# Clinical trial results:
# A Phase 4 Multicenter, Open-Label, Single Arm Study to Evaluate Switching From BRACET/Gilenya® to Natalizumab in Subjects With Relapsing Forms of Multiple Sclerosis (MS)

## Summary

| | |
|---|---|
| EudraCT number | 2013-005586-39 |
| Trial protocol | DE |
| Global end of trial date | 04 November 2015 |

### Results information

| | |
|---|---|
| Result version number | v1 (current) |
| This version publication date | 11 May 2017 |
| First version publication date | 11 May 2017 |

## Trial information

### Trial identification

| | |
|---|---|
| Sponsor protocol code | 101MS409 |

### Additional study identifiers

| | |
|---|---|
| ISRCTN number | - |
| ClinicalTrials.gov id (NCT number) | NCT02241785 |
| WHO universal trial number (UTN) | - |

Notes:

### Sponsors

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

Notes:

### Paediatric regulatory details

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

Notes:

## Results analysis stage

| | |
|---|---|
| Analysis stage | Final |
| Date of interim/final analysis | 04 November 2015 |
| Is this the analysis of the primary completion data? | No |

| | |
|---|---|
| Global end of trial reached? | Yes |
| Global end of trial date | 04 November 2015 |
| Was the trial ended prematurely? | Yes |

Notes:

## General information about the trial

Main objective of the trial:

The primary objective of the study is to determine the efficacy of natalizumab (Tysabri, BG00002) in participants with relapsing forms of multiple sclerosis (MS) who have failed Gilenya or BRACET (Betaseron, Rebif, Avonex, Copaxone, Extavia, Tecfidera) as measured by the proportion of participants with no evidence of disease activity (NEDA) at Year 1. The secondary objectives in this study population are: change in total T1 hypointense and total T2 hyperintense lesion volume; proportion of participants with NEDA at Year 2; evaluation of the impact of natalizumab on annualized relapse rate (ARR); and change in Multiple Sclerosis Impact Scale-29 (MSIS-29) physical impact score.

Protection of trial subjects:

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

Background therapy: -

Evidence for comparator: -

| | |
|---|---|
| Actual start date of recruitment | 18 September 2014 |
| Long term follow-up planned | No |
| Independent data monitoring committee (IDMC) involvement? | No |

Notes:

## Population of trial subjects

### Subjects enrolled per country

| | |
|---|---|
| Country: Number of subjects enrolled | United States: 47 |
| Worldwide total number of subjects | 47 |
| EEA total number of subjects | 0 |

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) | 47 |
| From 65 to 84 years | 0 |
| 85 years and over | 0 |

## Subject disposition

### Recruitment

Recruitment details: -

### Pre-assignment

Screening details:

The study included a 43-day screening period.

### 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:

natalizumab 300 mg intravenously (IV) every 4 weeks

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

Dosage and administration details:

Subjects received 1 open-label Tysabri 300 mg infusion every 4 weeks with the last dose planned to be administered at Week 104.

| **Number of subjects in period 1** | Natalizumab |
|---|---|
| Started | 47 |
| Completed | 0 |
| Not completed | 47 |
| Consent withdrawn by subject | 1 |
| Adverse event, non-fatal | 1 |
| Sponsor Termination | 43 |
| Lost to follow-up | 2 |

## Baseline characteristics

| Reporting groups | |
|---|---|
| Reporting group title | Natalizumab |
| Reporting group description: natalizumab 300 mg intravenously (IV) every 4 weeks | |

| Reporting group values | Natalizumab | Total | |
|---|---|---|---|
| Number of subjects | 47 | 47 | |
| Age categorical<br>Units: Subjects | | | |
| Adults (18-64 years) | 47 | 47 | |
| Age Continuous<br>Units: years | | | |
| arithmetic mean | 41.9 | | |
| standard deviation | ± 10.43 | - | |
| Gender, Male/Female<br>Units: Subjects | | | |
| Female | 34 | 34 | |
| Male | 13 | 13 | |

## End points

### End points reporting groups

| Reporting group title | Natalizumab |
|---|---|
| Reporting group description: natalizumab 300 mg intravenously (IV) every 4 weeks | |

### Primary: Proportion of Subjects With No Evidence of Disease Activity (NEDA) From Reset Baseline (Week 8) to Week 56

| End point title | Proportion of Subjects With No Evidence of Disease Activity (NEDA) From Reset Baseline (Week 8) to Week 56[1] |
|---|---|

End point description:

The proportion of subjects with NEDA, defined as follows: no Expanded Disability Status Scale (EDSS) progression (12-week sustained); no relapses; no gadolinium enhancing (Gd+) lesions; no new or enlarging T2 hyperintense lesions over 48 weeks after resetting the Baseline at Week 8 to remove contribution of combined unique active (CUA) lesions that occurred prior to Week 8, when natalizumab was not yet active. The EDSS quantifies disability in 8 functional systems. The final EDSS score is an ordinal clinical rating scale ranging from 0 (normal neurologic examination) to 10 (death due to MS) in half-point increments.

The limited number of subjects enrolled and the early termination of the study resulted in efficacy data not collected, and efficacy outcomes not analyzed, as per the pre-specified plan of analysis.

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

End point timeframe:

Reset Baseline (Week 8) to Week 56

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: The limited number of subjects enrolled and the early termination of the study resulted in efficacy data not collected, and efficacy outcomes not analyzed, as per the pre-specified plan of analysis.

| End point values | Natalizumab | | | |
|---|---|---|---|---|
| Subject group type | Reporting group | | | |
| Number of subjects analysed | 0[2] | | | |
| Units: proportion of subjects | | | | |

Notes:

[2] - Efficacy data not collected and outcomes not analyzed, as per the pre-specified plan of analysis.

### Statistical analyses

No statistical analyses for this end point

### Secondary: Change in T1 Unenhancing Lesion Volume and T2 Lesion Volume From Baseline (Day -1) to Reset Baseline (Week 8)

| End point title | Change in T1 Unenhancing Lesion Volume and T2 Lesion Volume From Baseline (Day -1) to Reset Baseline (Week 8) |
|---|---|

End point description:

As measured by magnetic resonance imaging.

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

End point timeframe:

Baseline (Day -1) to Reset Baseline (Week 8)

| End point values | Natalizumab | | | |
|---|---|---|---|---|
| Subject group type | Reporting group | | | |
| Number of subjects analysed | 43 | | | |
| Units: cc | | | | |
| arithmetic mean (standard deviation) | | | | |
| Change in T1 Unenhancing Lesion Volume | 0.11 (± 0.65) | | | |
| Change in T2 Lesion Volume | 0.01 (± 1.76) | | | |

### Statistical analyses

No statistical analyses for this end point

## Secondary: Proportion of Subjects With NEDA From Week 8 (Reset Baseline) to Week 104

| End point title | Proportion of Subjects With NEDA From Week 8 (Reset Baseline) to Week 104 |
|---|---|

End point description:

Proportion of subjects with NEDA from Week 8 (Reset Baseline) to Week 104 (with no 12-week confirmed EDSS progression determined at Week 116). NEDA was defined as follows: no EDSS progression (12-week sustained); no relapses; no Gd+ lesions; no new or enlarging T2 hyperintense lesions over 48 weeks after resetting the Baseline at Week 8 to remove contribution of CUA lesions that occurred prior to Week 8, when natalizumab was not yet active. The EDSS quantifies disability in 8 functional systems. The final EDSS score is an ordinal clinical rating scale ranging from 0 (normal neurologic examination) to 10 (death due to MS) in half-point increments.

The limited number of subjects enrolled and the early termination of the study resulted in efficacy data not collected, and efficacy outcomes not analyzed, as per the pre-specified plan of analysis.

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

End point timeframe:

from Week 8 (Reset Baseline) to Week 104

| End point values | Natalizumab | | | |
|---|---|---|---|---|
| Subject group type | Reporting group | | | |
| Number of subjects analysed | 0[3] | | | |
| Units: proportion of subjects | | | | |

Notes:

[3] - Efficacy data not collected and outcomes not analyzed, as per the pre-specified plan of analysis.

### Statistical analyses

No statistical analyses for this end point

## Secondary: Pre- and Post-Natalizumab Infusion Annualized Relapse Rate (ARR) Comparison at Month 12

| End point title | Pre- and Post-Natalizumab Infusion Annualized Relapse Rate (ARR) Comparison at Month 12 |
|---|---|

End point description:

An MS relapse was defined as the onset of new or recurrent neurological symptoms lasting at least 24 hours, accompanied by new objective abnormalities on a neurological examination, and not explained solely by non-MS processes such as fever, infection, severe stress, or drug toxicity. 95% confidence interval is based on a Poisson regression model.

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

End point timeframe:

From 12 months prior to natalizumab infusion and 12 months post-natalizumab infusion

| **End point values** | Natalizumab | | | |
|---|---|---|---|---|
| Subject group type | Reporting group | | | |
| Number of subjects analysed | 47 | | | |
| Units: relapses per subject-year | | | | |
| number (confidence interval 95%) | | | | |
| 12 months pre-natalizumab infusion | 1.553 (1.306 to 1.847) | | | |
| 12 months post-natalizumab infusion | 0.159 (0.076 to 0.331) | | | |

## Statistical analyses

No statistical analyses for this end point

## Secondary: Change in MSIS-29 Physical Impact Scores from Baseline (Day -1) to Reset Baseline (Week 8)

| End point title | Change in MSIS-29 Physical Impact Scores from Baseline (Day -1) to Reset Baseline (Week 8) |
|---|---|

End point description:

The MSIS-29 is a brief self-administered MS-specific instrument measuring physical (20 items) and mental/psychological (9 items) impact of MS. The physical score is generated by summing individual items and then transforming to a scale with a range of 0 to 100, where high scores indicate worse health.

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

End point timeframe:

Baseline (Day -1) to Reset Baseline (Week 8)

| **End point values** | Natalizumab | | | |
|---|---|---|---|---|
| Subject group type | Reporting group | | | |
| Number of subjects analysed | 45 | | | |
| Units: units on a scale | | | | |
| arithmetic mean (standard deviation) | -2.53 (± 12.42) | | | |

## Statistical analyses

No statistical analyses for this end point

## Adverse events

### Adverse events information[1]

Timeframe for reporting adverse events:

From Screening through end of study. Duration of study treatment was up to 13 months.

Adverse event reporting additional description:

SAEs only were collected. Events were not coded by MedDRA.

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

### Dictionary used

| | |
|---|---|
| Dictionary name | events not coded |
| Dictionary version | 0 |

### Reporting groups

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

Reporting group description:

natalizumab 300 mg IV every 4 weeks

Notes:

[1] - There are no non-serious adverse events recorded for these results. It is expected that there will be at least one non-serious adverse event reported.
Justification: The limited number of subjects enrolled and the early termination of the study resulted in serious adverse events data only being collected, as per the pre-specified plan of analysis.

| Serious adverse events | Natalizumab | | |
|---|---|---|---|
| Total subjects affected by serious adverse events | | | |
| subjects affected / exposed | 2 / 47 (4.26%) | | |
| number of deaths (all causes) | 0 | | |
| number of deaths resulting from adverse events | | | |
| Nervous system disorders | | | |
| Syncopal episode | | | |
| subjects affected / exposed | 1 / 47 (2.13%) | | |
| occurrences causally related to treatment / all | 0 / 1 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| General disorders and administration site conditions | | | |
| Non-cardiac chest pain | | | |
| subjects affected / exposed | 1 / 47 (2.13%) | | |
| occurrences causally related to treatment / all | 0 / 1 | | |
| deaths causally related to treatment / all | 0 / 0 | | |

Frequency threshold for reporting non-serious adverse events: 0 %

| **Non-serious adverse events** | Natalizumab | | |
|---|---|---|---|
| Total subjects affected by non-serious adverse events | | | |
| subjects affected / exposed | 0 / 47 (0.00%) | | |

## More information

## Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

| Date | Amendment |
|---|---|
| 16 July 2014 | The primary reasons for this amendment are to amend the term "free(dom) from measured disease activity (FMDA)" to "no evidence of disease activity (NEDA)", to allow sufficient time for MRI scan processing and determination of acceptability prior to Tysabri dosing, and to update procedures for the EDSS examination. In addition, minor revisions were made to study procedures to either clarify procedures or for consistency with other study procedures. |
| 12 August 2014 | The primary reason for this amendment to is to correct the version number listed on the Synopsis of the previous version. |
| 29 October 2014 | The primary reasons for this amendment are to remove the MS cognition composite battery assessments from the protocol, add the time period for the natalizumab infusion, change the number of participating sites from 50 to 30, revise the number of subjects from 200 to 130, revise the number of subjects in the exploratory DTI substudy from 70 to 50, revise the inclusion criteria for lymphocytes to be at or above the lower limit of normal instead of within the normal limits (the LLN value is also provided), revise the exclusion criteria to exclude Tysabri "or any of its ingredients". |
| 23 July 2015 | The primary reason for this amendment is to reduce the time required for subjects to have been on Gilenya® or BRACET at Screening and to increase the period during which disease activity can be observed prior to Screening for entry into the study. |

Notes:

## Interruptions (globally)

Were there any global interruptions to the trial? No

## Limitations and caveats

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

As a result of early study termination and limited available data, no meaningful conclusions can be drawn.

Notes: