds ratio larger than 1 means improvement from baseline to month 6 and 12, respectively.

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

End point timeframe:

Baseline, Month 6 and 12

| End point values | Natalizumab | | | |
|---|---|---|---|---|
| Subject group type | Reporting group | | | |
| Number of subjects analysed | 119[3] | | | |
| Units: odds ratio | | | | |
| number (confidence interval 95%) | | | | |
| Change at Month 6 | 0.91 (0.57 to 1.44) | | | |
| Change at Month 12 | 0.90 (0.57 to 1.42) | | | |

Notes:

[3] - Number of subjects evaluated for this endpoint.

### Statistical analyses

No statistical analyses for this end point

## Secondary: Change From Baseline in Health-Related Quality of Life (HRQoL) Short Form Questionnaire (SF-12) Score at Month 6 and 12

| End point title | Change From Baseline in Health-Related Quality of Life (HRQoL) Short Form Questionnaire (SF-12) Score at Month 6 and 12 |
|---|---|

End point description:

HRQoL SF-12 is a multipurpose short form survey with 12 questions. The questions were combined, scored, and weighted to create two scales that provide glimpses into mental and physical functioning and overall health-related-quality of life. Both components were computed using the scores of 12 questions and range from 0 to 100, where a 0 score indicates the lowest level of health and 100 indicates the highest level of health. A positive change from baseline indicates improvement. ITT population included all subjects who were enrolled and treated with Natalizumab. Here, 'n' signifies those subjects who were evaluable at specified timepoint.

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

End point timeframe:

Baseline, Month 6 and 12

| End point values | Natalizumab | | | |
|---|---|---|---|---|
| Subject group type | Reporting group | | | |
| Number of subjects analysed | 172[4] | | | |
| Units: score on a scale | | | | |
| least squares mean (standard error) | | | | |
| Physical; Baseline (n =172) | -0.37 (± 0.056) | | | |
| Physical; Change at Month 6 (n =143) | 3.84 (± 0.574) | | | |
| Physical; Change at Month 12 (n =137) | 3.89 (± 0.582) | | | |
| Mental; Baseline (n =172) | -0.57 (± 0.058) | | | |
| Mental; Change at Month 6 (n =143) | 4.20 (± 0.724) | | | |
| Mental; Change at Month 12 (n =137) | 4.17 (± 0.737) | | | |

Notes:

[4] - Number of subjects analysed are the subjects who were evaluated for this endpoint.

### Statistical analyses

No statistical analyses for this end point

## Secondary: Change From Baseline in Epworth Sleepiness Scale (ESS) Score at Month 6 and 12

| End point title | Change From Baseline in Epworth Sleepiness Scale (ESS) Score at Month 6 and 12 |
|---|---|

End point description:

The ESS was consisted of very short questionnaire to measure daytime sleepiness. The questionnaire asked the subjects to rate his or her probability of falling asleep on a scale of increasing probability from 0 to 3 for eight different situations that most people engage in during their daily lives, though not necessarily every day. The scores for the eight questions were added together to obtain a single number. A number in the 0–9 range was considered to be normal while a number in the 10–24 range indicated that expert medical advice was required. The total ESS score is the sum of 8 item-scores and can range between 0 and 24, where higher scores indicate higher levels of a person's level of daytime sleepiness. A negative change from baseline indicates improvement. ITT population included all subjects who were enrolled and treated with Natalizumab. Here, 'n' signifies those subjects who were evaluable at specified timepoint.

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

End point timeframe:

Baseline, Month 6 and 12

| **End point values** | Natalizumab | | | |
|---|---|---|---|---|
| Subject group type | Reporting group | | | |
| Number of subjects analysed | 172[5] | | | |
| Units: score on a scale | | | | |
| least squares mean (standard error) | | | | |
| Baseline (n =172) | -0.38 (± 0.054) | | | |
| Change at Month 6 (n =155) | -1.05 (± 0.271) | | | |
| Change at Month 12 (n =143) | -1.33 (± 0.278) | | | |

Notes:

[5] - Number of subjects analysed are the subjects who were evaluated for this endpoint.

### Statistical analyses

No statistical analyses for this end point

## Secondary: Change From Baseline in Center for Epidemiologic Studies Depression Scale (CES-D) Score at Month 6 and 12

| End point title | Change From Baseline in Center for Epidemiologic Studies Depression Scale (CES-D) Score at Month 6 and 12 |
|---|---|

End point description:

CES-D was used to assess depressive symptoms. It is based on a 20 items questionnaire with each score ranging from 0 to 3. If more than 4 items are missing the sum score will be set to missing as well. A score of 16 or greater is considered depressed. A negative change from baseline indicates improvement. ITT population included all subjects who were enrolled and treated with Natalizumab. Here, 'n' signifies those subjects who were evaluable at specified timepoint.

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

End point timeframe:

Baseline, Month 6 and 12

| End point values | Natalizumab | | | |
|---|---|---|---|---|
| Subject group type | Reporting group | | | |
| Number of subjects analysed | 172[6] | | | |
| Units: score on a scale | | | | |
| least squares mean (standard error) | | | | |
| Baseline (n =172) | -0.46 (± 0.053) | | | |
| Change at Month 6 (n =153) | -3.73 (± 0.667) | | | |
| Change at Month 12 (n =143) | -3.91 (± 0.685) | | | |

Notes:

[6] - Number of subjects analysed are the subjects who were evaluated for this endpoint.

## Statistical analyses

No statistical analyses for this end point

## Secondary: Change From Baseline in Paced Auditory Serial Addition Test (PASAT) Score at Month 6 and 12

| End point title | Change From Baseline in Paced Auditory Serial Addition Test (PASAT) Score at Month 6 and 12 |
|---|---|

End point description:

The PASAT is a measure of cognitive function that specifically assesses auditory information processing speed and flexibility, as well as calculation ability. Stimulus presentation rates were adapted for use with MS subjects. The PASAT is presented on audio compact disk to control the rate of stimulus presentation. Single digits are presented either every 3 seconds (PASAT 1) or every 2 seconds (PASAT 2), and the subject must add each new digit to the one immediately prior to it. The test score is the sum of the total number of correct sums given (out of 60 possible) in each trial. An increase in score indicates an improvement in condition. A positive change from baseline indicates improvement. ITT population included all subjects who were enrolled and treated with Natalizumab. Here, 'n' signifies those subjects who were evaluable at specified timepoint.

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

End point timeframe:

Baseline, Month 6 and 12

| End point values | Natalizumab | | | |
|---|---|---|---|---|
| Subject group type | Reporting group | | | |
| Number of subjects analysed | 172[7] | | | |
| Units: score on a scale | | | | |
| least squares mean (standard error) | | | | |
| Baseline (n =172) | -0.33 (± 0.05) | | | |
| Change at Month 6 (n =143) | 3.82 (± 0.66) | | | |
| Change at Month 12 (n =130) | 4.84 (± 0.68) | | | |

Notes:

[7] - Number of subjects analysed are the subjects who were evaluated for this endpoint.

### Statistical analyses

No statistical analyses for this end point

## Secondary: Symbol Digit Modalities Test (SDMT) Score at Baseline, Month 6, 12

| End point title | Symbol Digit Modalities Test (SDMT) Score at Baseline, Month 6, 12 |
|---|---|

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. The score is the number of correctly coded items from 0-110 in 90 seconds. The total score provides a measure of the speed and accuracy of symbol-digit substitution. ITT population included all subjects who were enrolled and treated with Natalizumab. Here, 'n' signifies those subjects who were evaluable at specified timepoint.

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

End point timeframe:

Baseline, Month 6 and 12

| End point values | Natalizumab | | | |
|---|---|---|---|---|
| Subject group type | Reporting group | | | |
| Number of subjects analysed | 172[8] | | | |
| Units: score on a scale | | | | |
| least squares mean (standard error) | | | | |
| Before 6MWT; Baseline (n =171) | 47.9 (± 0.99) | | | |
| Before 6MWT; Month 6 (n =156) | 51.0 (± 1.04) | | | |
| Before 6MWT; Month 12 (n =143) | 52.3 (± 1.07) | | | |
| After 6MWT; Baseline (n =169) | 51.0 (± 1.11) | | | |
| After 6MWT; Month 6 (n =151) | 55.1 (± 1.19) | | | |
| After 6MWT; Month 12 (n =138) | 56.8 (± 1.23) | | | |

Notes:

[8] - Number of subjects analysed are the subjects who were evaluated for this endpoint.

### Statistical analyses

No statistical analyses for this end point

## Secondary: Change From Baseline in Six-Minute Walk Test (6MWT) Score at Month 6 and 12

| End point title | Change From Baseline in Six-Minute Walk Test (6MWT) Score at Month 6 and 12 |
|---|---|

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. A positive change from baseline indicates improvement. ITT population included all subjects who were enrolled and treated with Natalizumab. Here, 'n' signifies those subjects who were evaluable at specified timepoint.

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

End point timeframe:

Baseline, Month 6 and 12

| End point values | Natalizumab | | | |
|---|---|---|---|---|
| Subject group type | Reporting group | | | |
| Number of subjects analysed | 172[9] | | | |
| Units: score on a scale | | | | |
| least squares mean (standard error) | | | | |
| Baseline (n =172) | -0.14 (± 0.043) | | | |
| Change at Month 6 (n =149) | 23.6 (± 6.2) | | | |
| Change at Month 12 (n =135) | 20.6 (± 6.5) | | | |

Notes:

[9] - Number of subjects analysed are the subjects who were evaluated for this endpoint.

### Statistical analyses

No statistical analyses for this end point

## Secondary: Change From Baseline in Expanded Disability Status Scale (EDSS) Score at Month 6 and 12

| End point title | Change From Baseline in Expanded Disability Status Scale (EDSS) Score at Month 6 and 12 |
|---|---|

End point description:

The EDSS measures disability status is a derived score based on functional system score and ambulation (actual distance walked). EDSS on a scale ranges from 0 to 10, with higher scores indicating more disability. ITT population included all subjects who were enrolled and treated with Natalizumab. Here, 'n' signifies those subjects who were evaluable at specified timepoint.

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

End point timeframe:

Baseline, Month 6 and 12

| End point values | Natalizumab | | | |
|---|---|---|---|---|
| Subject group type | Reporting group | | | |
| Number of subjects analysed | 195 | | | |
| Units: score on a scale | | | | |
| least squares mean (confidence interval 95%) | | | | |
| Change at Month 6 (n =176) | -0.50 (-0.750 to -0.250) | | | |
| Change at Month 12 (n =163) | -0.75 (-0.750 to -0.500) | | | |

### Statistical analyses

No statistical analyses for this end point

## Secondary: Average Daily Number of Steps

| End point title | Average Daily Number of Steps |
|---|---|

End point description:

Step counter is a device for measuring the number of steps a person has taken when actively walking.

to calculate amount of Walking. ITT population included all subjects who were enrolled and treated with Natalizumab. Here, 'n' signifies those subjects who were evaluable at specified timepoint.

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

End point timeframe:

Baseline, Month 6 and 12

| **End point values** | Natalizumab | | | |
|---|---|---|---|---|
| Subject group type | Reporting group | | | |
| Number of subjects analysed | 161[10] | | | |
| Units: number of steps | | | | |
| least squares mean (standard error) | | | | |
| Baseline (n =161) | 4808 (± 383) | | | |
| Month 6 (n =145) | 4866 (± 405) | | | |
| Month 12 (n =128) | 4962 (± 429) | | | |

Notes:

[10] - Number of subjects analysed are the subjects who were evaluated for this endpoint.

## Statistical analyses

No statistical analyses for this end point

## Secondary: Number of Subjects With Fatigue Medication at Baseline, Month 3, 6, 9 and 12

| End point title | Number of Subjects With Fatigue Medication at Baseline, Month 3, 6, 9 and 12 |
|---|---|

End point description:

ITT population included all subjects who were enrolled and treated with Natalizumab.

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

End point timeframe:

Baseline, Month 3, 6, 9 and 12

| **End point values** | Natalizumab | | | |
|---|---|---|---|---|
| Subject group type | Reporting group | | | |
| Number of subjects analysed | 195 | | | |
| Units: subjects | | | | |
| No fatigue medication at all at Baseline | 182 | | | |
| More than zero times but less at Baseline | 2 | | | |
| Five days per month or more but less at Baseline | 0 | | | |
| Every other day or more but less at Baseline | 2 | | | |
| Every day at Baseline | 9 | | | |
| No fatigue medication at all at Month 3 | 172 | | | |
| More than zero times but less at Month 3 | 3 | | | |

