



Clinical trial results:

A Multicenter, Randomized, Double-Blind, Placebo-Controlled Study With Optional

Open-Label Extension in Subjects With Relapsing Multiple Sclerosis to Evaluate the Efficacy and Safety of BII033 as an Add-On Therapy to Anti-Inflammatory Disease-Modifying Therapies

Summary

| | |
|--------------------------|----------------------------|
| EudraCT number | 2017-001224-22 |
| Trial protocol | GB DE CZ HU BE NL ES PL IT |
| Global end of trial date | 12 February 2021 |

Results information

| | |
|--------------------------------|---------------|
| Result version number | v1 |
| This version publication date | 01 March 2022 |
| First version publication date | 01 March 2022 |

Trial information

Trial identification

| | |
|-----------------------|----------|
| Sponsor protocol code | 215MS202 |
|-----------------------|----------|

Additional study identifiers

| | |
|------------------------------------|-------------|
| ISRCTN number | - |
| ClinicalTrials.gov id (NCT number) | NCT03222973 |
| 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 | 12 February 2021 |
| Is this the analysis of the primary completion data? | No |
| Global end of trial reached? | Yes |
| Global end of trial date | 12 February 2021 |
| Was the trial ended prematurely? | Yes |

Notes:

General information about the trial

Main objective of the trial:

The primary objective of Part 1 of this study was to evaluate the effects of BIIB033 versus placebo on disability improvement over 72 weeks. The primary objective of Part 2 of this study was to evaluate the long-term safety profile of BIIB033 as an add-on therapy in subjects with multiple sclerosis (MS).

The secondary objective of Part 1 was to evaluate the effects of BIIB033 versus placebo on additional measures of disability improvement. The secondary objective of Part 2 was to investigate long-term efficacy (disability improvement) and additional safety measures of BIIB033 as an add-on therapy in subjects with MS.

Protection of trial subjects:

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

Background therapy:

Disease modifying therapy (DMT) - The DMTs were a stable dose of Interferon-beta (IFN β) (Avonex, PlegriDy, Betaferon/Betaseron, or Rebif), dimethyl fumarate (DMF) (Tecfidera), and natalizumab (Tysabri), representing different mechanisms of action, anti inflammatory activities, and routes of administration. Based on the clinical judgment of the treating neurologist, subject can switch to another marketed DMT during the study (not limited to protocol-defined DMTs) or may discontinue the DMT altogether.

Evidence for comparator: -

| | |
|---|------------------|
| Actual start date of recruitment | 15 November 2017 |
| Long term follow-up planned | No |
| Independent data monitoring committee (IDMC) involvement? | Yes |

Notes:

Population of trial subjects

Subjects enrolled per country

| | |
|--------------------------------------|----------------|
| Country: Number of subjects enrolled | Australia: 7 |
| Country: Number of subjects enrolled | Belgium: 12 |
| Country: Number of subjects enrolled | Canada: 12 |
| Country: Number of subjects enrolled | Czechia: 34 |
| Country: Number of subjects enrolled | France: 6 |
| Country: Number of subjects enrolled | Germany: 4 |
| Country: Number of subjects enrolled | Hungary: 2 |
| Country: Number of subjects enrolled | Israel: 2 |
| Country: Number of subjects enrolled | Italy: 11 |
| Country: Number of subjects enrolled | Netherlands: 3 |

| | |
|--------------------------------------|--------------------|
| Country: Number of subjects enrolled | Poland: 43 |
| Country: Number of subjects enrolled | Spain: 14 |
| Country: Number of subjects enrolled | Switzerland: 6 |
| Country: Number of subjects enrolled | United Kingdom: 17 |
| Country: Number of subjects enrolled | United States: 90 |
| Worldwide total number of subjects | 263 |
| EEA total number of subjects | 129 |

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) | 263 |
| From 65 to 84 years | 0 |
| 85 years and over | 0 |

Subject disposition

Recruitment

Recruitment details:

Subjects were enrolled at the investigative sites in the Australia, Belgium, Canada, Czech Republic, France, Germany, Hungary, Israel, Italy, Netherlands, Poland, Spain, Switzerland, United Kingdom and United States from 15 November 2017 to 12 February 2021.

Pre-assignment

Screening details:

A total of 263 subjects with relapsing multiple sclerosis (RMS) were randomised in Part 1 (Placebo-controlled) of the study to receive BIIB033 or placebo. Subjects who completed Part 1 and were eligible were enrolled into Part 2 (Open-label) of the study to receive BIIB033.

Period 1

| | |
|------------------------------|---|
| Period 1 title | Part 1 (Week 0 to Week 72) |
| Is this the baseline period? | Yes |
| Allocation method | Randomised - controlled |
| Blinding used | Double blind |
| Roles blinded | Subject, Investigator, Monitor, Carer, Data analyst, Assessor |

Arms

| | |
|------------------------------|-----------------|
| Are arms mutually exclusive? | Yes |
| Arm title | Part 1: Placebo |

Arm description:

Subjects with RMS received placebo intravenously (IV) as an add-on therapy to a background disease-modifying therapy (DMT) once every 4 weeks over 72 weeks.

| | |
|--|--------------------------|
| Arm type | Placebo |
| Investigational medicinal product name | BIIB033-matching placebo |
| Investigational medicinal product code | |
| Other name | |
| Pharmaceutical forms | Solution for infusion |
| Routes of administration | Intravenous use |

Dosage and administration details:

BIIB033-matching placebo administered via IV infusion, once every 4 weeks over 72 weeks.

| | |
|------------------|------------------------|
| Arm title | Part 1: BIIB033 750 mg |
|------------------|------------------------|

Arm description:

Subjects with RMS received BIIB033 750 milligrams (mg) IV as an add-on therapy to a background DMT once every 4 weeks over 72 weeks.

| | |
|--|-----------------------|
| Arm type | Experimental |
| Investigational medicinal product name | BIIB033 |
| Investigational medicinal product code | |
| Other name | Opicinumab |
| Pharmaceutical forms | Solution for infusion |
| Routes of administration | Intravenous use |

Dosage and administration details:

BIIB033 750 mg administered via IV infusion, once every 4 weeks over 72 weeks.

| Number of subjects in period 1 | Part 1: Placebo | Part 1: BIIB033 750 mg |
|----------------------------------|-----------------|------------------------|
| Started | 131 | 132 |
| Intent-to-treat (ITT) Population | 131 | 132 |
| Safety Population | 131 | 132 |
| Completed | 107 | 118 |
| Not completed | 24 | 14 |
| Adverse Event | 3 | - |
| Death | - | 1 |
| Not Specified | 8 | 2 |
| Pregnancy | - | 1 |
| Lost to follow-up | 1 | 1 |
| Consent Withdrawn | 12 | 9 |

Period 2

| | |
|------------------------------|------------------------------|
| Period 2 title | Part 2 (Week 73 to Week 168) |
| Is this the baseline period? | No |
| Allocation method | Not applicable |
| Blinding used | Not blinded |

Arms

| | |
|------------------------------|-----------------------------------|
| Are arms mutually exclusive? | Yes |
| Arm title | Part 2: Placebo to BIIB033 750 mg |

Arm description:

Subjects who received placebo and completed Part 1 were enrolled into Part 2 to receive BIIB033 750 mg IV as an add-on therapy to a background DMT once every 4 weeks for up to a maximum of 80 weeks.

| | |
|--|-----------------------|
| Arm type | Experimental |
| Investigational medicinal product name | BIIB033 |
| Investigational medicinal product code | |
| Other name | Opicinumab |
| Pharmaceutical forms | Solution for infusion |
| Routes of administration | Intravenous use |

Dosage and administration details:

BIIB033 750 mg administered via IV infusion, once every 4 weeks over 80 weeks.

| | |
|------------------|------------------------|
| Arm title | Part 2: BIIB033 750 mg |
|------------------|------------------------|

Arm description:

Subjects who received BIIB033 and completed Part 1 were enrolled into Part 2 to receive BIIB033 750 mg IV as an add-on therapy to a background DMT once every 4 weeks for up to a maximum of 77 weeks.

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

| | |
|--|-----------------------|
| Investigational medicinal product name | BIIB033 |
| Investigational medicinal product code | |
| Other name | Opicinumab |
| Pharmaceutical forms | Solution for infusion |
| Routes of administration | Intravenous use |

Dosage and administration details:

BIIB033 750 mg administered via IV infusion, once every 4 weeks over 77 weeks.

| Number of subjects in period 2^[1] | Part 2: Placebo to BIIB033 750 mg | Part 2: BIIB033 750 mg |
|---|-----------------------------------|------------------------|
| Started | 101 | 113 |
| ITT Population | 101 | 113 |
| Safety Population | 101 | 113 |
| Completed | 0 | 0 |
| Not completed | 101 | 113 |
| Subjects Not Dosed | 1 | - |
| Adverse Event | 2 | - |
| Pregnancy | 2 | 1 |
| Not Specified | 84 | 100 |
| Investigator Decision | 2 | 1 |
| Consent Withdrawn | 10 | 11 |

Notes:

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

Justification: 11 subjects who completed Part 1 did not enter Part 2.

Baseline characteristics

Reporting groups

| | |
|--|------------------------|
| Reporting group title | Part 1: Placebo |
| Reporting group description: Subjects with RMS received placebo intravenously (IV) as an add-on therapy to a background disease-modifying therapy (DMT) once every 4 weeks over 72 weeks. | |
| Reporting group title | Part 1: BIIB033 750 mg |
| Reporting group description: Subjects with RMS received BIIB033 750 milligrams (mg) IV as an add-on therapy to a background DMT once every 4 weeks over 72 weeks. | |

| Reporting group values | Part 1: Placebo | Part 1: BIIB033 750 mg | Total |
|------------------------------------|-----------------|------------------------|-------|
| Number of subjects | 131 | 132 | 263 |
| Age Categorical Units: Subjects | | | |

| | | | |
|---|----------------|----------------|-----|
| Age Continuous Units: years arithmetic mean standard deviation | 37.7 ± 9.25 | 39.4 ± 9.12 | - |
| Gender Categorical Units: Subjects | | | |
| Female | 79 | 90 | 169 |
| Male | 52 | 42 | 94 |
| Race Units: Subjects | | | |
| Asian | 1 | 0 | 1 |
| Black or African American | 4 | 10 | 14 |
| White | 122 | 118 | 240 |
| Not Reported or Unknown | 4 | 4 | 8 |
| Ethnicity Units: Subjects | | | |
| Hispanic or Latino | 5 | 13 | 18 |
| Not Hispanic or Latino | 123 | 116 | 239 |
| Unknown or Not Reported | 3 | 3 | 6 |

End points

End points reporting groups

| | |
|--|-----------------------------------|
| Reporting group title | Part 1: Placebo |
| Reporting group description: Subjects with RMS received placebo intravenously (IV) as an add-on therapy to a background disease-modifying therapy (DMT) once every 4 weeks over 72 weeks. | |
| Reporting group title | Part 1: BIIB033 750 mg |
| Reporting group description: Subjects with RMS received BIIB033 750 milligrams (mg) IV as an add-on therapy to a background DMT once every 4 weeks over 72 weeks. | |
| Reporting group title | Part 2: Placebo to BIIB033 750 mg |
| Reporting group description: Subjects who received placebo and completed Part 1 were enrolled into Part 2 to receive BIIB033 750 mg IV as an add-on therapy to a background DMT once every 4 weeks for up to a maximum of 80 weeks. | |
| Reporting group title | Part 2: BIIB033 750 mg |
| Reporting group description: Subjects who received BIIB033 and completed Part 1 were enrolled into Part 2 to receive BIIB033 750 mg IV as an add-on therapy to a background DMT once every 4 weeks for up to a maximum of 77 weeks. | |

Primary: Part 1: Overall Response Score (ORS)

| | |
|---|--------------------------------------|
| End point title | Part 1: Overall Response Score (ORS) |
| End point description: ORS is a multicomponent score based on 4 components: Expanded Disability Status Scale (EDSS), Timed 25-Foot Walk (T25FW), 9-Hole Peg Test in dominant hand (9HPT-D), and 9HPT in nondominant hand (9HPT-ND). Overall Score=sum of 4 components at each visit [Range: +4 (improvement) to -4 (worsening)]. At each visit, each component is given a score relative to baseline (BL): -1 if threshold is met for worsening, 0 if no changes meet threshold criteria, or +1 if threshold is met for improvement. For T25FW and 9HPT improvement: $\geq 15\%$ decrease in time from BL and worsening: $\geq 15\%$ increase in time from BL. For EDSS, improvement: ≥ 1.0 -point decrease in EDSS from BL score ≤ 6.0 , worsening: ≥ 1 -point increase from a BL score ≤ 5.5 or ≥ 0.5 -point increase from BL score $= 6.0$. Positive ORS=improvement in more components than there was worsening. ITT population=all randomised subjects who received at least 1 dose of study treatment. Subjects were analysed according to their treatment assignment. | |
| End point type | Primary |
| End point timeframe: Part 1: Baseline to Week 72 | |

| End point values | Part 1: Placebo | Part 1: BIIB033 750 mg | | |
|---|-----------------------|------------------------|--|--|
| Subject group type | Reporting group | Reporting group | | |
| Number of subjects analysed | 131 | 132 | | |
| Units: score on a scale | | | | |
| arithmetic mean (confidence interval 95%) | -0.04 (-0.18 to 0.11) | 0.11 (-0.03 to 0.25) | | |

Statistical analyses

| | |
|---|--|
| Statistical analysis title | Over 72 weeks: Overall Response Score |
| Comparison groups | Part 1: Placebo v Part 1: BIIB033 750 mg |
| Number of subjects included in analysis | 263 |
| Analysis specification | Pre-specified |
| Analysis type | superiority |
| P-value | = 0.1479 ^[1] |
| Method | MMRM |
| Parameter estimate | Treatment Difference |
| Point estimate | 0.15 |
| Confidence interval | |
| level | 95 % |
| sides | 2-sided |
| lower limit | -0.05 |
| upper limit | 0.35 |

Notes:

[1] - P-values were based on the Mixed Model for Repeated Measures (MMRM) adjusted for background DMT group, baseline magnetization transfer ratio (MTR)/diffusion tensor imaging (DTI) category and baseline component assessments.

Primary: Part 2: Number of Subjects Experiencing Adverse Events (AEs) and Serious Adverse Events (SAEs)

| | |
|-----------------|---|
| End point title | Part 2: Number of Subjects Experiencing Adverse Events (AEs) and Serious Adverse Events (SAEs) ^[2] |
|-----------------|---|

End point description:

An AE is any untoward medical occurrence in a subject or clinical investigation subject administered a pharmaceutical product and that does not necessarily have a causal relationship with this treatment. An AE can therefore be any unfavorable and unintended sign (including an abnormal laboratory finding), symptom, or disease temporally associated with the use of a medicinal (investigational) product, whether or not related to the medicinal (investigational) product. A SAE is any untoward medical occurrence that at any dose results in death, life-threatening event, requires inpatient hospitalization, significant disability/incapacity or congenital anomaly. Safety population included all subjects who received at least 1 dose of study treatment. Subjects were analysed based on the actual treatment allocation.

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

End point timeframe:

Part 2: Baseline to Week 169

Notes:

[2] - 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: No statistical analysis was planned or performed for this endpoint.

| | | | | |
|-----------------------------|-----------------------------------|------------------------|--|--|
| End point values | Part 2: Placebo to BIIB033 750 mg | Part 2: BIIB033 750 mg | | |
| Subject group type | Reporting group | Reporting group | | |
| Number of subjects analysed | 100 | 113 | | |
| Units: subjects | | | | |
| AEs | 71 | 76 | | |
| SAEs | 9 | 2 | | |

Statistical analyses

No statistical analyses for this end point

Secondary: Part 1: Percentage of Subjects with 12-week Confirmed Improvement in at Least 1 of the Following Assessments: EDSS, T25FW, 9HPT-D, or 9HPT-ND

| | |
|-----------------|---|
| End point title | Part 1: Percentage of Subjects with 12-week Confirmed Improvement in at Least 1 of the Following Assessments: EDSS, T25FW, 9HPT-D, or 9HPT-ND |
|-----------------|---|

End point description:

EDSS measures disability status over time in MS (scale range: 0-10), higher scores=more disability and improvement is ≥ 1.0 -point decrease in EDSS from BL score ≤ 6.0 . T25FW is a quantitative mobility and leg function performance test based on a timed walk over 25 feet that is averaged between two completed trials. Longer time indicates slower walking. The 9HPT is a quantitative test of upper extremity function that measures the time it takes to place 9 pegs into 9 holes and then remove the pegs. Longer time indicates poorer upper limb function. For T25FW and 9HPT $\geq 15\%$ decrease in time from BL indicates improvement. ITT population included all randomised subjects who received at least 1 dose of study treatment. Subjects were analysed according to their treatment assignment regardless of actual treatment received.

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

End point timeframe:

Part 1: Baseline to Week 72

| | | | | |
|-------------------------------|-----------------|------------------------|--|--|
| End point values | Part 1: Placebo | Part 1: BIIB033 750 mg | | |
| Subject group type | Reporting group | Reporting group | | |
| Number of subjects analysed | 131 | 132 | | |
| Units: percentage of subjects | | | | |
| number (not applicable) | 37 | 39 | | |

Statistical analyses

| | |
|-----------------------------------|--|
| Statistical analysis title | Part 1: Placebo vs BIIB033 750 mg |
| Comparison groups | Part 1: Placebo v Part 1: BIIB033 750 mg |

| | |
|---|-------------------------|
| Number of subjects included in analysis | 263 |
| Analysis specification | Pre-specified |
| Analysis type | superiority |
| P-value | = 0.7682 ^[3] |
| Method | Regression, Logistic |
| Parameter estimate | Odds ratio (OR) |
| Point estimate | 1.08 |
| Confidence interval | |
| level | 95 % |
| sides | 2-sided |
| lower limit | 0.65 |
| upper limit | 1.79 |

Notes:

[3] - Odds ratio (active vs. placebo), 95% CI and p-value were based on logistic regression adjusted for background DMT group, baseline MTR/DTI category and baseline component assessments.

Secondary: Part 1: Percentage of Subjects with 12-week Confirmed Improvement in at Least 1 of the Following Assessments: EDSS, T25FW, 9HPT-D, 9HPT-ND, or 3-Second Paced Auditory Serial Addition Test (PASAT-3)

| | |
|-----------------|---|
| End point title | Part 1: Percentage of Subjects with 12-week Confirmed Improvement in at Least 1 of the Following Assessments: EDSS, T25FW, 9HPT-D, 9HPT-ND, or 3-Second Paced Auditory Serial Addition Test (PASAT-3) |
|-----------------|---|

End point description:

EDSS measures disability status over time in MS (scale range: 0-10), higher scores=more disability and improvement is ≥1.0-point decrease in EDSS from BL score ≤6.0. T25FW is quantitative mobility and leg function performance test, where timed walk over 25 feet that is averaged between two completed trials. Longer time=slower walking. 9HPT is quantitative test of upper extremity function, measures time to place 9 pegs into 9 holes and then remove pegs. Longer time=poorer upper limb function. PASAT assesses auditory information processing speed. In 3-second PASAT, numbers are presented at a rate of 1 every 3 seconds with scores (range 0-120), higher scores=better working memory. For T25FW and 9HPT ≥15% decrease in time from BL is improvement. For PASAT ≥15% increase from BL is improvement. ITT population.

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

End point timeframe:

Part 1: Baseline to Week 72

| | | | | |
|-------------------------------|-----------------|------------------------|--|--|
| End point values | Part 1: Placebo | Part 1: BIIB033 750 mg | | |
| Subject group type | Reporting group | Reporting group | | |
| Number of subjects analysed | 131 | 132 | | |
| Units: percentage of subjects | | | | |
| number (not applicable) | 60 | 52 | | |

Statistical analyses

| | |
|-----------------------------------|--|
| Statistical analysis title | Part 1: Placebo vs BIIB033 750 mg |
| Comparison groups | Part 1: Placebo v Part 1: BIIB033 750 mg |

| | |
|---|-------------------------|
| Number of subjects included in analysis | 263 |
| Analysis specification | Pre-specified |
| Analysis type | superiority |
| P-value | = 0.2131 ^[4] |
| Method | Regression, Logistic |
| Parameter estimate | Odds ratio (OR) |
| Point estimate | 0.71 |
| Confidence interval | |
| level | 95 % |
| sides | 2-sided |
| lower limit | 0.41 |
| upper limit | 1.22 |

Notes:

[4] - Odds ratio (active vs. placebo), 95% CI and p-value were based on logistic regression adjusted for background DMT group, baseline MTR/DTI category and baseline component assessments.

Secondary: Part 1: Percentage of Subjects with 12-week Confirmed Improvement in at Least 1 of the Following Assessments: EDSS, T25FW, 9HPT-D, or 9HPT-ND, and Without Confirmed Worsening in any of the 4 Assessments During the 72 Weeks of the Study

| | |
|-----------------|---|
| End point title | Part 1: Percentage of Subjects with 12-week Confirmed Improvement in at Least 1 of the Following Assessments: EDSS, T25FW, 9HPT-D, or 9HPT-ND, and Without Confirmed Worsening in any of the 4 Assessments During the 72 Weeks of the Study |
|-----------------|---|

End point description:

EDSS measures disability status over time in MS on a scale ranging from 0 to 10, with higher scores indicating more disability. For EDSS, improvement is defined as a ≥ 1.0 -point decrease in EDSS from a BL score of ≤ 6.0 , and worsening is defined as a ≥ 1 -point increase from a BL score of ≤ 5.5 or a ≥ 0.5 -point increase from a BL score equal to 6.0. T25FW is a quantitative mobility and leg function performance test based on a timed walk over 25 feet that is averaged between two completed trials. Longer time indicates slower walking. The 9HPT is a quantitative test of upper extremity function that measures the time it takes to place 9 pegs into 9 holes and then remove the pegs. Longer time indicates poorer upper limb function. For T25FW and 9HPT $\geq 15\%$ decrease in time from BL indicates improvement and $\geq 15\%$ increase in time from BL indicates worsening. ITT population.

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

End point timeframe:

Part 1: Baseline to Week 72

| End point values | Part 1: Placebo | Part 1: BIIB033 750 mg | | |
|-------------------------------|-----------------|------------------------|--|--|
| Subject group type | Reporting group | Reporting group | | |
| Number of subjects analysed | 131 | 132 | | |
| Units: percentage of subjects | | | | |
| number (not applicable) | 31 | 28 | | |

Statistical analyses

| | |
|-----------------------------------|--|
| Statistical analysis title | Part 1: Placebo vs BIIB033 750 mg |
| Comparison groups | Part 1: Placebo v Part 1: BIIB033 750 mg |

| | |
|---|-------------------------|
| Number of subjects included in analysis | 263 |
| Analysis specification | Pre-specified |
| Analysis type | superiority |
| P-value | = 0.4654 ^[5] |
| Method | Regression, Logistic |
| Parameter estimate | Odds ratio (OR) |
| Point estimate | 0.81 |
| Confidence interval | |
| level | 95 % |
| sides | 2-sided |
| lower limit | 0.47 |
| upper limit | 1.41 |

Notes:

[5] - Odds ratio (active vs. placebo), 95% CI and p-value were based on logistic regression adjusted for background DMT group, baseline MTR/DTI category and baseline component assessments.

Secondary: Part 1: Percentage of Subjects with 12-week Confirmed Improvement in at Least 1 of the Following Assessments: EDSS, T25FW, 9HPT-D, 9HPT-ND, and Symbol Digit Modalities Test (SDMT)

| | |
|-----------------|---|
| End point title | Part 1: Percentage of Subjects with 12-week Confirmed Improvement in at Least 1 of the Following Assessments: EDSS, T25FW, 9HPT-D, 9HPT-ND, and Symbol Digit Modalities Test (SDMT) |
|-----------------|---|

End point description:

EDSS measures disability status over time in MS on a scale (range 0-10), higher scores=more disability. For EDSS, improvement is a ≥ 1.0 -point decrease in EDSS from a BL score of ≤ 6.0 . T25FW is a quantitative mobility and leg function performance test based on a timed walk over 25 feet that is averaged between two completed trials. Longer time=slower walking. 9HPT is quantitative test of upper extremity function that measures time it takes to place 9 pegs into 9 holes and then remove pegs. Longer time=poorer upper limb function. For T25FW and 9HPT $\geq 15\%$ decrease in time from BL is improvement. The SDMT measures time to pair abstract geometric symbols with specific numbers. The score is the number of correctly coded items (range 0-110) in 90 seconds, higher scores=better outcome. Improvement is: ≥ 4 -point increase from BL. ITT population.

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

End point timeframe:

Part 1: Baseline to Week 72

| End point values | Part 1: Placebo | Part 1: BIIB033 750 mg | | |
|-------------------------------|-----------------|------------------------|--|--|
| Subject group type | Reporting group | Reporting group | | |
| Number of subjects analysed | 131 | 132 | | |
| Units: percentage of subjects | | | | |
| number (not applicable) | 63 | 75 | | |

Statistical analyses

| | |
|-----------------------------------|--|
| Statistical analysis title | Part 1: Placebo vs BIIB033 750 mg |
| Comparison groups | Part 1: Placebo v Part 1: BIIB033 750 mg |

| | |
|---|-------------------------|
| Number of subjects included in analysis | 263 |
| Analysis specification | Pre-specified |
| Analysis type | superiority |
| P-value | = 0.0417 ^[6] |
| Method | Regression, Logistic |
| Parameter estimate | Odds ratio (OR) |
| Point estimate | 1.78 |
| Confidence interval | |
| level | 95 % |
| sides | 2-sided |
| lower limit | 1.02 |
| upper limit | 3.11 |

Notes:

[6] - Odds ratio (active vs. placebo), 95% CI and p-value were based on logistic regression adjusted for background DMT group, baseline MTR/DTI category and baseline component assessments.

Secondary: Part 1: Percentage of Subjects with 12-week Confirmed Improvement in at Least 1 of the Following Assessments: EDSS, T25FW, 9HPT-D, or 9HPT-ND (20% Thresholds for T25FW and 9HPT)

| | |
|-----------------|---|
| End point title | Part 1: Percentage of Subjects with 12-week Confirmed Improvement in at Least 1 of the Following Assessments: EDSS, T25FW, 9HPT-D, or 9HPT-ND (20% Thresholds for T25FW and 9HPT) |
|-----------------|---|

End point description:

EDSS measures disability status over time in MS on a scale ranging from 0 to 10, with higher scores indicating more disability. For EDSS, improvement is defined as a ≥ 1.0 -point decrease in EDSS from a BL score of ≤ 6.0 . T25FW is a quantitative mobility and leg function performance test based on a timed walk over 25 feet that is averaged between two completed trials. Longer time indicates slower walking. The 9HPT is a quantitative test of upper extremity function that measures the time it takes to place 9 pegs into 9 holes and then remove the pegs. Longer time indicates poorer upper limb function. For T25FW and 9HPT $\geq 15\%$ decrease in time from BL indicates improvement. ITT population.

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

End point timeframe:

Part 1: Baseline to Week 72

| | | | | |
|-------------------------------|-----------------|------------------------|--|--|
| End point values | Part 1: Placebo | Part 1: BIIB033 750 mg | | |
| Subject group type | Reporting group | Reporting group | | |
| Number of subjects analysed | 131 | 132 | | |
| Units: percentage of subjects | | | | |
| number (not applicable) | 25 | 32 | | |

Statistical analyses

| | |
|-----------------------------------|--|
| Statistical analysis title | Part 1: Placebo vs BIIB033 750 mg |
| Comparison groups | Part 1: Placebo v Part 1: BIIB033 750 mg |

| | |
|---|-------------------------|
| Number of subjects included in analysis | 263 |
| Analysis specification | Pre-specified |
| Analysis type | superiority |
| P-value | = 0.2908 ^[7] |
| Method | Regression, Logistic |
| Parameter estimate | Odds ratio (OR) |
| Point estimate | 1.35 |
| Confidence interval | |
| level | 95 % |
| sides | 2-sided |
| lower limit | 0.78 |
| upper limit | 2.33 |

Notes:

[7] - Odds ratio (active vs. placebo), 95% CI and p-value were based on logistic regression adjusted for background DMT group, baseline MTR/DTI category and baseline component assessments.

Secondary: Part 2: Overall Response Score

| | |
|--|--------------------------------|
| End point title | Part 2: Overall Response Score |
| End point description: | |
| Part 1 of Study 215MS202 failed to meet its primary endpoint of ORS over 72 weeks. Trial also failed to show efficacy in its secondary endpoints. Thus, Sponsor decided to terminate Part 2 of study early. Hence, protocol prespecified Part 2 analyses that were designed to assess long-term efficacy of BIIB033 in Part 2 were not performed. Protocol prespecified Part 2 analyses that were designed to assess long-term safety of BIIB033 were performed with data available up to study early termination. | |
| End point type | Secondary |
| End point timeframe: | |
| Part 2: Baseline to Week 96 | |

| End point values | Part 2: Placebo to BIIB033 750 mg | Part 2: BIIB033 750 mg | | |
|---|-----------------------------------|------------------------|--|--|
| Subject group type | Reporting group | Reporting group | | |
| Number of subjects analysed | 0 ^[8] | 0 ^[9] | | |
| Units: score on a scale | | | | |
| arithmetic mean (confidence interval 95%) | (to) | (to) | | |

Notes:

[8] - Part 2 efficacy analyses was not performed since study was early terminated due to lack of efficacy.

[9] - Part 2 efficacy analyses was not performed since study was early terminated due to lack of efficacy.

Statistical analyses

No statistical analyses for this end point

Secondary: Part 2: Percentage of Subjects with 24-week Confirmed Improvement in at Least 1 of the Following Assessments: EDSS, T25FW, 9HPT-D, or 9HPT-ND

| | |
|-----------------|---|
| End point title | Part 2: Percentage of Subjects with 24-week Confirmed Improvement in at Least 1 of the Following Assessments: EDSS, T25FW, 9HPT-D, or 9HPT-ND |
|-----------------|---|

End point description:

Part 1 of Study 215MS202 failed to meet its primary endpoint of ORS over 72 weeks. Trial also failed to

show efficacy in its secondary endpoints. Thus, Sponsor decided to terminate Part 2 of study early. Hence, protocol prespecified Part 2 analyses that were designed to assess long-term efficacy of BIIB033 in Part 2 were not performed. Protocol prespecified Part 2 analyses that were designed to assess long-term safety of BIIB033 were performed with data available up to study early termination.

| | |
|------------------------------|-----------|
| End point type | Secondary |
| End point timeframe: | |
| Part 2: Baseline to Week 108 | |

| End point values | Part 2: Placebo to BIIB033 750 mg | Part 2: BIIB033 750 mg | | |
|-------------------------------|-----------------------------------|------------------------|--|--|
| Subject group type | Reporting group | Reporting group | | |
| Number of subjects analysed | 0 ^[10] | 0 ^[11] | | |
| Units: percentage of subjects | | | | |
| number (not applicable) | | | | |

Notes:

[10] - Part 2 efficacy analyses was not performed since study was early terminated due to lack of efficacy.

[11] - Part 2 efficacy analyses was not performed since study was early terminated due to lack of efficacy.

Statistical analyses

No statistical analyses for this end point

Secondary: Part 2: Percentage of Subjects with 24-week Confirmed Improvement in at Least 1 of the Following Assessments: EDSS, T25FW, 9HPT-D, 9HPT-ND, or PASAT-3

| | |
|-----------------|--|
| End point title | Part 2: Percentage of Subjects with 24-week Confirmed Improvement in at Least 1 of the Following Assessments: EDSS, T25FW, 9HPT-D, 9HPT-ND, or PASAT-3 |
|-----------------|--|

End point description:

Part 1 of Study 215MS202 failed to meet its primary endpoint of ORS over 72 weeks. Trial also failed to show efficacy in its secondary endpoints. Thus, Sponsor decided to terminate Part 2 of study early. Hence, protocol prespecified Part 2 analyses that were designed to assess long-term efficacy of BIIB033 in Part 2 were not performed. Protocol prespecified Part 2 analyses that were designed to assess long-term safety of BIIB033 were performed with data available up to study early termination.

| | |
|------------------------------|-----------|
| End point type | Secondary |
| End point timeframe: | |
| Part 2: Baseline to Week 108 | |

| End point values | Part 2: Placebo to BIIB033 750 mg | Part 2: BIIB033 750 mg | | |
|-------------------------------|-----------------------------------|------------------------|--|--|
| Subject group type | Reporting group | Reporting group | | |
| Number of subjects analysed | 0 ^[12] | 0 ^[13] | | |
| Units: percentage of subjects | | | | |
| number (not applicable) | | | | |

Notes:

[12] - Part 2 efficacy analyses was not performed since study was early terminated due to lack of efficacy.

[13] - Part 2 efficacy analyses was not performed since study was early terminated due to lack of efficacy.

Statistical analyses

No statistical analyses for this end point

Secondary: Part 2: Percentage of Subjects with 24-week Confirmed Improvement in at Least 1 of the Following Assessments: EDSS, T25FW, 9HPT-D, or 9HPT-ND, and Without Confirmed Worsening in any of the 4 Assessments During the 96 Weeks of the Study

| | |
|-----------------|---|
| End point title | Part 2: Percentage of Subjects with 24-week Confirmed Improvement in at Least 1 of the Following Assessments: EDSS, T25FW, 9HPT-D, or 9HPT-ND, and Without Confirmed Worsening in any of the 4 Assessments During the 96 Weeks of the Study |
|-----------------|---|

End point description:

Part 1 of Study 215MS202 failed to meet its primary endpoint of ORS over 72 weeks. Trial also failed to show efficacy in its secondary endpoints. Thus, Sponsor decided to terminate Part 2 of study early. Hence, protocol prespecified Part 2 analyses that were designed to assess long-term efficacy of BIIB033 in Part 2 were not performed. Protocol prespecified Part 2 analyses that were designed to assess long-term safety of BIIB033 were performed with data available up to study early termination.

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

End point timeframe:

Part 2: Baseline to Week 96

| End point values | Part 2: Placebo to BIIB033 750 mg | Part 2: BIIB033 750 mg | | |
|-------------------------------|-----------------------------------|------------------------|--|--|
| Subject group type | Reporting group | Reporting group | | |
| Number of subjects analysed | 0 ^[14] | 0 ^[15] | | |
| Units: percentage of subjects | | | | |
| number (not applicable) | | | | |

Notes:

[14] - Part 2 efficacy analyses was not performed since study was early terminated due to lack of efficacy.

[15] - Part 2 efficacy analyses was not performed since study was early terminated due to lack of efficacy.

Statistical analyses

No statistical analyses for this end point

Secondary: Part 2: Percentage of Subjects with 24-week Confirmed Improvement in at Least 1 of the Following Assessments: EDSS, T25FW, 9HPT-D, 9HPT-ND, and SDMT

| | |
|-----------------|--|
| End point title | Part 2: Percentage of Subjects with 24-week Confirmed Improvement in at Least 1 of the Following Assessments: EDSS, T25FW, 9HPT-D, 9HPT-ND, and SDMT |
|-----------------|--|

End point description:

Part 1 of Study 215MS202 failed to meet its primary endpoint of ORS over 72 weeks. Trial also failed to

show efficacy in its secondary endpoints. Thus, Sponsor decided to terminate Part 2 of study early. Hence, protocol prespecified Part 2 analyses that were designed to assess long-term efficacy of BIIB033 in Part 2 were not performed. Protocol prespecified Part 2 analyses that were designed to assess long-term safety of BIIB033 were performed with data available up to study early termination.

| | |
|------------------------------|-----------|
| End point type | Secondary |
| End point timeframe: | |
| Part 2: Baseline to Week 108 | |

| End point values | Part 2: Placebo to BIIB033 750 mg | Part 2: BIIB033 750 mg | | |
|-------------------------------|-----------------------------------|------------------------|--|--|
| Subject group type | Reporting group | Reporting group | | |
| Number of subjects analysed | 0 ^[16] | 0 ^[17] | | |
| Units: percentage of subjects | | | | |
| number (not applicable) | | | | |

Notes:

[16] - Part 2 efficacy analyses was not performed since study was early terminated due to lack of efficacy.

[17] - Part 2 efficacy analyses was not performed since study was early terminated due to lack of efficacy.

Statistical analyses

No statistical analyses for this end point

Secondary: Part 2: Percentage of Subjects with 24-week Confirmed Improvement in at Least 1 of the Following Assessments: EDSS, T25FW, 9HPT-D, or 9HPT-ND (20% Thresholds for T25FW and 9HPT)

| | |
|-----------------|---|
| End point title | Part 2: Percentage of Subjects with 24-week Confirmed Improvement in at Least 1 of the Following Assessments: EDSS, T25FW, 9HPT-D, or 9HPT-ND (20% Thresholds for T25FW and 9HPT) |
|-----------------|---|

End point description:

Part 1 of Study 215MS202 failed to meet its primary endpoint of ORS over 72 weeks. Trial also failed to show efficacy in its secondary endpoints. Thus, Sponsor decided to terminate Part 2 of study early. Hence, protocol prespecified Part 2 analyses that were designed to assess long-term efficacy of BIIB033 in Part 2 were not performed. Protocol prespecified Part 2 analyses that were designed to assess long-term safety of BIIB033 were performed with data available up to study early termination.

| | |
|------------------------------|-----------|
| End point type | Secondary |
| End point timeframe: | |
| Part 2: Baseline to Week 108 | |

| End point values | Part 2: Placebo to BIIB033 750 mg | Part 2: BIIB033 750 mg | | |
|-------------------------------|-----------------------------------|------------------------|--|--|
| Subject group type | Reporting group | Reporting group | | |
| Number of subjects analysed | 0 ^[18] | 0 ^[19] | | |
| Units: percentage of subjects | | | | |
| number (not applicable) | | | | |

Notes:

[18] - Part 2 efficacy analyses was not performed since study was early terminated due to lack of efficacy.

[19] - Part 2 efficacy analyses was not performed since study was early terminated due to lack of efficacy.

Statistical analyses

No statistical analyses for this end point

Secondary: Part 2: Number of Subjects with Potentially Clinically Significant Abnormal Laboratory Values

| | |
|-----------------|---|
| End point title | Part 2: Number of Subjects with Potentially Clinically Significant Abnormal Laboratory Values |
|-----------------|---|

End point description:

Laboratory assessments-hematology, blood chemistry were evaluated for safety. Safety population. Number analysed (n)=number of subjects analysed for this endpoint. Abnormality criteria: In 10^9 /liter (L) [white blood cells $<3.0/ >16$, neutrophils $<1.5/ >13.5$, lymphocytes $<0.8/ >12$, monocytes >2.5 , eosinophils >1.6 , basophils >1.6 , platelets $\leq 75/ \geq 700$], hemoglobin ≤ 95 [female (F)] or ≤ 115 [male (M)] or ≥ 175 (F) or ≥ 190 (M) gram per L (g/L), hematocrit ≤ 32 (F) or ≤ 37 (M) or ≥ 54 (F) or ≥ 60 (M) percentage (%), red blood cells $\leq 3.5/ \geq 6.4$ 10^{12} /L, in millimoles (mmol)/L [sodium $\leq 126/ \geq 156$, potassium $\leq 3/ \geq 6$, chloride $\leq 90/ \geq 118$, bicarbonate $\leq 16/ \geq 35$, calcium $\leq 2/ \geq 3$, phosphorous $\leq 0.5491/ \geq 1.7119$, glucose (non-fasting) $\leq 2.2/ \geq 13.75$], AST/SGOT ≥ 3 x upper limit of normal (ULN), ALT/SGPT ≥ 3 xULN, alkaline phosphatase ≥ 3 xULN, creatinine ≥ 1.5 xULN, total bilirubin ≥ 1.5 xULN, total protein $\leq 45/ \geq 100$ g/L, albumin ≤ 25 g/L, uric acid ≥ 501.5 (F)/ ≥ 619.5 (M) micromole (umol)/L.

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

End point timeframe:

Part 2: Baseline to Week 96

| End point values | Part 2: Placebo to BIIB033 750 mg | Part 2: BIIB033 750 mg | | |
|--|-----------------------------------|------------------------|--|--|
| Subject group type | Reporting group | Reporting group | | |
| Number of subjects analysed | 100 | 113 | | |
| Units: subjects | | | | |
| White blood cells [10^9 /L]: <3.0 (n=98,113) | 3 | 3 | | |
| White blood cells (10^9 /L): >16 (n=98,113) | 2 | 0 | | |
| Neutrophils (10^9 /L): <1.5 (n=98,113) | 3 | 3 | | |
| Neutrophils (10^9 /L): >13.5 (n=98,113) | 0 | 0 | | |
| Lymphocytes (10^9 /L): <0.8 (n=98,113) | 13 | 15 | | |
| Lymphocytes (10^9 /L): >12 (n=98,113) | 1 | 0 | | |
| Monocytes (10^9 /L): >2.5 (n=98,113) | 0 | 0 | | |
| Eosinophils (10^9 /L): >1.6 (n=98,113) | 1 | 0 | | |
| Basophils (10^9 /L): >1.6 (n=98,113) | 0 | 0 | | |
| Hemoglobin (g/L): ≤ 95 (F) / ≤ 115 (M) (n=98,113) | 0 | 2 | | |
| Hemoglobin (g/L): ≥ 175 (F) / ≥ 190 (M) (n=98,113) | 0 | 0 | | |

| | | | | |
|---|---|---|--|--|
| Hematocrit (%): ≤32 (F) or ≤37 (M) (n=98,113) | 2 | 5 | | |
| Hematocrit (%): ≥54 (F) or ≥60 (M) (n=98,113) | 0 | 0 | | |
| Red blood cells (10 ¹² /L): ≤3.5 (n=98,113) | 0 | 0 | | |
| Red blood cells (10 ¹² /L): ≥6.4 (n=98,113) | 0 | 0 | | |
| Platelets (10 ⁹ /L): ≤75 (n=98,113) | 0 | 0 | | |
| Platelets (10 ⁹ /L): ≥700 (n=98,113) | 0 | 0 | | |
| Sodium (mmol/L): ≤126 | 0 | 0 | | |
| Sodium (mmol/L): ≥156 | 0 | 0 | | |
| Potassium (mmol/L): ≤3 | 0 | 1 | | |
| Potassium (mmol/L): ≥6 | 0 | 0 | | |
| Chloride (mmol/L): ≤90 | 0 | 0 | | |
| Chloride (mmol/L): ≥118 | 0 | 0 | | |
| Bicarbonate (mmol/L): ≤16 | 1 | 1 | | |
| Bicarbonate (mmol/L): ≥35 | 0 | 0 | | |
| Calcium (mmol/L): ≤2 | 0 | 1 | | |
| Calcium (mmol/L): ≥3 | 0 | 0 | | |
| Phosphorus (mmol/L): ≤0.5491 | 0 | 1 | | |
| Phosphorus (mmol/L): ≥1.7119 | 0 | 0 | | |
| Aspartate aminotransferase (AST)/SGOT: ≥3xULN | 0 | 0 | | |
| Alanine aminotransferase (ALT)/SGPT: ≥3xULN | 0 | 0 | | |
| Alkaline phosphatase: ≥3xULN | 0 | 0 | | |
| Creatinine: ≥1.5xULN | 0 | 0 | | |
| Total bilirubin: ≥1.5xULN | 0 | 1 | | |
| Total protein (g/L): ≤45 | 0 | 0 | | |
| Total protein (g/L): ≥100 | 0 | 0 | | |
| Albumin (g/L): ≤25 | 0 | 0 | | |
| Uric acid (umol)/L: ≥501.5 (F)/≥619.5 (M) | 1 | 0 | | |
| Glucose (non-fasting) (mmol/L): ≤2.2 | 0 | 0 | | |
| Glucose (non-fasting) (mmol/L): ≥13.75 | 1 | 1 | | |

Statistical analyses

No statistical analyses for this end point

Secondary: Part 2: Number of Subjects with Potentially Clinically Significant Electrocardiogram (ECG) Values

| | |
|-----------------|---|
| End point title | Part 2: Number of Subjects with Potentially Clinically Significant Electrocardiogram (ECG) Values |
|-----------------|---|

End point description:

The ECG result was classified as "normal", "abnormal", "abnormal, not adverse event", or "abnormal, adverse event". Shift to 'abnormal, not adverse event' included shift from normal or unknown to 'abnormal, not adverse event'. Shift to 'abnormal, adverse event' included shift from normal or unknown to 'abnormal, adverse event'. Safety population included all subjects who received at least 1 dose of study treatment. Subjects were analysed based on the actual treatment allocation. 'Number analysed (n)' signifies number of subjects analysed at the specified timepoint for this endpoint.

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

| End point values | Part 2: Placebo to BIIB033 750 mg | Part 2: BIIB033 750 mg | | |
|--|---|------------------------------|--|--|
| Subject group type | Reporting group | Reporting group | | |
| Number of subjects analysed | 100 | 113 | | |
| Units: subjects | | | | |
| At Day (D) 1: Normal | 83 | 89 | | |
| At D1: Abnormal, not Adverse Event (AE) | 10 | 16 | | |
| D1 to Week(W)12: Shift to Abnormal, not AE(n=80,82) | 7 | 6 | | |
| D1 to W12: Shift to Abnormal, AE (n=80,82) | 1 | 0 | | |
| D1 to W24: Shift to Abnormal, not AE (n=79,88) | 4 | 8 | | |
| D1 to W24: Shift to Abnormal, AE (n=79,88) | 0 | 0 | | |
| D1 to W36: Shift to Abnormal, not AE (n=75,85) | 3 | 10 | | |
| D1 to W36: Shift to Abnormal, AE (n=75,85) | 0 | 1 | | |
| D1 to W48: Shift to Abnormal, not AE (n=71,79) | 2 | 7 | | |
| D1 to W48: Shift to Abnormal, AE (n=71,79) | 0 | 1 | | |
| D1 to W60: Shift to Abnormal, not AE (n=52,50) | 3 | 5 | | |
| D1 to W60: Shift to Abnormal, AE (n=52,50) | 0 | 0 | | |
| D1 to W72: Shift to Abnormal, not AE (n=23,23) | 1 | 2 | | |
| D1 to W72: Shift to Abnormal, AE (n=23,23) | 0 | 0 | | |
| D1 to W84: Shift to Abnormal, not AE (n=4,8) | 0 | 2 | | |
| D1 to W84: Shift to Abnormal, AE (n=4,8) | 0 | 0 | | |
| D1 to W96: Shift to Abnormal, not AE (n=2,0) | 0 | 0 | | |
| D1 to W96: Shift to Abnormal, AE (n=2,0) | 0 | 0 | | |
| At W12: Normal | 80 | 81 | | |
| At W12: Abnormal, not AE | 9 | 16 | | |
| At W12: Abnormal, AE | 1 | 0 | | |
| W12 to W24: Shift to Abnormal, not AE (n=79,87) | 4 | 7 | | |
| W12 to W24: Shift to Abnormal, AE (n=79,87) | 0 | 0 | | |
| W12 to W36: Shift to Abnormal, not AE (n=76,86) | 4 | 8 | | |
| W12 to W36: Shift to Abnormal, AE (n=76,86) | 0 | 0 | | |
| W12 to W48: Shift to Abnormal, not AE (n=73,81) | 3 | 6 | | |

| | | | | |
|--|----|----|--|--|
| W12 to W48: Shift to Abnormal, AE (n=73,81) | 0 | 2 | | |
| W12 to W60: Shift to Abnormal, not AE (n=54,52) | 5 | 5 | | |
| W12 to W60: Shift to Abnormal, AE (n=54,52) | 0 | 0 | | |
| W12 to W72: Shift to Abnormal, not AE (n=26,24) | 2 | 1 | | |
| W12 to W72: Shift to Abnormal, AE (n=26,24) | 0 | 0 | | |
| W12 to W84: Shift to Abnormal, not AE (n=6,7) | 0 | 2 | | |
| W12 to W84: Shift to Abnormal, AE (n=6,7) | 0 | 0 | | |
| W12 to W96: Shift to Abnormal, not AE (n=2,0) | 0 | 0 | | |
| W12 to W96: Shift to Abnormal, AE (n=2,0) | 0 | 0 | | |
| At W24: Normal | 83 | 83 | | |
| At W24: Abnormal, not AE | 6 | 20 | | |
| W24 to W36: Shift to Abnormal, not AE (n=78,81) | 5 | 4 | | |
| W24 to W36: Shift to Abnormal, AE (n=78,81) | 0 | 1 | | |
| W24 to W48: Shift to Abnormal, not AE (n=74,77) | 1 | 5 | | |
| W24 to W48: Shift to Abnormal, AE (n=74,77) | 0 | 1 | | |
| W24 to W60: Shift to Abnormal, not AE (n=56,50) | 4 | 3 | | |
| W24 to W60: Shift to Abnormal, AE (n=56,50) | 0 | 0 | | |
| W24 to W72: Shift to Abnormal, not AE (n=27,22) | 2 | 1 | | |
| W24 to W72: Shift to Abnormal, AE (n=27,22) | 0 | 0 | | |
| W24 to W84: Shift to Abnormal, not AE (n=6,5) | 0 | 2 | | |
| W24 to W84: Shift to Abnormal, AE (n=6,5) | 0 | 0 | | |
| W24 to W96: Shift to Abnormal, not AE (n=3,0) | 0 | 0 | | |
| W24 to W96: Shift to Abnormal, AE (n=3,0) | 0 | 0 | | |
| At W36: Normal | 77 | 80 | | |
| At W36: Abnormal, not AE | 7 | 20 | | |
| At W36: Abnormal, AE | 0 | 1 | | |
| W36 to W48: Shift to Abnormal, not AE (n=75,75) | 3 | 3 | | |
| W36 to W48: Shift to Abnormal, AE (n=75,75) | 0 | 2 | | |
| W36 to W60: Shift to Abnormal, not AE (n=57,51) | 6 | 5 | | |
| W36 to W60: Shift to Abnormal, AE (n=57,51) | 0 | 0 | | |
| W36 to W72: Shift to Abnormal, not AE (n=26,24) | 2 | 1 | | |
| W36 to W72: Shift to Abnormal, AE (n=26,24) | 0 | 0 | | |
| W36 to W84: Shift to Abnormal, not AE (n=5,7) | 0 | 2 | | |

| | | | | |
|--|----|----|--|--|
| W36 to W84: Shift to Abnormal, AE (n=5,7) | 0 | 0 | | |
| W36 to W96: Shift to Abnormal, not AE (n=3,0) | 0 | 0 | | |
| W36 to W96: Shift to Abnormal, AE (n=3,0) | 0 | 0 | | |
| At W48: Normal | 74 | 76 | | |
| At W48: Abnormal, not AE | 4 | 15 | | |
| At W48: Abnormal, AE | 0 | 2 | | |
| W48 to W60: Shift to Abnormal, not AE (n=56,52) | 4 | 4 | | |
| W48 to W60: Shift to Abnormal, AE (n=56,52) | 0 | 0 | | |
| W48 to W72: Shift to Abnormal, not AE (n=27,24) | 2 | 2 | | |
| W48 to W72: Shift to Abnormal, AE (n=27,24) | 0 | 0 | | |
| W48 to W84: Shift to Abnormal, not AE (n=6,8) | 0 | 1 | | |
| W48 to W84: Shift to Abnormal, AE (n=6,8) | 0 | 0 | | |
| W48 to W96: Shift to Abnormal, not AE (n=3,0) | 0 | 0 | | |
| W48 to W96: Shift to Abnormal, AE (n=3,0) | 0 | 0 | | |
| At W60: Normal | 53 | 52 | | |
| At W60: Abnormal, not AE | 6 | 10 | | |
| W60 to W72: Shift to Abnormal, not AE (n=26,24) | 1 | 2 | | |
| W60 to W72: Shift to Abnormal, AE (n=26,24) | 0 | 0 | | |
| W60 to W84: Shift to Abnormal, not AE (n=6,7) | 0 | 2 | | |
| W60 to W84: Shift to Abnormal, AE (n=6,7) | 0 | 0 | | |
| W60 to W96: Shift to Abnormal, not AE (n=2,0) | 0 | 0 | | |
| W60 to W96: Shift to Abnormal, AE (n=2,0) | 0 | 0 | | |
| At W72: Normal | 26 | 24 | | |
| At W72: Abnormal, not AE | 2 | 4 | | |
| W72 to W84: Shift to Abnormal, not AE (n=5,7) | 0 | 1 | | |
| W72 to W84: Shift to Abnormal, AE (n=5,7) | 0 | 0 | | |
| W72 to W96: Shift to Abnormal, not AE (n=2,0) | 0 | 0 | | |
| W72 to W96: Shift to Abnormal, AE (n=2,0) | 0 | 0 | | |
| At W84: Normal | 7 | 7 | | |
| At W84: Abnormal, not AE | 0 | 3 | | |
| W84 to W96: Shift to Abnormal, not AE (n=3,0) | 0 | 0 | | |
| W84 to W96: Shift to Abnormal, AE (n=3,0) | 0 | 0 | | |
| At W96: Normal | 3 | 0 | | |
| At W96: Abnormal, not AE | 0 | 1 | | |

Statistical analyses

No statistical analyses for this end point

Secondary: Part 2: Percentage of Subjects with Potentially Clinically Significant Abnormal Vital Signs Values

| | |
|-----------------|--|
| End point title | Part 2: Percentage of Subjects with Potentially Clinically Significant Abnormal Vital Signs Values |
|-----------------|--|

End point description:

Vital sign measurements including temperature, pulse rate (supine), systolic blood pressure (BP) and diastolic (supine) BP were evaluated for safety. Criteria for abnormalities: Temperature: >38 degree celsius (°C) or >=1 °C increase from baseline (BL); Pulse (1): [>100 beats per minute (bpm) or increase from BL of >30 bpm] or (<40 bpm or decrease from BL of >20 bpm); Systolic BP (2): [>160 millimeters of mercury (mmHg)/increase from BL of >40 mmHg] or (<90 mmHg/decrease from BL of >30 mmHg); Diastolic BP (3): (>100 mmHg/increase from BL of >30 mmHg) or (<45 mmHg/decrease from BL of >20 mmHg). Safety population included all subjects who received at least 1 dose of study treatment. Subjects were analysed based on the actual treatment allocation.

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

End point timeframe:

Part 2: Baseline to Week 96

| End point values | Part 2: Placebo to BIIB033 750 mg | Part 2: BIIB033 750 mg | | |
|--|-----------------------------------|------------------------|--|--|
| Subject group type | Reporting group | Reporting group | | |
| Number of subjects analysed | 100 | 113 | | |
| Units: percentage of subjects | | | | |
| number (not applicable) | | | | |
| Temperature: >38°C / >=1°C Increase From BL | 4 | 5 | | |
| Pulse: (1) | 22 | 25 | | |
| Pulse: >100 bpm or >30 bpm increase from BL | 11 | 15 | | |
| Pulse: <40 bpm or >20 bpm decrease from BL | 13 | 11 | | |
| Systolic BP: (2) | 8 | 10 | | |
| Systolic BP: >160 mmHg / >40 mmHg increase from BL | 4 | 4 | | |
| Systolic BP: <90 mmHg or >30 mmHg decrease from BL | 4 | 8 | | |
| Diastolic BP: (3) | 13 | 9 | | |
| Diastolic BP: >100 mmHg/>30 mmHg increase from BL | 3 | 4 | | |
| Diastolic BP: <45 mmHg/>20 mmHg decrease from BL | 11 | 5 | | |

Statistical analyses

No statistical analyses for this end point

Secondary: Part 2: Percentage of Subjects with Potentially Clinically Significant Abnormal Weight Values

| | |
|---|---|
| End point title | Part 2: Percentage of Subjects with Potentially Clinically Significant Abnormal Weight Values |
| End point description: | |
| Criteria for abnormality was defined as a >7% increase or decrease in weight at the specified time point. Safety population included all subjects who received at least 1 dose of study treatment. Subjects were analysed based on the actual treatment allocation. 'Number analysed (n)' signifies number of subjects analysed at the specified timepoint for this endpoint. | |
| End point type | Secondary |
| End point timeframe: | |
| Part 2: Baseline, Week 12, 24, 36, 48, 72 and 96 | |

| End point values | Part 2: Placebo to BIIB033 750 mg | Part 2: BIIB033 750 mg | | |
|--|-----------------------------------|------------------------|--|--|
| Subject group type | Reporting group | Reporting group | | |
| Number of subjects analysed | 100 | 113 | | |
| Units: percentage of subjects | | | | |
| number (not applicable) | | | | |
| At Baseline with Increase >7% (n=97,112) | 27 | 15 | | |
| At Baseline with Decrease >7% (n=97,112) | 4 | 15 | | |
| At Week 12 with Increase >7% (n=89,101) | 4 | 3 | | |
| At Week 12 with Decrease >7% (n=89,101) | 1 | 2 | | |
| At Week 24 with Increase >7% (n=92,104) | 10 | 10 | | |
| At Week 24 with Decrease >7% (n=92,104) | 1 | 5 | | |
| At Week 36 with Increase >7% (n=87,103) | 18 | 5 | | |
| At Week 36 with Decrease >7% (n=87,103) | 1 | 7 | | |
| At Week 48 with Increase >7% (n=79,96) | 20 | 8 | | |
| At Week 48 with Decrease >7% (n=79,96) | 0 | 10 | | |
| At Week 72 with Increase >7% (n=59,66) | 19 | 15 | | |
| At Week 72 with Decrease >7% (n=59,66) | 3 | 12 | | |

| | | | | |
|---|----|----|--|--|
| At Week 96 with Increase >7% (n=27,31) | 30 | 13 | | |
| At Week 96 with Decrease >7% (n=27,31) | 4 | 16 | | |

Statistical analyses

No statistical analyses for this end point

Secondary: Part 2: Number of Subjects With Columbia Suicide Severity Rating Scale (C-SSRS) Score at any Post-Baseline Visit

| | |
|-----------------|--|
| End point title | Part 2: Number of Subjects With Columbia Suicide Severity Rating Scale (C-SSRS) Score at any Post-Baseline Visit |
|-----------------|--|

End point description:

C-SSRS systematically assess suicidal ideation (SI) and suicidal behavior (SB) rating scale. It rates an individual's degree of suicidal ideation on a scale, ranging from "wish to be dead" to "active suicidal ideation with (w) specific plan and intent and behaviors". The scale identifies specific behaviors ranging from "preparatory acts or behavior" to "suicide" which may be indicative of an individual's intent to complete suicide. Safety population included all subjects who received at least 1 dose of study treatment. Subjects were analysed based on the actual treatment allocation. 'Number analysed (n)' signifies number of subjects analysed for this endpoint. w/o = without

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

End point timeframe:

Part 2: Baseline to Week 96

| End point values | Part 2: Placebo to BIIB033 750 mg | Part 2: BIIB033 750 mg | | |
|--|-----------------------------------|------------------------|--|--|
| Subject group type | Reporting group | Reporting group | | |
| Number of subjects analysed | 100 | 113 | | |
| Units: subjects | | | | |
| SI: Wish to be Dead (n=98,113) | 2 | 3 | | |
| SI: Non-specific Active Suicidal Thoughts (n=98,113) | 0 | 1 | | |
| SI: SI w Methods (not Plan) w/o Intent (n=98,113) | 0 | 1 | | |
| SI: SI w Some Intent, w/o Specific Plan (n=98,113) | 0 | 1 | | |
| SI: Active SI w Specific Plan and Intent (n=98,113) | 0 | 1 | | |
| SB: Preparatory Acts or Behavior (n=98,113) | 0 | 1 | | |
| SB: Aborted Attempt (n=98,113) | 0 | 1 | | |
| SB: Interrupted Attempt (n=98,113) | 0 | 1 | | |
| SB: Actual Attempt (n=98,113) | 0 | 1 | | |
| SB: Suicidal Behavior (n=98,113) | 0 | 1 | | |
| SB: Suicide (n=97,112) | 0 | 0 | | |
| Self-injurious Behavior w/o Intent (n=98,113) | 0 | 0 | | |

Statistical analyses

No statistical analyses for this end point

Adverse events

Adverse events information

Timeframe for reporting adverse events:

Part 1: From first dose through 12 weeks after administration of the last dose of study treatment (Up to Week 84); Part 2: From first dose through 12 weeks after administration of the last dose of study treatment (Up to Week 169)

Adverse event reporting additional description:

Safety population included all subjects who received at least 1 dose of study treatment. Subjects were analysed based on the actual treatment allocation.

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

Dictionary used

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

| | |
|--------------------|------|
| Dictionary version | 23.0 |
|--------------------|------|

Reporting groups

| | |
|-----------------------|-----------------|
| Reporting group title | Part 1: Placebo |
|-----------------------|-----------------|

Reporting group description:

Subjects with RMS received placebo IV as an add-on therapy to a background DMT once every 4 weeks over 72 weeks.

| | |
|-----------------------|------------------------|
| Reporting group title | Part 1: BIIB033 750 mg |
|-----------------------|------------------------|

Reporting group description:

Subjects with RMS received BIIB033 750 mg IV as an add-on therapy to a background DMT once every 4 weeks over 72 weeks.

| | |
|-----------------------|-----------------------------------|
| Reporting group title | Part 2: Placebo to BIIB033 750 mg |
|-----------------------|-----------------------------------|

Reporting group description:

Subjects who received placebo and completed Part 1 were enrolled into Part 2 to receive BIIB033 750 mg IV as an add-on therapy to a background DMT once every 4 weeks for up to a maximum of 80 weeks.

| | |
|-----------------------|------------------------|
| Reporting group title | Part 2: BIIB033 750 mg |
|-----------------------|------------------------|

Reporting group description:

Subjects who received BIIB033 and completed Part 1 were enrolled into Part 2 to receive BIIB033 750 mg IV as an add-on therapy to a background DMT once every 4 weeks for up to a maximum of 77 weeks.

| Serious adverse events | Part 1: Placebo | Part 1: BIIB033 750 mg | Part 2: Placebo to BIIB033 750 mg |
|---|-----------------|------------------------|-----------------------------------|
| Total subjects affected by serious adverse events | | | |
| subjects affected / exposed | 6 / 131 (4.58%) | 9 / 132 (6.82%) | 9 / 100 (9.00%) |
| number of deaths (all causes) | 0 | 1 | 0 |
| number of deaths resulting from adverse events | | | |
| Neoplasms benign, malignant and unspecified (incl cysts and polyps) | | | |
| Chronic lymphocytic leukaemia stage 1 | | | |
| subjects affected / exposed | 0 / 131 (0.00%) | 0 / 132 (0.00%) | 1 / 100 (1.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 1 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Lung neoplasm malignant | | | |

| | | | |
|---|-----------------|-----------------|-----------------|
| subjects affected / exposed | 0 / 131 (0.00%) | 0 / 132 (0.00%) | 1 / 100 (1.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 1 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Parathyroid tumour benign | | | |
| subjects affected / exposed | 0 / 131 (0.00%) | 0 / 132 (0.00%) | 0 / 100 (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 |
| Rectal adenocarcinoma | | | |
| subjects affected / exposed | 1 / 131 (0.76%) | 0 / 132 (0.00%) | 0 / 100 (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 |
| Injury, poisoning and procedural complications | | | |
| Ankle fracture | | | |
| subjects affected / exposed | 0 / 131 (0.00%) | 1 / 132 (0.76%) | 0 / 100 (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 |
| Fall | | | |
| subjects affected / exposed | 0 / 131 (0.00%) | 1 / 132 (0.76%) | 1 / 100 (1.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | 0 / 1 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Femur fracture | | | |
| subjects affected / exposed | 0 / 131 (0.00%) | 0 / 132 (0.00%) | 1 / 100 (1.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 1 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Ligament rupture | | | |
| subjects affected / exposed | 0 / 131 (0.00%) | 0 / 132 (0.00%) | 1 / 100 (1.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 1 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Road traffic accident | | | |
| subjects affected / exposed | 0 / 131 (0.00%) | 1 / 132 (0.76%) | 0 / 100 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 1 | 0 / 0 |
| Congenital, familial and genetic disorders | | | |

| | | | |
|--|-----------------|-----------------|-----------------|
| Congenital anomaly | | | |
| subjects affected / exposed | 0 / 131 (0.00%) | 1 / 132 (0.76%) | 0 / 100 (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 |
| Nervous system disorders | | | |
| Meningocele acquired | | | |
| subjects affected / exposed | 0 / 131 (0.00%) | 0 / 132 (0.00%) | 1 / 100 (1.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 1 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Multiple sclerosis relapse | | | |
| subjects affected / exposed | 1 / 131 (0.76%) | 0 / 132 (0.00%) | 0 / 100 (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 |
| Uhthoff's phenomenon | | | |
| subjects affected / exposed | 1 / 131 (0.76%) | 0 / 132 (0.00%) | 0 / 100 (0.00%) |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Pregnancy, puerperium and perinatal conditions | | | |
| Abortion spontaneous | | | |
| subjects affected / exposed | 0 / 131 (0.00%) | 0 / 132 (0.00%) | 1 / 100 (1.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 1 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| General disorders and administration site conditions | | | |
| Chest pain | | | |
| subjects affected / exposed | 0 / 131 (0.00%) | 1 / 132 (0.76%) | 0 / 100 (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 | | | |
| Coeliac artery compression syndrome | | | |
| subjects affected / exposed | 0 / 131 (0.00%) | 1 / 132 (0.76%) | 0 / 100 (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 |
| Reproductive system and breast disorders | | | |

| | | | |
|---|-----------------|-----------------|-----------------|
| Adenomyosis | | | |
| subjects affected / exposed | 0 / 131 (0.00%) | 1 / 132 (0.76%) | 0 / 100 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Endometriosis | | | |
| subjects affected / exposed | 0 / 131 (0.00%) | 1 / 132 (0.76%) | 0 / 100 (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 |
| Psychiatric disorders | | | |
| Alcohol use disorder | | | |
| subjects affected / exposed | 1 / 131 (0.76%) | 0 / 132 (0.00%) | 0 / 100 (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 |
| Major depression | | | |
| subjects affected / exposed | 0 / 131 (0.00%) | 0 / 132 (0.00%) | 0 / 100 (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 | | | |
| Cervical spinal stenosis | | | |
| subjects affected / exposed | 1 / 131 (0.76%) | 0 / 132 (0.00%) | 0 / 100 (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 |
| Infections and infestations | | | |
| Appendicitis | | | |
| subjects affected / exposed | 0 / 131 (0.00%) | 0 / 132 (0.00%) | 1 / 100 (1.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 1 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Escherichia urinary tract infection | | | |
| subjects affected / exposed | 0 / 131 (0.00%) | 0 / 132 (0.00%) | 1 / 100 (1.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 1 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Pelvic abscess | | | |

| | | | |
|---|-----------------|-----------------|-----------------|
| subjects affected / exposed | 1 / 131 (0.76%) | 0 / 132 (0.00%) | 0 / 100 (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 |
| Pneumonia | | | |
| subjects affected / exposed | 0 / 131 (0.00%) | 1 / 132 (0.76%) | 0 / 100 (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 |
| Pyelonephritis | | | |
| subjects affected / exposed | 1 / 131 (0.76%) | 1 / 132 (0.76%) | 0 / 100 (0.00%) |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 1 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Systemic infection | | | |
| subjects affected / exposed | 0 / 131 (0.00%) | 0 / 132 (0.00%) | 1 / 100 (1.00%) |
| 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 | Part 2: BIIB033 750 mg | | |
| Total subjects affected by serious adverse events | | | |
| subjects affected / exposed | 2 / 113 (1.77%) | | |
| number of deaths (all causes) | 0 | | |
| number of deaths resulting from adverse events | | | |
| Neoplasms benign, malignant and unspecified (incl cysts and polyps) | | | |
| Chronic lymphocytic leukaemia stage 1 | | | |
| subjects affected / exposed | 0 / 113 (0.00%) | | |
| occurrences causally related to treatment / all | 0 / 0 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Lung neoplasm malignant | | | |
| subjects affected / exposed | 0 / 113 (0.00%) | | |
| occurrences causally related to treatment / all | 0 / 0 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Parathyroid tumour benign | | | |

| | | | |
|---|-----------------|--|--|
| subjects affected / exposed | 1 / 113 (0.88%) | | |
| occurrences causally related to treatment / all | 0 / 1 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Rectal adenocarcinoma | | | |
| subjects affected / exposed | 0 / 113 (0.00%) | | |
| occurrences causally related to treatment / all | 0 / 0 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Injury, poisoning and procedural complications | | | |
| Ankle fracture | | | |
| subjects affected / exposed | 0 / 113 (0.00%) | | |
| occurrences causally related to treatment / all | 0 / 0 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Fall | | | |
| subjects affected / exposed | 0 / 113 (0.00%) | | |
| occurrences causally related to treatment / all | 0 / 0 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Femur fracture | | | |
| subjects affected / exposed | 0 / 113 (0.00%) | | |
| occurrences causally related to treatment / all | 0 / 0 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Ligament rupture | | | |
| subjects affected / exposed | 0 / 113 (0.00%) | | |
| occurrences causally related to treatment / all | 0 / 0 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Road traffic accident | | | |
| subjects affected / exposed | 0 / 113 (0.00%) | | |
| occurrences causally related to treatment / all | 0 / 0 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Congenital, familial and genetic disorders | | | |
| Congenital anomaly | | | |
| subjects affected / exposed | 0 / 113 (0.00%) | | |
| occurrences causally related to treatment / all | 0 / 0 | | |
| deaths causally related to treatment / all | 0 / 0 | | |

| | | | |
|--|-----------------|--|--|
| Nervous system disorders | | | |
| Meningocele acquired | | | |
| subjects affected / exposed | 0 / 113 (0.00%) | | |
| occurrences causally related to treatment / all | 0 / 0 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Multiple sclerosis relapse | | | |
| subjects affected / exposed | 0 / 113 (0.00%) | | |
| occurrences causally related to treatment / all | 0 / 0 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Uhthoff's phenomenon | | | |
| subjects affected / exposed | 0 / 113 (0.00%) | | |
| occurrences causally related to treatment / all | 0 / 0 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Pregnancy, puerperium and perinatal conditions | | | |
| Abortion spontaneous | | | |
| subjects affected / exposed | 0 / 113 (0.00%) | | |
| occurrences causally related to treatment / all | 0 / 0 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| General disorders and administration site conditions | | | |
| Chest pain | | | |
| subjects affected / exposed | 0 / 113 (0.00%) | | |
| occurrences causally related to treatment / all | 0 / 0 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Gastrointestinal disorders | | | |
| Coeliac artery compression syndrome | | | |
| subjects affected / exposed | 0 / 113 (0.00%) | | |
| occurrences causally related to treatment / all | 0 / 0 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Reproductive system and breast disorders | | | |
| Adenomyosis | | | |
| subjects affected / exposed | 0 / 113 (0.00%) | | |
| occurrences causally related to treatment / all | 0 / 0 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Endometriosis | | | |

| | | | |
|---|-----------------|--|--|
| subjects affected / exposed | 0 / 113 (0.00%) | | |
| occurrences causally related to treatment / all | 0 / 0 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Psychiatric disorders | | | |
| Alcohol use disorder | | | |
| subjects affected / exposed | 0 / 113 (0.00%) | | |
| occurrences causally related to treatment / all | 0 / 0 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Major depression | | | |
| subjects affected / exposed | 1 / 113 (0.88%) | | |
| occurrences causally related to treatment / all | 0 / 1 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Musculoskeletal and connective tissue disorders | | | |
| Cervical spinal stenosis | | | |
| subjects affected / exposed | 0 / 113 (0.00%) | | |
| occurrences causally related to treatment / all | 0 / 0 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Infections and infestations | | | |
| Appendicitis | | | |
| subjects affected / exposed | 0 / 113 (0.00%) | | |
| occurrences causally related to treatment / all | 0 / 0 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Escherichia urinary tract infection | | | |
| subjects affected / exposed | 0 / 113 (0.00%) | | |
| occurrences causally related to treatment / all | 0 / 0 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Pelvic abscess | | | |
| subjects affected / exposed | 0 / 113 (0.00%) | | |
| occurrences causally related to treatment / all | 0 / 0 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Pneumonia | | | |
| subjects affected / exposed | 0 / 113 (0.00%) | | |
| occurrences causally related to treatment / all | 0 / 0 | | |
| deaths causally related to treatment / all | 0 / 0 | | |

| | | | |
|---|-----------------|--|--|
| Pyelonephritis | | | |
| subjects affected / exposed | 0 / 113 (0.00%) | | |
| occurrences causally related to treatment / all | 0 / 0 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Systemic infection | | | |
| subjects affected / exposed | 0 / 113 (0.00%) | | |
| occurrences causally related to treatment / all | 0 / 0 | | |
| deaths causally related to treatment / all | 0 / 0 | | |

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

| Non-serious adverse events | Part 1: Placebo | Part 1: BIIB033 750 mg | Part 2: Placebo to BIIB033 750 mg |
|---|-------------------|------------------------|-----------------------------------|
| Total subjects affected by non-serious adverse events | | | |
| subjects affected / exposed | 91 / 131 (69.47%) | 93 / 132 (70.45%) | 34 / 100 (34.00%) |
| Investigations | | | |
| Weight increased | | | |
| subjects affected / exposed | 3 / 131 (2.29%) | 8 / 132 (6.06%) | 0 / 100 (0.00%) |
| occurrences (all) | 3 | 8 | 0 |
| Injury, poisoning and procedural complications | | | |
| Fall | | | |
| subjects affected / exposed | 12 / 131 (9.16%) | 17 / 132 (12.88%) | 4 / 100 (4.00%) |
| occurrences (all) | 22 | 23 | 8 |
| Nervous system disorders | | | |
| Dizziness | | | |
| subjects affected / exposed | 9 / 131 (6.87%) | 5 / 132 (3.79%) | 0 / 100 (0.00%) |
| occurrences (all) | 9 | 6 | 0 |
| Headache | | | |
| subjects affected / exposed | 23 / 131 (17.56%) | 19 / 132 (14.39%) | 11 / 100 (11.00%) |
| occurrences (all) | 61 | 29 | 20 |
| Multiple sclerosis relapse | | | |
| subjects affected / exposed | 20 / 131 (15.27%) | 23 / 132 (17.42%) | 12 / 100 (12.00%) |
| occurrences (all) | 25 | 29 | 15 |
| Paraesthesia | | | |
| subjects affected / exposed | 8 / 131 (6.11%) | 7 / 132 (5.30%) | 0 / 100 (0.00%) |
| occurrences (all) | 14 | 8 | 0 |
| General disorders and administration | | | |

| | | | |
|---|-------------------|-------------------|-----------------|
| site conditions | | | |
| Fatigue | | | |
| subjects affected / exposed | 14 / 131 (10.69%) | 14 / 132 (10.61%) | 0 / 100 (0.00%) |
| occurrences (all) | 19 | 15 | 0 |
| Gastrointestinal disorders | | | |
| Diarrhoea | | | |
| subjects affected / exposed | 11 / 131 (8.40%) | 6 / 132 (4.55%) | 3 / 100 (3.00%) |
| occurrences (all) | 11 | 6 | 3 |
| Nausea | | | |
| subjects affected / exposed | 10 / 131 (7.63%) | 11 / 132 (8.33%) | 0 / 100 (0.00%) |
| occurrences (all) | 14 | 14 | 0 |
| Vomiting | | | |
| subjects affected / exposed | 7 / 131 (5.34%) | 4 / 132 (3.03%) | 0 / 100 (0.00%) |
| occurrences (all) | 7 | 5 | 0 |
| Respiratory, thoracic and mediastinal disorders | | | |
| Cough | | | |
| subjects affected / exposed | 8 / 131 (6.11%) | 9 / 132 (6.82%) | 0 / 100 (0.00%) |
| occurrences (all) | 8 | 10 | 0 |
| Musculoskeletal and connective tissue disorders | | | |
| Arthralgia | | | |
| subjects affected / exposed | 10 / 131 (7.63%) | 8 / 132 (6.06%) | 0 / 100 (0.00%) |
| occurrences (all) | 12 | 8 | 0 |
| Back pain | | | |
| subjects affected / exposed | 8 / 131 (6.11%) | 8 / 132 (6.06%) | 0 / 100 (0.00%) |
| occurrences (all) | 11 | 10 | 0 |
| Muscle spasms | | | |
| subjects affected / exposed | 7 / 131 (5.34%) | 2 / 132 (1.52%) | 5 / 100 (5.00%) |
| occurrences (all) | 7 | 2 | 5 |
| Pain in extremity | | | |
| subjects affected / exposed | 7 / 131 (5.34%) | 10 / 132 (7.58%) | 0 / 100 (0.00%) |
| occurrences (all) | 9 | 16 | 0 |
| Infections and infestations | | | |
| Bronchitis | | | |
| subjects affected / exposed | 6 / 131 (4.58%) | 10 / 132 (7.58%) | 0 / 100 (0.00%) |
| occurrences (all) | 7 | 12 | 0 |
| Nasopharyngitis | | | |

| | | | |
|-----------------------------------|-------------------|-------------------|-----------------|
| subjects affected / exposed | 30 / 131 (22.90%) | 26 / 132 (19.70%) | 4 / 100 (4.00%) |
| occurrences (all) | 44 | 37 | 4 |
| Sinusitis | | | |
| subjects affected / exposed | 5 / 131 (3.82%) | 9 / 132 (6.82%) | 0 / 100 (0.00%) |
| occurrences (all) | 6 | 9 | 0 |
| Upper respiratory tract infection | | | |
| subjects affected / exposed | 20 / 131 (15.27%) | 31 / 132 (23.48%) | 5 / 100 (5.00%) |
| occurrences (all) | 29 | 42 | 6 |
| Urinary tract infection | | | |
| subjects affected / exposed | 19 / 131 (14.50%) | 18 / 132 (13.64%) | 6 / 100 (6.00%) |
| occurrences (all) | 33 | 29 | 6 |

| | | | |
|---|------------------------|--|--|
| Non-serious adverse events | Part 2: BIIB033 750 mg | | |
| Total subjects affected by non-serious adverse events | | | |
| subjects affected / exposed | 46 / 113 (40.71%) | | |
| Investigations | | | |
| Weight increased | | | |
| subjects affected / exposed | 0 / 113 (0.00%) | | |
| occurrences (all) | 0 | | |
| Injury, poisoning and procedural complications | | | |
| Fall | | | |
| subjects affected / exposed | 8 / 113 (7.08%) | | |
| occurrences (all) | 8 | | |
| Nervous system disorders | | | |
| Dizziness | | | |
| subjects affected / exposed | 0 / 113 (0.00%) | | |
| occurrences (all) | 0 | | |
| Headache | | | |
| subjects affected / exposed | 9 / 113 (7.96%) | | |
| occurrences (all) | 12 | | |
| Multiple sclerosis relapse | | | |
| subjects affected / exposed | 13 / 113 (11.50%) | | |
| occurrences (all) | 14 | | |
| Paraesthesia | | | |
| subjects affected / exposed | 0 / 113 (0.00%) | | |
| occurrences (all) | 0 | | |

| | | | |
|--|-----------------|--|--|
| General disorders and administration site conditions | | | |
| Fatigue | | | |
| subjects affected / exposed | 0 / 113 (0.00%) | | |
| occurrences (all) | 0 | | |
| Gastrointestinal disorders | | | |
| Diarrhoea | | | |
| subjects affected / exposed | 6 / 113 (5.31%) | | |
| occurrences (all) | 6 | | |
| Nausea | | | |
| subjects affected / exposed | 0 / 113 (0.00%) | | |
| occurrences (all) | 0 | | |
| Vomiting | | | |
| subjects affected / exposed | 0 / 113 (0.00%) | | |
| occurrences (all) | 0 | | |
| Respiratory, thoracic and mediastinal disorders | | | |
| Cough | | | |
| subjects affected / exposed | 0 / 113 (0.00%) | | |
| occurrences (all) | 0 | | |
| Musculoskeletal and connective tissue disorders | | | |
| Arthralgia | | | |
| subjects affected / exposed | 0 / 113 (0.00%) | | |
| occurrences (all) | 0 | | |
| Back pain | | | |
| subjects affected / exposed | 0 / 113 (0.00%) | | |
| occurrences (all) | 0 | | |
| Muscle spasms | | | |
| subjects affected / exposed | 0 / 113 (0.00%) | | |
| occurrences (all) | 0 | | |
| Pain in extremity | | | |
| subjects affected / exposed | 0 / 113 (0.00%) | | |
| occurrences (all) | 0 | | |
| Infections and infestations | | | |
| Bronchitis | | | |
| subjects affected / exposed | 0 / 113 (0.00%) | | |
| occurrences (all) | 0 | | |
| Nasopharyngitis | | | |

| | | | |
|-----------------------------------|------------------|--|--|
| subjects affected / exposed | 7 / 113 (6.19%) | | |
| occurrences (all) | 7 | | |
| Sinusitis | | | |
| subjects affected / exposed | 0 / 113 (0.00%) | | |
| occurrences (all) | 0 | | |
| Upper respiratory tract infection | | | |
| subjects affected / exposed | 9 / 113 (7.96%) | | |
| occurrences (all) | 11 | | |
| Urinary tract infection | | | |
| subjects affected / exposed | 10 / 113 (8.85%) | | |
| occurrences (all) | 11 | | |

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

| Date | Amendment |
|------------------|--|
| 14 June 2017 | Updated the safety reporting sections of the protocol for accurate representation of serious adverse event (SAE) and suspected unexpected serious adverse reaction reporting responsibilities. |
| 13 February 2019 | Added an optional open-label extension (OLE) phase (Part 2) that will investigate the long-term safety and efficacy of BIIB033 treatment as an add-on therapy to anti-inflammatory DMT for approximately 2 years (96 weeks). |

Notes:

Interruptions (globally)

Were there any global interruptions to the trial? No

Limitations and caveats

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

The top-line results from the Part 1 did not meet the pre-specified primary endpoint nor the key secondary endpoints. The decision to discontinue study 215MS202 Part 2 was not based on safety concerns.

Notes: