



Clinical trial results:

A Randomized, Double-Blind, Placebo-Controlled, Parallel-Group, Dose-Ranging Study to Assess the Efficacy, Safety, Tolerability, and Pharmacokinetics of BII033 in Subjects With Relapsing Forms of Multiple Sclerosis When Used Concurrently With Avonex®

Summary

| | |
|--------------------------|-------------------|
| EudraCT number | 2011-006262-40 |
| Trial protocol | CZ IT NL HU ES GB |
| Global end of trial date | 29 March 2016 |

Results information

| | |
|--------------------------------|---------------|
| Result version number | v1 (current) |
| This version publication date | 08 April 2017 |
| First version publication date | 08 April 2017 |

Trial information

Trial identification

| | |
|-----------------------|----------|
| Sponsor protocol code | 215MS201 |
|-----------------------|----------|

Additional study identifiers

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

Notes:

Sponsors

| | |
|------------------------------|---|
| Sponsor organisation name | Biogen |
| Sponsor organisation address | 225 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 | 29 March 2016 |
| Is this the analysis of the primary completion data? | No |

| | |
|----------------------------------|---------------|
| Global end of trial reached? | Yes |
| Global end of trial date | 29 March 2016 |
| Was the trial ended prematurely? | No |

Notes:

General information about the trial

Main objective of the trial:

The primary objective of the study is to evaluate the efficacy of BIIB033 in participants with active relapsing multiple sclerosis (MS) when used concurrently with Avonex.

Secondary objectives of this study in this study population are to assess the safety, tolerability, and population pharmacokinetics of BIIB033 when used concurrently with Avonex.

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:

Avonex at 30 µg administered IM once weekly is marketed around the world as a therapeutic agent for patients with relapsing forms of MS to slow the accumulation of physical disability and decrease the frequency of clinical exacerbations. Efficacy has also been demonstrated in MS patients who have experienced a first clinical episode and have MRI features consistent with MS.

Evidence for comparator: -

| | |
|---|----------------|
| Actual start date of recruitment | 13 August 2013 |
| 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 | Poland: 118 |
| Country: Number of subjects enrolled | Serbia: 75 |
| Country: Number of subjects enrolled | United States: 52 |
| Country: Number of subjects enrolled | Czech Republic: 48 |
| Country: Number of subjects enrolled | Russian Federation: 35 |
| Country: Number of subjects enrolled | Spain: 23 |
| Country: Number of subjects enrolled | Italy: 18 |
| Country: Number of subjects enrolled | Netherlands: 12 |
| Country: Number of subjects enrolled | Canada: 11 |
| Country: Number of subjects enrolled | United Kingdom: 11 |
| Country: Number of subjects enrolled | France: 9 |
| Country: Number of subjects enrolled | Hungary: 7 |

| | |
|------------------------------------|-----|
| Worldwide total number of subjects | 419 |
| EEA total number of subjects | 246 |

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) | 419 |
| From 65 to 84 years | 0 |
| 85 years and over | 0 |

Subject disposition

Recruitment

Recruitment details: -

Pre-assignment

Screening details:

Subjects were screened within 28 days prior to the first dose of study treatment.

Pre-assignment period milestones

| | |
|----------------------------|-----|
| Number of subjects started | 419 |
|----------------------------|-----|

| | |
|------------------------------|-----|
| Number of subjects completed | 418 |
|------------------------------|-----|

Pre-assignment subject non-completion reasons

| | |
|----------------------------|-----------------------------|
| Reason: Number of subjects | randomized and not dosed: 1 |
|----------------------------|-----------------------------|

Period 1

| | |
|----------------|--------------------------------|
| Period 1 title | Overall Study (overall period) |
|----------------|--------------------------------|

| | |
|------------------------------|-----|
| Is this the baseline period? | Yes |
|------------------------------|-----|

| | |
|-------------------|-------------------------|
| Allocation method | Randomised - controlled |
|-------------------|-------------------------|

| | |
|---------------|--------------|
| Blinding used | Double blind |
|---------------|--------------|

| | |
|---------------|------------------------------|
| Roles blinded | Subject, Investigator, Carer |
|---------------|------------------------------|

Blinding implementation details:

All study staff were blinded to the subject treatment assignments (BIIB033 plus Avonex or placebo plus Avonex) with the exception of the unblinded Pharmacist or designee, who was responsible for preparing the study treatments, and the unblinded Pharmacy Monitor. Avonex was supplied open label.

Arms

| | |
|------------------------------|-----|
| Are arms mutually exclusive? | Yes |
|------------------------------|-----|

| | |
|-----------|---------|
| Arm title | Placebo |
|-----------|---------|

Arm description:

Placebo once every 4 weeks intravenous (IV) infusion up to Week 72. Avonex once-weekly intramuscular (IM) injection up to Week 84.

| | |
|----------|---------|
| Arm type | Placebo |
|----------|---------|

| | |
|--|--|
| Investigational medicinal product name | sterile normal saline (0.9% sodium chloride) |
|--|--|

| | |
|--|--|
| Investigational medicinal product code | |
|--|--|

| | |
|------------|--|
| Other name | |
|------------|--|

| | |
|----------------------|-----------------------|
| Pharmaceutical forms | Solution for infusion |
|----------------------|-----------------------|

| | |
|--------------------------|-----------------|
| Routes of administration | Intravenous use |
|--------------------------|-----------------|

Dosage and administration details:

The manufacturer's directions for material storage and handling were followed, as were standard clinical practices for ensuring sterility of the material.

| | |
|--|--------|
| Investigational medicinal product name | Avonex |
|--|--------|

| | |
|--|--|
| Investigational medicinal product code | |
|--|--|

| | |
|------------|--------------------|
| Other name | interferon beta-1a |
|------------|--------------------|

| | |
|----------------------|------------------------|
| Pharmaceutical forms | Solution for injection |
|----------------------|------------------------|

| | |
|--------------------------|-------------------|
| Routes of administration | Intramuscular use |
|--------------------------|-------------------|

Dosage and administration details:

Avonex was supplied as liquid prefilled (Luer lock) syringes (i.e., Avonex Prefilled Syringe) and autoinjector pens (i.e., Avonex Pen®) for self-administration by IM (or via a proxy) once weekly in countries in which the Avonex Pen is approved. In countries in which the Avonex Pen is not approved, the Avonex Prefilled Syringe was provided.