| | | | | |
|---|---|---|---|---|
| Five days per month or more but less at Month 3 | 3 | | | |
| Every other day or more but less at Month 3 | 1 | | | |
| Every day at Month 3 | 6 | | | |
| No fatigue medication at all at Month 6 | 164 | | | |
| More than zero times but less at Month 6 | 5 | | | |
| Five days per month or more but less at Month 6 | 0 | | | |
| Every other day or more but less at Month 6 | 3 | | | |
| Every day at Month 6 | 7 | | | |
| No fatigue medication at all at Month 9 | 154 | | | |
| More than zero times but less at Month 9 | 2 | | | |
| Five days per month or more but less at Month 9 | 0 | | | |
| Every other day or more but less at Month 9 | 0 | | | |
| Every day at Month 9 | 10 | | | |
| No fatigue medication at all at Month 12 | 151 | | | |
| More than zero times but less at Month 12 | 2 | | | |
| Five days per month or more but less at Month 12 | 0 | | | |
| Every other day or more but less at Month 12 | 1 | | | |
| Every day at Month 12 | 10 | | | |

## Statistical analyses

No statistical analyses for this end point

## Adverse events

### Adverse events information

Timeframe for reporting adverse events:

Baseline up to Month 12

Adverse event reporting additional description:

Adverse events were only recorded and collected for the subjects recruited in Sweden (83 subjects). ITT population, here equivalent to the safety population. Due to non-availability of MedDRA version, we have reported version as 0.0.

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

### Dictionary used

| | |
|---|---|
| Dictionary name | MedDRA |
| Dictionary version | 0.0 |

### Reporting groups

| | |
|---|---|
| Reporting group title | Natalizumab |

Reporting group description:

Subjects with MS-related fatigue received Natalizumab infusion as per the summary of product characteristics (SmPC).

| Serious adverse events | Natalizumab | | |
|---|---|---|---|
| Total subjects affected by serious adverse events | | | |
| subjects affected / exposed | 6 / 83 (7.23%) | | |
| number of deaths (all causes) | 0 | | |
| number of deaths resulting from adverse events | 0 | | |
| Nervous system disorders | | | |
| Syncope | | | |
| subjects affected / exposed | 1 / 83 (1.20%) | | |
| occurrences causally related to treatment / all | 0 / 1 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Blood and lymphatic system disorders | | | |
| Leukocytosis | | | |
| subjects affected / exposed | 1 / 83 (1.20%) | | |
| occurrences causally related to treatment / all | 0 / 1 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| General disorders and administration site conditions | | | |
| Chest pain | | | |
| subjects affected / exposed | 2 / 83 (2.41%) | | |
| occurrences causally related to treatment / all | 1 / 2 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Pain | | | |

| | | | |
|---|---|---|---|
| subjects affected / exposed | 1 / 83 (1.20%) | | |
| occurrences causally related to treatment / all | 0 / 1 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Respiratory, thoracic and mediastinal disorders | | | |
| Pulmonary embolism | | | |
| subjects affected / exposed | 1 / 83 (1.20%) | | |
| occurrences causally related to treatment / all | 0 / 1 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Infections and infestations | | | |
| Urinary tract infection | | | |
| subjects affected / exposed | 1 / 83 (1.20%) | | |
| occurrences causally related to treatment / all | 0 / 1 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Pilonidal cyst | | | |
| subjects affected / exposed | 1 / 83 (1.20%) | | |
| occurrences causally related to treatment / all | 0 / 1 | | |
| deaths causally related to treatment / all | 0 / 0 | | |

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

| **Non-serious adverse events** | Natalizumab | | |
|---|---|---|---|
| Total subjects affected by non-serious adverse events | | | |
| subjects affected / exposed | 73 / 83 (87.95%) | | |
| Nervous system disorders | | | |
| Headache | | | |
| subjects affected / exposed | 20 / 83 (24.10%) | | |
| occurrences (all) | 22 | | |
| General disorders and administration site conditions | | | |
| Influenza like illness | | | |
| subjects affected / exposed | 5 / 83 (6.02%) | | |
| occurrences (all) | 6 | | |
| Skin and subcutaneous tissue disorders | | | |
| Pruritus | | | |
| subjects affected / exposed | 5 / 83 (6.02%) | | |
| occurrences (all) | 5 | | |

| | | | |
|---|---|---|---|
| Infections and infestations<br>Nasopharyngitis<br>subjects affected / exposed<br>occurrences (all)<br><br>Urinary tract infection<br>subjects affected / exposed<br>occurrences (all) | <br><br>36 / 83 (43.37%)<br>48<br><br><br>7 / 83 (8.43%)<br>11 | | |

## More information

### Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? No

### Interruptions (globally)

Were there any global interruptions to the trial? No

### Limitations and caveats

None reported