| | |
|---|--|
| Arm title | BIIB033, 3 mg/kg |
| Arm description: BIIB033 3 mg/kg once every 4 weeks IV infusion up to Week 72. Avonex once-weekly IM injection up to Week 84. | |
| Arm type | Experimental |
| Investigational medicinal product name | Avonex |
| Investigational medicinal product code | |
| Other name | interferon beta-1a |
| Pharmaceutical forms | Solution for injection |
| Routes of administration | Intramuscular use |
| Dosage and administration details: Avonex was supplied as liquid prefilled (Luer lock) syringes (i.e., Avonex Prefilled Syringe) and autoinjector pens (i.e., Avonex Pen®) for self-administration by IM (or via a proxy) once weekly in countries in which the Avonex Pen is approved. In countries in which the Avonex Pen is not approved, the Avonex Prefilled Syringe was provided. | |
| Investigational medicinal product name | BIIB033 |
| Investigational medicinal product code | |
| Other name | Human anti-LINGO-1 monoclonal antibody |
| Pharmaceutical forms | Solution for infusion |
| Routes of administration | Intravenous use |
| Dosage and administration details: BIIB033 was administered by IV infusion following dilution into saline as specified in the Directions for Handling and Administration (DHA). | |
| Arm title | BIIB033, 10 mg/kg |
| Arm description: BIIB033 10 mg/kg once every 4 weeks IV infusion up to Week 72. Avonex once-weekly IM injection up to Week 84. | |
| Arm type | Experimental |
| Investigational medicinal product name | Avonex |
| Investigational medicinal product code | |
| Other name | interferon beta-1a |
| Pharmaceutical forms | Solution for injection |
| Routes of administration | Intramuscular use |
| Dosage and administration details: Avonex was supplied as liquid prefilled (Luer lock) syringes (i.e., Avonex Prefilled Syringe) and autoinjector pens (i.e., Avonex Pen®) for self-administration by IM (or via a proxy) once weekly in countries in which the Avonex Pen is approved. In countries in which the Avonex Pen is not approved, the Avonex Prefilled Syringe was provided. | |
| Investigational medicinal product name | BIIB033 |
| Investigational medicinal product code | |
| Other name | Human anti-LINGO-1 monoclonal antibody |
| Pharmaceutical forms | Solution for infusion |
| Routes of administration | Intravenous use |
| Dosage and administration details: BIIB033 was administered by IV infusion following dilution into saline as specified in the Directions for Handling and Administration (DHA). | |
| Arm title | BIIB033, 30 mg/kg |
| Arm description: BIIB033 30 mg/kg once every 4 weeks IV infusion up to Week 72. Avonex once-weekly IM injection up to Week 84. | |
| Arm type | Experimental |

| | |
|--|--|
| Investigational medicinal product name | BIIB033 |
| Investigational medicinal product code | |
| Other name | Human anti-LINGO-1 monoclonal antibody |
| Pharmaceutical forms | Solution for infusion |
| Routes of administration | Intravenous use |

Dosage and administration details:

BIIB033 was administered by IV infusion following dilution into saline as specified in the Directions for Handling and Administration (DHA).

| | |
|--|------------------------|
| Investigational medicinal product name | Avonex |
| Investigational medicinal product code | |
| Other name | interferon beta-1a |
| Pharmaceutical forms | Solution for injection |
| Routes of administration | Intramuscular use |

Dosage and administration details:

Avonex was supplied as liquid prefilled (Luer lock) syringes (i.e., Avonex Prefilled Syringe) and autoinjector pens (i.e., Avonex Pen®) for self-administration by IM (or via a proxy) once weekly in countries in which the Avonex Pen is approved. In countries in which the Avonex Pen is not approved, the Avonex Prefilled Syringe was provided.

| | |
|------------------|--------------------|
| Arm title | BIIB033, 100 mg/kg |
|------------------|--------------------|

Arm description:

BIIB033 100 mg/kg once every 4 weeks IV infusion up to Week 72. Avonex once-weekly IM injection up to Week 84.

| | |
|--|------------------------|
| Arm type | Experimental |
| Investigational medicinal product name | Avonex |
| Investigational medicinal product code | |
| Other name | interferon beta-1a |
| Pharmaceutical forms | Solution for injection |
| Routes of administration | Intramuscular use |

Dosage and administration details:

Avonex was supplied as liquid prefilled (Luer lock) syringes (i.e., Avonex Prefilled Syringe) and autoinjector pens (i.e., Avonex Pen®) for self-administration by IM (or via a proxy) once weekly in countries in which the Avonex Pen is approved. In countries in which the Avonex Pen is not approved, the Avonex Prefilled Syringe was provided.

| | |
|--|--|
| Investigational medicinal product name | BIIB033 |
| Investigational medicinal product code | |
| Other name | Human anti-LINGO-1 monoclonal antibody |
| Pharmaceutical forms | Solution for infusion |
| Routes of administration | Intravenous use |

Dosage and administration details:

BIIB033 was administered by IV infusion following dilution into saline as specified in the Directions for Handling and Administration (DHA).

| Number of subjects in period 1^[1] | Placebo | BIIB033, 3 mg/kg | BIIB033, 10 mg/kg |
|---|---------|------------------|-------------------|
| Started | 93 | 45 | 95 |
| Randomized and Dosed | 93 | 45 | 95 |
| Completed | 73 | 40 | 84 |
| Not completed | 20 | 5 | 11 |
| Adverse event, serious fatal | - | - | - |
| Consent withdrawn by subject | 9 | 2 | 6 |

| | | | |
|--------------------------|---|---|---|
| Adverse event, non-fatal | 4 | 2 | 4 |
| NotSpecified | 2 | 1 | 1 |
| Investigator Decision | 5 | - | - |
| Lost to follow-up | - | - | - |

| Number of subjects in period 1 ^[1] | BIIB033, 30 mg/kg | BIIB033, 100 mg/kg |
|--|-------------------|--------------------|
| | | |
| Started | 93 | 92 |
| Randomized and Dosed | 93 | 92 |
| Completed | 68 | 69 |
| Not completed | 25 | 23 |
| Adverse event, serious fatal | 1 | - |
| Consent withdrawn by subject | 8 | 8 |
| Adverse event, non-fatal | 7 | 7 |
| NotSpecified | 3 | 1 |
| Investigator Decision | 4 | 6 |
| Lost to follow-up | 2 | 1 |

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: One subject in the BIIB033 30 mg/kg arm was randomized and not dosed.

Baseline characteristics

Reporting groups

| | |
|--|--------------------|
| Reporting group title | Placebo |
| Reporting group description: Placebo once every 4 weeks intravenous (IV) infusion up to Week 72. Avonex once-weekly intramuscular (IM) injection up to Week 84. | |
| Reporting group title | BIIB033, 3 mg/kg |
| Reporting group description: BIIB033 3 mg/kg once every 4 weeks IV infusion up to Week 72. Avonex once-weekly IM injection up to Week 84. | |
| Reporting group title | BIIB033, 10 mg/kg |
| Reporting group description: BIIB033 10 mg/kg once every 4 weeks IV infusion up to Week 72. Avonex once-weekly IM injection up to Week 84. | |
| Reporting group title | BIIB033, 30 mg/kg |
| Reporting group description: BIIB033 30 mg/kg once every 4 weeks IV infusion up to Week 72. Avonex once-weekly IM injection up to Week 84. | |
| Reporting group title | BIIB033, 100 mg/kg |
| Reporting group description: BIIB033 100 mg/kg once every 4 weeks IV infusion up to Week 72. Avonex once-weekly IM injection up to Week 84. | |

| Reporting group values | Placebo | BIIB033, 3 mg/kg | BIIB033, 10 mg/kg |
|--|---------|------------------|-------------------|
| Number of subjects | 93 | 45 | 95 |
| Age categorical Units: Subjects | | | |
| Adults (18-64 years) | 93 | 45 | 95 |
| Age Continuous Units: years | | | |
| arithmetic mean | 39.5 | 36.5 | 40.5 |
| standard deviation | ± 9.29 | ± 9.47 | ± 9.78 |
| Gender, Male/Female Units: Subjects | | | |
| Female | 67 | 24 | 59 |
| Male | 26 | 21 | 36 |

| Reporting group values | BIIB033, 30 mg/kg | BIIB033, 100 mg/kg | Total |
|--|-------------------|--------------------|-------|
| Number of subjects | 93 | 92 | 418 |
| Age categorical Units: Subjects | | | |
| Adults (18-64 years) | 93 | 92 | 418 |
| Age Continuous Units: years | | | |
| arithmetic mean | 40.9 | 39.8 | - |
| standard deviation | ± 9.7 | ± 9.1 | - |
| Gender, Male/Female Units: Subjects | | | |
| Female | 61 | 66 | 277 |

| | | | |
|------|----|----|-----|
| Male | 32 | 26 | 141 |
|------|----|----|-----|

End points

End points reporting groups

| | |
|--|--------------------|
| Reporting group title | Placebo |
| Reporting group description: Placebo once every 4 weeks intravenous (IV) infusion up to Week 72. Avonex once-weekly intramuscular (IM) injection up to Week 84. | |
| Reporting group title | BIIB033, 3 mg/kg |
| Reporting group description: BIIB033 3 mg/kg once every 4 weeks IV infusion up to Week 72. Avonex once-weekly IM injection up to Week 84. | |
| Reporting group title | BIIB033, 10 mg/kg |
| Reporting group description: BIIB033 10 mg/kg once every 4 weeks IV infusion up to Week 72. Avonex once-weekly IM injection up to Week 84. | |
| Reporting group title | BIIB033, 30 mg/kg |
| Reporting group description: BIIB033 30 mg/kg once every 4 weeks IV infusion up to Week 72. Avonex once-weekly IM injection up to Week 84. | |
| Reporting group title | BIIB033, 100 mg/kg |
| Reporting group description: BIIB033 100 mg/kg once every 4 weeks IV infusion up to Week 72. Avonex once-weekly IM injection up to Week 84. | |
| Subject analysis set title | BIIB033 Total |
| Subject analysis set type | Safety analysis |
| Subject analysis set description: BIIB033 3, 10, 30, or 100 mg/kg once every 4 weeks IV infusion | |

Primary: Proportion of Participants Confirmed as Improvement Responders for Primary Multicomponent Endpoint

| | |
|---|--|
| End point title | Proportion of Participants Confirmed as Improvement Responders for Primary Multicomponent Endpoint |
| End point description: Estimated proportion of participants experiencing confirmed improvement in any 1 or more of the following components: a ≥ 1 point decrease in the Expanded Disability Status Scale (EDSS) score from a baseline score of ≤ 6.0 (decrease sustained for ≥ 3 months); a $\geq 15\%$ improvement from baseline in time to complete 9-Hole Peg Test (9HPT) by either hand (improvement sustained for ≥ 3 months for the same hand), where the time is the average time of 2 trials per hand at the same visit; a $\geq 15\%$ improvement from baseline in time to complete Timed 25-Foot Walk (T25FW) test (improvement sustained for ≥ 3 months), where the time is the average time of 2 trials at the same visit; or a $\geq 15\%$ improvement from baseline 3-Second Paced Auditory Serial Addition Test (PASAT-3) score (improvement sustained for 3 months or greater). Estimated proportion of responders is based on logistic regression adjusted for multiple sclerosis (MS) type, region and baseline component assessments. | |
| End point type | Primary |
| End point timeframe: 72 weeks | |

| End point values | Placebo | BIIB033, 3 mg/kg | BIIB033, 10 mg/kg | BIIB033, 30 mg/kg |
|-----------------------------------|-----------------|------------------|-------------------|-------------------|
| Subject group type | Reporting group | Reporting group | Reporting group | Reporting group |
| Number of subjects analysed | 91 | 45 | 94 | 91 |
| Units: proportion of participants | | | | |
| number (not applicable) | 0.516 | 0.511 | 0.656 | 0.688 |

| End point values | BIIB033, 100 mg/kg | | | |
|-----------------------------------|--------------------|--|--|--|
| Subject group type | Reporting group | | | |
| Number of subjects analysed | 91 | | | |
| Units: proportion of participants | | | | |
| number (not applicable) | 0.412 | | | |

Statistical analyses

| Statistical analysis title | Statistical Analysis 1 |
|---|----------------------------|
| Comparison groups | BIIB033, 3 mg/kg v Placebo |
| Number of subjects included in analysis | 136 |
| Analysis specification | Pre-specified |
| Analysis type | superiority |
| P-value | = 0.9584 |
| Method | Regression, Logistic |
| Parameter estimate | Odds ratio (OR) |
| Point estimate | 0.98 |
| Confidence interval | |
| level | 95 % |
| sides | 2-sided |
| lower limit | 0.46 |
| upper limit | 2.07 |

| Statistical analysis title | Statistical Analysis 2 |
|---|-----------------------------|
| Comparison groups | Placebo v BIIB033, 10 mg/kg |
| Number of subjects included in analysis | 185 |
| Analysis specification | Pre-specified |
| Analysis type | superiority |
| P-value | = 0.0636 |
| Method | Regression, Logistic |
| Parameter estimate | Odds ratio (OR) |
| Point estimate | 1.79 |
| Confidence interval | |
| level | 95 % |
| sides | 2-sided |
| lower limit | 0.97 |
| upper limit | 3.31 |

| | |
|---|-----------------------------|
| Statistical analysis title | Statistical Analysis 3 |
| Comparison groups | Placebo v BIIB033, 30 mg/kg |
| Number of subjects included in analysis | 182 |
| Analysis specification | Pre-specified |
| Analysis type | superiority |
| P-value | = 0.022 |
| Method | Regression, Logistic |
| Parameter estimate | Odds ratio (OR) |
| Point estimate | 2.06 |
| Confidence interval | |
| level | 95 % |
| sides | 2-sided |
| lower limit | 1.11 |
| upper limit | 3.84 |

| | |
|---|------------------------------|
| Statistical analysis title | Statistical Analysis 4 |
| Comparison groups | Placebo v BIIB033, 100 mg/kg |
| Number of subjects included in analysis | 182 |
| Analysis specification | Pre-specified |
| Analysis type | superiority |
| P-value | = 0.1771 |
| Method | Regression, Logistic |
| Parameter estimate | Odds ratio (OR) |
| Point estimate | 0.66 |
| Confidence interval | |
| level | 95 % |
| sides | 2-sided |
| lower limit | 0.36 |
| upper limit | 1.21 |

| | |
|---|---|
| Statistical analysis title | Statistical Analysis 5 |
| Comparison groups | Placebo v BIIB033, 3 mg/kg v BIIB033, 10 mg/kg v BIIB033, 30 mg/kg v BIIB033, 100 mg/kg |
| Number of subjects included in analysis | 412 |
| Analysis specification | Pre-specified |
| Analysis type | superiority |
| P-value | = 0.8931 |
| Method | Trend test |

Secondary: Proportion of Participants Confirmed as Worsening Responders for

Primary Multicomponent Endpoint

| | |
|-----------------|--|
| End point title | Proportion of Participants Confirmed as Worsening Responders for Primary Multicomponent Endpoint |
|-----------------|--|

End point description:

Estimated proportion of participants experiencing confirmed clinical worsening in 1 or more components of the multicomponent endpoint (EDSS, T25FW, 9HPT, or PASAT-3) over 72 weeks, defined as: a ≥ 1.0 point increase in EDSS from a baseline score of ≤ 5.5 or a ≥ 0.5 point increase from a baseline score equal to 6.0 (increase sustained for 3 months or greater); a $\geq 15\%$ worsening from baseline in time to complete T25FW test (worsening sustained for 3 months or greater), where the time is the average of 2 trials at the same visit; a $\geq 15\%$ worsening from baseline in time to complete 9HPT by either hand (worsening sustained for 3 months or greater for the same hand), where the time is the average of 2 trials for each hand at the same visit; a $\geq 15\%$ worsening from baseline in PASAT-3 score (worsening sustained for 3 months or greater). Estimated proportion of responders is based on logistic regression adjusted for MS type, region and baseline component assessments.

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

End point timeframe:

72 weeks

| End point values | Placebo | BIIB033, 3 mg/kg | BIIB033, 10 mg/kg | BIIB033, 30 mg/kg |
|-----------------------------------|-----------------|------------------|-------------------|-------------------|
| Subject group type | Reporting group | Reporting group | Reporting group | Reporting group |
| Number of subjects analysed | 91 | 45 | 94 | 91 |
| Units: proportion of participants | | | | |
| number (not applicable) | 0.403 | 0.304 | 0.509 | 0.489 |

| End point values | BIIB033, 100 mg/kg | | | |
|-----------------------------------|--------------------|--|--|--|
| Subject group type | Reporting group | | | |
| Number of subjects analysed | 91 | | | |
| Units: proportion of participants | | | | |
| number (not applicable) | 0.369 | | | |

Statistical analyses

| Statistical analysis title | Statistical Analysis 1 |
|---|----------------------------|
| Comparison groups | Placebo v BIIB033, 3 mg/kg |
| Number of subjects included in analysis | 136 |
| Analysis specification | Pre-specified |
| Analysis type | superiority |
| P-value | = 0.3058 |
| Method | Regression, Logistic |
| Parameter estimate | Odds ratio (OR) |
| Point estimate | 0.65 |

| | |
|---------------------|---------|
| Confidence interval | |
| level | 95 % |
| sides | 2-sided |
| lower limit | 0.28 |
| upper limit | 1.49 |

| | |
|---|-----------------------------|
| Statistical analysis title | Statistical Analysis 2 |
| Comparison groups | Placebo v BIIB033, 10 mg/kg |
| Number of subjects included in analysis | 185 |
| Analysis specification | Pre-specified |
| Analysis type | superiority |
| P-value | = 0.1873 |
| Method | Regression, Logistic |
| Parameter estimate | Odds ratio (OR) |
| Point estimate | 1.53 |
| Confidence interval | |
| level | 95 % |
| sides | 2-sided |
| lower limit | 0.81 |
| upper limit | 2.89 |

| | |
|---|-----------------------------|
| Statistical analysis title | Statistical Analysis 3 |
| Comparison groups | Placebo v BIIB033, 30 mg/kg |
| Number of subjects included in analysis | 182 |
| Analysis specification | Pre-specified |
| Analysis type | superiority |
| P-value | = 0.2766 |
| Method | Regression, Logistic |
| Parameter estimate | Odds ratio (OR) |
| Point estimate | 1.42 |
| Confidence interval | |
| level | 95 % |
| sides | 2-sided |
| lower limit | 0.76 |
| upper limit | 2.65 |

| | |
|-----------------------------------|------------------------------|
| Statistical analysis title | Statistical Analysis 4 |
| Comparison groups | Placebo v BIIB033, 100 mg/kg |

| | |
|---|----------------------|
| Number of subjects included in analysis | 182 |
| Analysis specification | Pre-specified |
| Analysis type | superiority |
| P-value | = 0.6578 |
| Method | Regression, Logistic |
| Parameter estimate | Odds ratio (OR) |
| Point estimate | 0.86 |
| Confidence interval | |
| level | 95 % |
| sides | 2-sided |
| lower limit | 0.45 |
| upper limit | 1.65 |

| | |
|---|---|
| Statistical analysis title | Statistical Analysis 5 |
| Comparison groups | Placebo v BIIB033, 3 mg/kg v BIIB033, 10 mg/kg v BIIB033, 30 mg/kg v BIIB033, 100 mg/kg |
| Number of subjects included in analysis | 412 |
| Analysis specification | Pre-specified |
| Analysis type | superiority |
| P-value | = 0.5255 |
| Method | Trend test |

Secondary: Number of Participants Experiencing Adverse Events (AEs) and Serious Adverse Events (SAEs) and Discontinuations Due to AEs

| | |
|-----------------|--|
| End point title | Number of Participants Experiencing Adverse Events (AEs) and Serious Adverse Events (SAEs) and Discontinuations Due to AEs |
|-----------------|--|

End point description:

An AE was any untoward medical occurrence that did not necessarily have a causal relationship with this treatment. An SAE was any untoward medical occurrence that at any dose: resulted in death; in the view of the Investigators, placed the participant at immediate risk of death (a life-threatening event); however, this did not include an event that, had it occurred in a more severe form, might have caused death; required inpatient hospitalization or prolongation of existing hospitalization; resulted in persistent or significant disability/incapacity; resulted in a congenital anomaly/birth defect; any other medically important event that, in the opinion of the Investigators, could have jeopardized the participant or may have required intervention to prevent one of the other outcomes listed in the definition above.

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

End point timeframe:

Up to 84 weeks

| End point values | Placebo | BIIB033, 3 mg/kg | BIIB033, 10 mg/kg | BIIB033, 30 mg/kg |
|-----------------------------|-----------------|------------------|-------------------|-------------------|
| Subject group type | Reporting group | Reporting group | Reporting group | Reporting group |
| Number of subjects analysed | 93 | 45 | 95 | 93 |
| Units: participants | | | | |
| Any event | 79 | 39 | 84 | 79 |
| Moderate or severe event | 59 | 26 | 59 | 59 |

| | | | | |
|---|----|----|----|----|
| Severe event | 7 | 2 | 6 | 6 |
| BIIB033/placebo-related event | 8 | 8 | 15 | 12 |
| Avonex-related event | 51 | 28 | 58 | 54 |
| Serious event | 13 | 4 | 11 | 20 |
| BIIB033/placebo-related serious event | 1 | 0 | 0 | 1 |
| Avonex-related serious event | 1 | 0 | 0 | 2 |
| Event leading to discontinuation of treatment | 4 | 2 | 3 | 7 |
| Event leading to withdrawal from study | 4 | 2 | 4 | 8 |

| End point values | BIIB033, 100 mg/kg | BIIB033 Total | | |
|---|--------------------|----------------------|--|--|
| Subject group type | Reporting group | Subject analysis set | | |
| Number of subjects analysed | 92 | 325 | | |
| Units: participants | | | | |
| Any event | 73 | 275 | | |
| Moderate or severe event | 58 | 202 | | |
| Severe event | 7 | 21 | | |
| BIIB033/placebo-related event | 16 | 51 | | |
| Avonex-related event | 50 | 190 | | |
| Serious event | 16 | 51 | | |
| BIIB033/placebo-related serious event | 5 | 6 | | |
| Avonex-related serious event | 1 | 3 | | |
| Event leading to discontinuation of treatment | 8 | 20 | | |
| Event leading to withdrawal from study | 7 | 21 | | |

Statistical analyses

No statistical analyses for this end point

Secondary: Pharmacokinetics: BIIB033 Plasma Concentrations up to Week 84

| | |
|-----------------|--|
| End point title | Pharmacokinetics: BIIB033 Plasma Concentrations up to Week 84 ^[1] |
|-----------------|--|

End point description:

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

End point timeframe:

Up to 84 weeks

Notes:

[1] - The end point is not reporting statistics for all the arms in the baseline period. It is expected all the baseline period arms will be reported on when providing values for an end point on the baseline period.
Justification: BIIB033 plasma concentrations are not applicable to the placebo arm.

| End point values | BIIB033, 3 mg/kg | BIIB033, 10 mg/kg | BIIB033, 30 mg/kg | BIIB033, 100 mg/kg |
|--------------------------------------|-------------------|-------------------|-------------------|---------------------|
| Subject group type | Reporting group | Reporting group | Reporting group | Reporting group |
| Number of subjects analysed | 45 | 95 | 92 | 92 |
| Units: µg/mL | | | | |
| arithmetic mean (standard deviation) | | | | |
| Baseline, predose; n=44, 95, 92, 92 | 0 (± 0) | 0.01 (± 0.13) | 7.79 (± 74.75) | 0.42 (± 4.07) |
| Baseline, postdose; n=44, 95, 91, 92 | 66.7 (± 16) | 244.76 (± 77.9) | 688.47 (± 245.73) | 2298.2 (± 712.91) |
| Week 4, predose; n=45, 93, 91, 88 | 10.82 (± 4.11) | 46.28 (± 33.15) | 138.54 (± 92.82) | 457.96 (± 308.09) |
| Week 4, postdose; n=45, 94, 89, 85 | 123.96 (± 315.66) | 279.67 (± 100.01) | 784.08 (± 204.31) | 2763.26 (± 823.42) |
| Week 8, predose; n=45, 95, 89, 85 | 23.55 (± 54.96) | 65.48 (± 52.53) | 195.29 (± 118.24) | 603.11 (± 425.58) |
| Week 8, postdose; n=44, 94, 88, 79 | 86.29 (± 52.74) | 294.44 (± 78.61) | 861.6 (± 274.56) | 2751.25 (± 697.42) |
| Week 16, predose; n=43, 94, 86, 79 | 19.96 (± 9.74) | 71.8 (± 25.13) | 231.94 (± 125.42) | 695.11 (± 438.57) |
| Week 16, postdose; n=41, 93, 85, 78 | 85.95 (± 29.04) | 309.38 (± 83.38) | 881.45 (± 211.32) | 2921.09 (± 1118.88) |
| Week 24, predose; n=42, 93, 85, 74 | 36.41 (± 85.48) | 77.88 (± 33.68) | 230.46 (± 77.4) | 699.63 (± 400.49) |
| Week 24, postdose; n=42, 92, 82, 76 | 144.12 (± 373.36) | 318.01 (± 84.74) | 940.29 (± 231.35) | 2870.29 (± 874.28) |
| Week 36, predose; n=41, 88, 79, 74 | 25.33 (± 18.28) | 85.05 (± 44.67) | 238.48 (± 73.75) | 725.22 (± 344.01) |
| Week 36, postdose; n=42, 88, 77, 73 | 94.62 (± 21.89) | 339.17 (± 88.96) | 917.86 (± 197.96) | 3048.66 (± 989.34) |
| Week 48, predose; n=39, 85, 74, 70 | 20.78 (± 6.26) | 80.28 (± 31.62) | 272.88 (± 167.79) | 806.7 (± 541.78) |
| Week 48, postdose; n=42, 85, 75, 72 | 90.07 (± 23.37) | 334.12 (± 78.43) | 955.25 (± 193.34) | 3167.07 (± 1144.25) |
| Week 60, predose; n=41, 84, 70, 68 | 21.29 (± 12.34) | 81.77 (± 30.24) | 243.18 (± 78.57) | 694.12 (± 200.41) |
| Week 60, postdose; n=42, 84, 71, 71 | 93.11 (± 35.98) | 335.1 (± 93.29) | 939.17 (± 255.64) | 3330.7 (± 1076.88) |
| Week 72, predose; n=41, 85, 72, 68 | 19.53 (± 9.34) | 78.94 (± 29.95) | 215.09 (± 62.98) | 819.39 (± 577.6) |
| Week 72, postdose; n=38, 84, 69, 68 | 82.96 (± 31.84) | 313.13 (± 87.22) | 868.39 (± 231.14) | 3145.82 (± 1233.66) |
| Week 84; n=40, 81, 69, 69 | 2.44 (± 1.25) | 12.77 (± 6.8) | 46.16 (± 31.52) | 127.69 (± 65.46) |

Statistical analyses

No statistical analyses for this end point

Adverse events

Adverse events information

Timeframe for reporting adverse events:

From first dosing of study treatment through end of study (Week 84)

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

Dictionary used

| | |
|-----------------|--------|
| Dictionary name | MedDRA |
|-----------------|--------|

| | |
|--------------------|------|
| Dictionary version | 18.1 |
|--------------------|------|

Reporting groups

| | |
|-----------------------|-----------------|
| Reporting group title | BIIB033 3 mg/kg |
|-----------------------|-----------------|

Reporting group description: -

| | |
|-----------------------|---------|
| Reporting group title | Placebo |
|-----------------------|---------|

Reporting group description: -

| | |
|-----------------------|------------------|
| Reporting group title | BIIB033 30 mg/kg |
|-----------------------|------------------|

Reporting group description: -

| | |
|-----------------------|-------------------|
| Reporting group title | BIIB033 100 mg/kg |
|-----------------------|-------------------|

Reporting group description: -

| | |
|-----------------------|------------------|
| Reporting group title | BIIB033 10 mg/kg |
|-----------------------|------------------|

Reporting group description: -

| Serious adverse events | BIIB033 3 mg/kg | Placebo | BIIB033 30 mg/kg |
|---|-----------------|------------------|------------------|
| Total subjects affected by serious adverse events | | | |
| subjects affected / exposed | 4 / 45 (8.89%) | 13 / 93 (13.98%) | 20 / 93 (21.51%) |
| number of deaths (all causes) | 0 | 0 | 1 |
| number of deaths resulting from adverse events | | | |
| Neoplasms benign, malignant and unspecified (incl cysts and polyps) | | | |
| Breast cancer | | | |
| subjects affected / exposed | 0 / 45 (0.00%) | 0 / 93 (0.00%) | 1 / 93 (1.08%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 1 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Malignant melanoma | | | |
| subjects affected / exposed | 0 / 45 (0.00%) | 0 / 93 (0.00%) | 0 / 93 (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 |
| Thyroid adenoma | | | |
| subjects affected / exposed | 0 / 45 (0.00%) | 0 / 93 (0.00%) | 1 / 93 (1.08%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 1 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |

| | | | |
|---|----------------|----------------|----------------|
| Uterine leiomyoma | | | |
| subjects affected / exposed | 0 / 45 (0.00%) | 0 / 93 (0.00%) | 1 / 93 (1.08%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 1 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Immune system disorders | | | |
| Hypersensitivity | | | |
| subjects affected / exposed | 0 / 45 (0.00%) | 0 / 93 (0.00%) | 0 / 93 (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 |
| Reproductive system and breast disorders | | | |
| Benign prostatic hyperplasia | | | |
| subjects affected / exposed | 0 / 45 (0.00%) | 0 / 93 (0.00%) | 0 / 93 (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 |
| Menorrhagia | | | |
| subjects affected / exposed | 0 / 45 (0.00%) | 0 / 93 (0.00%) | 1 / 93 (1.08%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 1 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Metrorrhagia | | | |
| subjects affected / exposed | 0 / 45 (0.00%) | 0 / 93 (0.00%) | 0 / 93 (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 |
| Uterine polyp | | | |
| subjects affected / exposed | 0 / 45 (0.00%) | 0 / 93 (0.00%) | 0 / 93 (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 |
| Psychiatric disorders | | | |
| Acute psychosis | | | |
| subjects affected / exposed | 0 / 45 (0.00%) | 0 / 93 (0.00%) | 0 / 93 (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 |
| Anxiety | | | |

| | | | |
|---|----------------|----------------|----------------|
| subjects affected / exposed | 0 / 45 (0.00%) | 0 / 93 (0.00%) | 1 / 93 (1.08%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 1 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Bipolar disorder | | | |
| subjects affected / exposed | 0 / 45 (0.00%) | 0 / 93 (0.00%) | 0 / 93 (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 |
| Bipolar i disorder | | | |
| subjects affected / exposed | 0 / 45 (0.00%) | 0 / 93 (0.00%) | 0 / 93 (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 / 45 (0.00%) | 0 / 93 (0.00%) | 1 / 93 (1.08%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 1 / 1 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Investigations | | | |
| Hepatic enzyme increased | | | |
| subjects affected / exposed | 0 / 45 (0.00%) | 1 / 93 (1.08%) | 0 / 93 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Injury, poisoning and procedural complications | | | |
| Fall | | | |
| subjects affected / exposed | 1 / 45 (2.22%) | 0 / 93 (0.00%) | 0 / 93 (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 |
| Femur fracture | | | |
| subjects affected / exposed | 1 / 45 (2.22%) | 0 / 93 (0.00%) | 0 / 93 (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 |
| Intentional overdose | | | |
| subjects affected / exposed | 0 / 45 (0.00%) | 0 / 93 (0.00%) | 1 / 93 (1.08%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 2 / 2 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |

| | | | |
|---|----------------|----------------|------------------|
| Road traffic accident | | | |
| subjects affected / exposed | 0 / 45 (0.00%) | 0 / 93 (0.00%) | 1 / 93 (1.08%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 1 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 1 |
| Cardiac disorders | | | |
| Acute myocardial infarction | | | |
| subjects affected / exposed | 0 / 45 (0.00%) | 0 / 93 (0.00%) | 1 / 93 (1.08%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 1 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Myocardial infarction | | | |
| subjects affected / exposed | 0 / 45 (0.00%) | 0 / 93 (0.00%) | 0 / 93 (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 |
| Myocardial ischaemia | | | |
| subjects affected / exposed | 1 / 45 (2.22%) | 0 / 93 (0.00%) | 0 / 93 (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 |
| Nervous system disorders | | | |
| Multiple sclerosis | | | |
| subjects affected / exposed | 0 / 45 (0.00%) | 0 / 93 (0.00%) | 0 / 93 (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 | 2 / 45 (4.44%) | 7 / 93 (7.53%) | 10 / 93 (10.75%) |
| occurrences causally related to treatment / all | 0 / 3 | 0 / 9 | 0 / 14 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Radicular syndrome | | | |
| subjects affected / exposed | 0 / 45 (0.00%) | 1 / 93 (1.08%) | 0 / 93 (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 |
| Secondary progressive multiple sclerosis | | | |
| subjects affected / exposed | 0 / 45 (0.00%) | 0 / 93 (0.00%) | 1 / 93 (1.08%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 1 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |

| | | | |
|---|----------------|----------------|----------------|
| Seizure | | | |
| subjects affected / exposed | 0 / 45 (0.00%) | 1 / 93 (1.08%) | 0 / 93 (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 |
| Trigeminal neuralgia | | | |
| subjects affected / exposed | 1 / 45 (2.22%) | 0 / 93 (0.00%) | 0 / 93 (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 |
| Blood and lymphatic system disorders | | | |
| Hypochromic anaemia | | | |
| subjects affected / exposed | 0 / 45 (0.00%) | 1 / 93 (1.08%) | 0 / 93 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Gastrointestinal disorders | | | |
| Ileus | | | |
| subjects affected / exposed | 0 / 45 (0.00%) | 0 / 93 (0.00%) | 0 / 93 (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 |
| Pancreatitis | | | |
| subjects affected / exposed | 0 / 45 (0.00%) | 0 / 93 (0.00%) | 0 / 93 (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 |
| Small intestinal obstruction | | | |
| subjects affected / exposed | 0 / 45 (0.00%) | 1 / 93 (1.08%) | 0 / 93 (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 |
| Hepatobiliary disorders | | | |
| Bile duct stone | | | |
| subjects affected / exposed | 0 / 45 (0.00%) | 0 / 93 (0.00%) | 1 / 93 (1.08%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 1 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Cholecystitis acute | | | |

| | | | |
|---|----------------|----------------|----------------|
| subjects affected / exposed | 0 / 45 (0.00%) | 0 / 93 (0.00%) | 1 / 93 (1.08%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 1 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Drug-induced liver injury | | | |
| subjects affected / exposed | 0 / 45 (0.00%) | 0 / 93 (0.00%) | 0 / 93 (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 |
| Musculoskeletal and connective tissue disorders | | | |
| Osteoarthritis | | | |
| subjects affected / exposed | 0 / 45 (0.00%) | 1 / 93 (1.08%) | 0 / 93 (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 |
| Infections and infestations | | | |
| Cystitis | | | |
| subjects affected / exposed | 0 / 45 (0.00%) | 0 / 93 (0.00%) | 1 / 93 (1.08%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 1 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Urinary tract infection | | | |
| subjects affected / exposed | 0 / 45 (0.00%) | 2 / 93 (2.15%) | 0 / 93 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 1 / 2 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Metabolism and nutrition disorders | | | |
| Diabetes mellitus inadequate control | | | |
| subjects affected / exposed | 0 / 45 (0.00%) | 0 / 93 (0.00%) | 1 / 93 (1.08%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 1 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |

| | | | |
|---|-------------------|------------------|--|
| Serious adverse events | BIIB033 100 mg/kg | BIIB033 10 mg/kg | |
| Total subjects affected by serious adverse events | | | |
| subjects affected / exposed | 16 / 92 (17.39%) | 11 / 95 (11.58%) | |
| number of deaths (all causes) | 0 | 0 | |
| number of deaths resulting from adverse events | | | |
| Neoplasms benign, malignant and unspecified (incl cysts and polyps) | | | |
| Breast cancer | | | |

| | | | |
|---|----------------|----------------|--|
| subjects affected / exposed | 0 / 92 (0.00%) | 0 / 95 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Malignant melanoma | | | |
| subjects affected / exposed | 0 / 92 (0.00%) | 1 / 95 (1.05%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Thyroid adenoma | | | |
| subjects affected / exposed | 0 / 92 (0.00%) | 0 / 95 (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 / 92 (0.00%) | 0 / 95 (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 | | | |
| Hypersensitivity | | | |
| subjects affected / exposed | 4 / 92 (4.35%) | 0 / 95 (0.00%) | |
| occurrences causally related to treatment / all | 4 / 4 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Reproductive system and breast disorders | | | |
| Benign prostatic hyperplasia | | | |
| subjects affected / exposed | 0 / 92 (0.00%) | 1 / 95 (1.05%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Menorrhagia | | | |
| subjects affected / exposed | 0 / 92 (0.00%) | 0 / 95 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Metrorrhagia | | | |
| subjects affected / exposed | 0 / 92 (0.00%) | 1 / 95 (1.05%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |

| | | | |
|---|----------------|----------------|--|
| Uterine polyp | | | |
| subjects affected / exposed | 1 / 92 (1.09%) | 0 / 95 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Psychiatric disorders | | | |
| Acute psychosis | | | |
| subjects affected / exposed | 1 / 92 (1.09%) | 0 / 95 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Anxiety | | | |
| subjects affected / exposed | 0 / 92 (0.00%) | 0 / 95 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Bipolar disorder | | | |
| subjects affected / exposed | 1 / 92 (1.09%) | 0 / 95 (0.00%) | |
| occurrences causally related to treatment / all | 1 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Bipolar i disorder | | | |
| subjects affected / exposed | 1 / 92 (1.09%) | 0 / 95 (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 | 0 / 92 (0.00%) | 0 / 95 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Investigations | | | |
| Hepatic enzyme increased | | | |
| subjects affected / exposed | 0 / 92 (0.00%) | 0 / 95 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Injury, poisoning and procedural complications | | | |
| Fall | | | |

| | | | |
|---|----------------|----------------|--|
| subjects affected / exposed | 0 / 92 (0.00%) | 0 / 95 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Femur fracture | | | |
| subjects affected / exposed | 0 / 92 (0.00%) | 0 / 95 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Intentional overdose | | | |
| subjects affected / exposed | 0 / 92 (0.00%) | 0 / 95 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Road traffic accident | | | |
| subjects affected / exposed | 0 / 92 (0.00%) | 0 / 95 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Cardiac disorders | | | |
| Acute myocardial infarction | | | |
| subjects affected / exposed | 0 / 92 (0.00%) | 0 / 95 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Myocardial infarction | | | |
| subjects affected / exposed | 0 / 92 (0.00%) | 1 / 95 (1.05%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Myocardial ischaemia | | | |
| subjects affected / exposed | 0 / 92 (0.00%) | 0 / 95 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Nervous system disorders | | | |
| Multiple sclerosis | | | |
| subjects affected / exposed | 0 / 92 (0.00%) | 1 / 95 (1.05%) | |
| 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 | 6 / 92 (6.52%) | 6 / 95 (6.32%) | |
| occurrences causally related to treatment / all | 0 / 6 | 0 / 11 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Radicular syndrome | | | |
| subjects affected / exposed | 0 / 92 (0.00%) | 0 / 95 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Secondary progressive multiple sclerosis | | | |
| subjects affected / exposed | 0 / 92 (0.00%) | 0 / 95 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Seizure | | | |
| subjects affected / exposed | 0 / 92 (0.00%) | 0 / 95 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Trigeminal neuralgia | | | |
| subjects affected / exposed | 0 / 92 (0.00%) | 0 / 95 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Blood and lymphatic system disorders | | | |
| Hypochromic anaemia | | | |
| subjects affected / exposed | 0 / 92 (0.00%) | 0 / 95 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Gastrointestinal disorders | | | |
| Ileus | | | |
| subjects affected / exposed | 0 / 92 (0.00%) | 1 / 95 (1.05%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Pancreatitis | | | |
| subjects affected / exposed | 1 / 92 (1.09%) | 0 / 95 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |

| | | | |
|---|----------------|----------------|--|
| Small intestinal obstruction subjects affected / exposed | 0 / 92 (0.00%) | 0 / 95 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Hepatobiliary disorders | | | |
| Bile duct stone subjects affected / exposed | 0 / 92 (0.00%) | 0 / 95 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Cholecystitis acute subjects affected / exposed | 0 / 92 (0.00%) | 0 / 95 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Drug-induced liver injury subjects affected / exposed | 1 / 92 (1.09%) | 0 / 95 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Musculoskeletal and connective tissue disorders | | | |
| Osteoarthritis subjects affected / exposed | 0 / 92 (0.00%) | 0 / 95 (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 | | | |
| Cystitis subjects affected / exposed | 0 / 92 (0.00%) | 0 / 95 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Urinary tract infection subjects affected / exposed | 1 / 92 (1.09%) | 0 / 95 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Metabolism and nutrition disorders | | | |
| Diabetes mellitus inadequate control | | | |

| | | | |
|---|----------------|----------------|--|
| subjects affected / exposed | 0 / 92 (0.00%) | 0 / 95 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 0 | 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 | BIIB033 3 mg/kg | Placebo | BIIB033 30 mg/kg |
|---|------------------|------------------|------------------|
| Total subjects affected by non-serious adverse events | | | |
| subjects affected / exposed | 38 / 45 (84.44%) | 74 / 93 (79.57%) | 70 / 93 (75.27%) |
| Investigations | | | |
| Alanine aminotransferase increased | | | |
| subjects affected / exposed | 2 / 45 (4.44%) | 3 / 93 (3.23%) | 6 / 93 (6.45%) |
| occurrences (all) | 2 | 6 | 8 |
| Injury, poisoning and procedural complications | | | |
| Fall | | | |
| subjects affected / exposed | 0 / 45 (0.00%) | 10 / 93 (10.75%) | 8 / 93 (8.60%) |
| occurrences (all) | 0 | 12 | 11 |
| Nervous system disorders | | | |
| Headache | | | |
| subjects affected / exposed | 8 / 45 (17.78%) | 23 / 93 (24.73%) | 13 / 93 (13.98%) |
| occurrences (all) | 22 | 115 | 124 |
| Multiple sclerosis relapse | | | |
| subjects affected / exposed | 17 / 45 (37.78%) | 30 / 93 (32.26%) | 36 / 93 (38.71%) |
| occurrences (all) | 28 | 50 | 69 |
| General disorders and administration site conditions | | | |
| Asthenia | | | |
| subjects affected / exposed | 1 / 45 (2.22%) | 8 / 93 (8.60%) | 6 / 93 (6.45%) |
| occurrences (all) | 3 | 21 | 10 |
| Chills | | | |
| subjects affected / exposed | 4 / 45 (8.89%) | 5 / 93 (5.38%) | 8 / 93 (8.60%) |
| occurrences (all) | 16 | 20 | 29 |
| Fatigue | | | |
| subjects affected / exposed | 6 / 45 (13.33%) | 8 / 93 (8.60%) | 7 / 93 (7.53%) |
| occurrences (all) | 59 | 9 | 100 |
| Influenza like illness | | | |

| | | | |
|---|------------------------|-------------------------|-------------------------|
| subjects affected / exposed occurrences (all) | 17 / 45 (37.78%) 81 | 37 / 93 (39.78%) 494 | 34 / 93 (36.56%) 456 |
| Pyrexia subjects affected / exposed occurrences (all) | 9 / 45 (20.00%) 43 | 7 / 93 (7.53%) 54 | 12 / 93 (12.90%) 36 |
| Gastrointestinal disorders Diarrhoea subjects affected / exposed occurrences (all) | 5 / 45 (11.11%) 7 | 3 / 93 (3.23%) 3 | 3 / 93 (3.23%) 3 |
| Psychiatric disorders Anxiety subjects affected / exposed occurrences (all) | 0 / 45 (0.00%) 0 | 4 / 93 (4.30%) 7 | 2 / 93 (2.15%) 2 |
| Depressed mood subjects affected / exposed occurrences (all) | 3 / 45 (6.67%) 3 | 2 / 93 (2.15%) 2 | 2 / 93 (2.15%) 2 |
| Depression subjects affected / exposed occurrences (all) | 2 / 45 (4.44%) 2 | 6 / 93 (6.45%) 8 | 7 / 93 (7.53%) 7 |
| Insomnia subjects affected / exposed occurrences (all) | 2 / 45 (4.44%) 2 | 1 / 93 (1.08%) 1 | 6 / 93 (6.45%) 7 |
| Musculoskeletal and connective tissue disorders Arthralgia subjects affected / exposed occurrences (all) | 2 / 45 (4.44%) 2 | 3 / 93 (3.23%) 3 | 7 / 93 (7.53%) 8 |
| Back pain subjects affected / exposed occurrences (all) | 3 / 45 (6.67%) 3 | 9 / 93 (9.68%) 9 | 6 / 93 (6.45%) 7 |
| Muscle spasms subjects affected / exposed occurrences (all) | 3 / 45 (6.67%) 3 | 3 / 93 (3.23%) 3 | 2 / 93 (2.15%) 2 |
| Musculoskeletal pain subjects affected / exposed occurrences (all) | 3 / 45 (6.67%) 3 | 1 / 93 (1.08%) 1 | 2 / 93 (2.15%) 2 |
| Myalgia | | | |

| | | | |
|---|-----------------------|------------------------|------------------------|
| subjects affected / exposed occurrences (all) | 1 / 45 (2.22%) 1 | 5 / 93 (5.38%) 74 | 4 / 93 (4.30%) 8 |
| Pain in extremity subjects affected / exposed occurrences (all) | 5 / 45 (11.11%) 5 | 4 / 93 (4.30%) 6 | 7 / 93 (7.53%) 15 |
| Infections and infestations | | | |
| Influenza subjects affected / exposed occurrences (all) | 3 / 45 (6.67%) 3 | 4 / 93 (4.30%) 5 | 4 / 93 (4.30%) 4 |
| Nasopharyngitis subjects affected / exposed occurrences (all) | 3 / 45 (6.67%) 5 | 16 / 93 (17.20%) 27 | 8 / 93 (8.60%) 11 |
| Pharyngitis subjects affected / exposed occurrences (all) | 5 / 45 (11.11%) 5 | 2 / 93 (2.15%) 3 | 3 / 93 (3.23%) 3 |
| Sinusitis subjects affected / exposed occurrences (all) | 2 / 45 (4.44%) 2 | 5 / 93 (5.38%) 6 | 0 / 93 (0.00%) 0 |
| Upper respiratory tract infection subjects affected / exposed occurrences (all) | 4 / 45 (8.89%) 5 | 13 / 93 (13.98%) 14 | 11 / 93 (11.83%) 16 |
| Urinary tract infection subjects affected / exposed occurrences (all) | 7 / 45 (15.56%) 15 | 12 / 93 (12.90%) 13 | 9 / 93 (9.68%) 13 |

| | | | |
|--|---------------------|---------------------|--|
| Non-serious adverse events | BIIB033 100 mg/kg | BIIB033 10 mg/kg | |
| Total subjects affected by non-serious adverse events subjects affected / exposed | 67 / 92 (72.83%) | 79 / 95 (83.16%) | |
| Investigations Alanine aminotransferase increased subjects affected / exposed occurrences (all) | 7 / 92 (7.61%) 7 | 5 / 95 (5.26%) 5 | |
| Injury, poisoning and procedural complications Fall subjects affected / exposed occurrences (all) | 5 / 92 (5.43%) 7 | 4 / 95 (4.21%) 9 | |
| Nervous system disorders | | | |

| | | | |
|--|-------------------------|-------------------------|--|
| Headache subjects affected / exposed occurrences (all) | 11 / 92 (11.96%) 40 | 19 / 95 (20.00%) 61 | |
| Multiple sclerosis relapse subjects affected / exposed occurrences (all) | 28 / 92 (30.43%) 38 | 35 / 95 (36.84%) 52 | |
| General disorders and administration site conditions | | | |
| Asthenia subjects affected / exposed occurrences (all) | 3 / 92 (3.26%) 4 | 5 / 95 (5.26%) 11 | |
| Chills subjects affected / exposed occurrences (all) | 4 / 92 (4.35%) 18 | 4 / 95 (4.21%) 18 | |
| Fatigue subjects affected / exposed occurrences (all) | 7 / 92 (7.61%) 16 | 5 / 95 (5.26%) 5 | |
| Influenza like illness subjects affected / exposed occurrences (all) | 38 / 92 (41.30%) 383 | 51 / 95 (53.68%) 962 | |
| Pyrexia subjects affected / exposed occurrences (all) | 11 / 92 (11.96%) 45 | 8 / 95 (8.42%) 35 | |
| Gastrointestinal disorders | | | |
| Diarrhoea subjects affected / exposed occurrences (all) | 3 / 92 (3.26%) 3 | 3 / 95 (3.16%) 4 | |
| Psychiatric disorders | | | |
| Anxiety subjects affected / exposed occurrences (all) | 3 / 92 (3.26%) 3 | 5 / 95 (5.26%) 7 | |
| Depressed mood subjects affected / exposed occurrences (all) | 1 / 92 (1.09%) 1 | 1 / 95 (1.05%) 1 | |
| Depression subjects affected / exposed occurrences (all) | 2 / 92 (2.17%) 2 | 6 / 95 (6.32%) 6 | |

| | | | |
|---|---|---|--|
| Insomnia subjects affected / exposed occurrences (all) | 5 / 92 (5.43%) 6 | 4 / 95 (4.21%) 5 | |
| Musculoskeletal and connective tissue disorders Arthralgia subjects affected / exposed occurrences (all) Back pain subjects affected / exposed occurrences (all) Muscle spasms subjects affected / exposed occurrences (all) Musculoskeletal pain subjects affected / exposed occurrences (all) Myalgia subjects affected / exposed occurrences (all) Pain in extremity subjects affected / exposed occurrences (all) | 3 / 92 (3.26%) 6 6 / 92 (6.52%) 10 1 / 92 (1.09%) 1 2 / 92 (2.17%) 2 3 / 92 (3.26%) 4 1 / 92 (1.09%) 2 | 4 / 95 (4.21%) 5 9 / 95 (9.47%) 11 2 / 95 (2.11%) 8 1 / 95 (1.05%) 1 5 / 95 (5.26%) 8 5 / 95 (5.26%) 5 | |
| Infections and infestations Influenza subjects affected / exposed occurrences (all) Nasopharyngitis subjects affected / exposed occurrences (all) Pharyngitis subjects affected / exposed occurrences (all) Sinusitis subjects affected / exposed occurrences (all) Upper respiratory tract infection | 6 / 92 (6.52%) 6 10 / 92 (10.87%) 17 3 / 92 (3.26%) 3 2 / 92 (2.17%) 2 | 6 / 95 (6.32%) 6 12 / 95 (12.63%) 22 4 / 95 (4.21%) 4 2 / 95 (2.11%) 4 | |

| | | | |
|-----------------------------|------------------|------------------|--|
| subjects affected / exposed | 9 / 92 (9.78%) | 21 / 95 (22.11%) | |
| occurrences (all) | 14 | 29 | |
| Urinary tract infection | | | |
| subjects affected / exposed | 13 / 92 (14.13%) | 14 / 95 (14.74%) | |
| occurrences (all) | 22 | 18 | |

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

| Date | Amendment |
|------------------|---|
| 19 December 2012 | The primary reasons for the first global amendment (Version 2), dated 19 December 2012, were to change the information for the contact research organization associated with this study, change the use of the Avonex Prefilled Syringe to only Weeks 0 to 3, add the use of the Avonex Pen for the weeks after Week 3, make it mandatory that subjects titrate Avonex in Month 1 using the Avostartgrip Titration Kit and Prefilled Syringes, and define the DSRC and its members. |
| 10 March 2015 | The primary reason for the second global amendment (Version 3), dated 10 March 2015, was to include Avonex assignment during the 3-month safety Follow-Up Period (Weeks 72 to 84). |
| 18 August 2015 | The primary reason for the third global amendment (Version 4) was to omit the interim analysis. Additionally, the following 4 MRI endpoints for pre-existing brain lesions were made optional and ultimately were not measured in this study: <ul style="list-style-type: none">- Change in magnetization transfer ratio (MTR) from Baseline for abnormal T1 volume.- Change in MTR from Baseline for abnormal T2 volume not associated with T1 hypointensity.- Change in diffusion tensor imaging (DTI) from Baseline for abnormal T1 volume.- Change in DTI from Baseline for abnormal T2 volume not associated with T1 hypointensity. |

Notes:

Interruptions (globally)

Were there any global interruptions to the trial? No

Limitations and caveats

None reported