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 BIIB033 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	v2 (current)
This version publication date	20 May 2022
First version publication date	01 March 2022
Version creation reason	

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	37.7	39.4	
standard deviation	± 9.25	± 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: ≥15% decrease in time from BL and worsening: ≥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 ≥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 ≥15% decrease in time from BL indicates improvement and ≥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 ≥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 ≥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, and no participants had the opportunity to complete Part 2 of the study. No data was collected as per the protocol prespecified Part 2 efficacy analyses to assess the long-term efficacy of BIIB033 in Part 2.

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, and

no participants had the opportunity to complete Part 2 of the study. No data was collected as per the protocol prespecified Part 2 efficacy analyses to assess the long-term efficacy of BIIB033 in Part 2.

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, and no participants had the opportunity to complete Part 2 of the study. No data was collected as per the protocol prespecified Part 2 efficacy analyses to assess the long-term efficacy of BIIB033 in Part 2.

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, and no participants had the opportunity to complete Part 2 of the study. No data was collected as per the protocol prespecified Part 2 efficacy analyses to assess the long-term efficacy of BIIB033 in Part 2.

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, and no participants had the opportunity to complete Part 2 of the study. No data was collected as per the protocol prespecified Part 2 efficacy analyses to assess the long-term efficacy of BIIB033 in Part 2.

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, and no participants had the opportunity to complete Part 2 of the study. No data was collected as per the protocol prespecified Part 2 efficacy analyses to assess the long-term efficacy of BIIB033 in Part 2.

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 <=75/ >=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 <=3.5/ >=6.4 10^12/L, in millimoles (mmol)/L [sodium <=126/ >=156, potassium <=3/ >=6, chloride <=90/ >=118, bicarbonate <=16/ >=35, calcium <=2/ >=3, phosphorous <=0.5491/ >=1.7119, glucose (non-fasting) <=2.2/>=13.75], AST/SGOT >=3x upper limit of normal (ULN), ALT/SGPT >=3xULN, alkaline phosphatase >=3xULN, creatinine >=1.5xULN, total bilirubin >=1.5xULN, total protein <=45/ >=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 was “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 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				
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 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.

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.

Serious adverse events	Part 1: Placebo	Part 2: Placebo to BIIB033 750 mg	Part 2: BIIB033 750 mg
Total subjects affected by serious adverse events			
subjects affected / exposed	6 / 131 (4.58%)	9 / 100 (9.00%)	2 / 113 (1.77%)
number of deaths (all causes)	0	0	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%)	1 / 100 (1.00%)	0 / 113 (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
Lung neoplasm malignant			

subjects affected / exposed	0 / 131 (0.00%)	1 / 100 (1.00%)	0 / 113 (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
Parathyroid tumour benign			
subjects affected / exposed	0 / 131 (0.00%)	0 / 100 (0.00%)	1 / 113 (0.88%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Rectal adenocarcinoma			
subjects affected / exposed	1 / 131 (0.76%)	0 / 100 (0.00%)	0 / 113 (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%)	0 / 100 (0.00%)	0 / 113 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Fall			
subjects affected / exposed	0 / 131 (0.00%)	1 / 100 (1.00%)	0 / 113 (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
Femur fracture			
subjects affected / exposed	0 / 131 (0.00%)	1 / 100 (1.00%)	0 / 113 (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
Ligament rupture			
subjects affected / exposed	0 / 131 (0.00%)	1 / 100 (1.00%)	0 / 113 (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
Road traffic accident			
subjects affected / exposed	0 / 131 (0.00%)	0 / 100 (0.00%)	0 / 113 (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
Congenital, familial and genetic disorders			

Congenital anomaly			
subjects affected / exposed	0 / 131 (0.00%)	0 / 100 (0.00%)	0 / 113 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Nervous system disorders			
Meningocele acquired			
subjects affected / exposed	0 / 131 (0.00%)	1 / 100 (1.00%)	0 / 113 (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
Multiple sclerosis relapse			
subjects affected / exposed	1 / 131 (0.76%)	0 / 100 (0.00%)	0 / 113 (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 / 100 (0.00%)	0 / 113 (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%)	1 / 100 (1.00%)	0 / 113 (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
General disorders and administration site conditions			
Chest pain			
subjects affected / exposed	0 / 131 (0.00%)	0 / 100 (0.00%)	0 / 113 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Gastrointestinal disorders			
Coeliac artery compression syndrome			
subjects affected / exposed	0 / 131 (0.00%)	0 / 100 (0.00%)	0 / 113 (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			

Adenomyosis			
subjects affected / exposed	0 / 131 (0.00%)	0 / 100 (0.00%)	0 / 113 (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
Endometriosis			
subjects affected / exposed	0 / 131 (0.00%)	0 / 100 (0.00%)	0 / 113 (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			
Alcohol use disorder			
subjects affected / exposed	1 / 131 (0.76%)	0 / 100 (0.00%)	0 / 113 (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 / 100 (0.00%)	1 / 113 (0.88%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
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 / 100 (0.00%)	0 / 113 (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%)	1 / 100 (1.00%)	0 / 113 (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
Escherichia urinary tract infection			
subjects affected / exposed	0 / 131 (0.00%)	1 / 100 (1.00%)	0 / 113 (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
Pelvic abscess			

subjects affected / exposed	1 / 131 (0.76%)	0 / 100 (0.00%)	0 / 113 (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%)	0 / 100 (0.00%)	0 / 113 (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
Pyelonephritis			
subjects affected / exposed	1 / 131 (0.76%)	0 / 100 (0.00%)	0 / 113 (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
Systemic infection			
subjects affected / exposed	0 / 131 (0.00%)	1 / 100 (1.00%)	0 / 113 (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

Serious adverse events	Part 1: BIIB033 750 mg		
Total subjects affected by serious adverse events			
subjects affected / exposed	9 / 132 (6.82%)		
number of deaths (all causes)	1		
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 / 132 (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 / 132 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Parathyroid tumour benign			

subjects affected / exposed	0 / 132 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Rectal adenocarcinoma			
subjects affected / exposed	0 / 132 (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	1 / 132 (0.76%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Fall			
subjects affected / exposed	1 / 132 (0.76%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Femur fracture			
subjects affected / exposed	0 / 132 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Ligament rupture			
subjects affected / exposed	0 / 132 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Road traffic accident			
subjects affected / exposed	1 / 132 (0.76%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 1		
Congenital, familial and genetic disorders			
Congenital anomaly			
subjects affected / exposed	1 / 132 (0.76%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		

Nervous system disorders			
Meningocele acquired			
subjects affected / exposed	0 / 132 (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 / 132 (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 / 132 (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 / 132 (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	1 / 132 (0.76%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Gastrointestinal disorders			
Coeliac artery compression syndrome			
subjects affected / exposed	1 / 132 (0.76%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Reproductive system and breast disorders			
Adenomyosis			
subjects affected / exposed	1 / 132 (0.76%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Endometriosis			

subjects affected / exposed	1 / 132 (0.76%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Psychiatric disorders			
Alcohol use disorder			
subjects affected / exposed	0 / 132 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Major depression			
subjects affected / exposed	0 / 132 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Musculoskeletal and connective tissue disorders			
Cervical spinal stenosis			
subjects affected / exposed	0 / 132 (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 / 132 (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 / 132 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Pelvic abscess			
subjects affected / exposed	0 / 132 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Pneumonia			
subjects affected / exposed	1 / 132 (0.76%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		

Pyelonephritis			
subjects affected / exposed	1 / 132 (0.76%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Systemic infection			
subjects affected / exposed	0 / 132 (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 2: Placebo to BIIB033 750 mg	Part 2: BIIB033 750 mg
Total subjects affected by non-serious adverse events			
subjects affected / exposed	91 / 131 (69.47%)	34 / 100 (34.00%)	46 / 113 (40.71%)
Investigations			
Weight increased			
subjects affected / exposed	3 / 131 (2.29%)	0 / 100 (0.00%)	0 / 113 (0.00%)
occurrences (all)	3	0	0
Injury, poisoning and procedural complications			
Fall			
subjects affected / exposed	12 / 131 (9.16%)	4 / 100 (4.00%)	8 / 113 (7.08%)
occurrences (all)	22	8	8
Nervous system disorders			
Dizziness			
subjects affected / exposed	9 / 131 (6.87%)	0 / 100 (0.00%)	0 / 113 (0.00%)
occurrences (all)	9	0	0
Headache			
subjects affected / exposed	23 / 131 (17.56%)	11 / 100 (11.00%)	9 / 113 (7.96%)
occurrences (all)	61	20	12
Multiple sclerosis relapse			
subjects affected / exposed	20 / 131 (15.27%)	12 / 100 (12.00%)	13 / 113 (11.50%)
occurrences (all)	25	15	14
Paraesthesia			
subjects affected / exposed	8 / 131 (6.11%)	0 / 100 (0.00%)	0 / 113 (0.00%)
occurrences (all)	14	0	0
General disorders and administration			

site conditions			
Fatigue			
subjects affected / exposed	14 / 131 (10.69%)	0 / 100 (0.00%)	0 / 113 (0.00%)
occurrences (all)	19	0	0
Gastrointestinal disorders			
Diarrhoea			
subjects affected / exposed	11 / 131 (8.40%)	3 / 100 (3.00%)	6 / 113 (5.31%)
occurrences (all)	11	3	6
Nausea			
subjects affected / exposed	10 / 131 (7.63%)	0 / 100 (0.00%)	0 / 113 (0.00%)
occurrences (all)	14	0	0
Vomiting			
subjects affected / exposed	7 / 131 (5.34%)	0 / 100 (0.00%)	0 / 113 (0.00%)
occurrences (all)	7	0	0
Respiratory, thoracic and mediastinal disorders			
Cough			
subjects affected / exposed	8 / 131 (6.11%)	0 / 100 (0.00%)	0 / 113 (0.00%)
occurrences (all)	8	0	0
Musculoskeletal and connective tissue disorders			
Arthralgia			
subjects affected / exposed	10 / 131 (7.63%)	0 / 100 (0.00%)	0 / 113 (0.00%)
occurrences (all)	12	0	0
Back pain			
subjects affected / exposed	8 / 131 (6.11%)	0 / 100 (0.00%)	0 / 113 (0.00%)
occurrences (all)	11	0	0
Muscle spasms			
subjects affected / exposed	7 / 131 (5.34%)	5 / 100 (5.00%)	0 / 113 (0.00%)
occurrences (all)	7	5	0
Pain in extremity			
subjects affected / exposed	7 / 131 (5.34%)	0 / 100 (0.00%)	0 / 113 (0.00%)
occurrences (all)	9	0	0
Infections and infestations			
Bronchitis			
subjects affected / exposed	6 / 131 (4.58%)	0 / 100 (0.00%)	0 / 113 (0.00%)
occurrences (all)	7	0	0
Nasopharyngitis			

subjects affected / exposed	30 / 131 (22.90%)	4 / 100 (4.00%)	7 / 113 (6.19%)
occurrences (all)	44	4	7
Sinusitis			
subjects affected / exposed	5 / 131 (3.82%)	0 / 100 (0.00%)	0 / 113 (0.00%)
occurrences (all)	6	0	0
Upper respiratory tract infection			
subjects affected / exposed	20 / 131 (15.27%)	5 / 100 (5.00%)	9 / 113 (7.96%)
occurrences (all)	29	6	11
Urinary tract infection			
subjects affected / exposed	19 / 131 (14.50%)	6 / 100 (6.00%)	10 / 113 (8.85%)
occurrences (all)	33	6	11

Non-serious adverse events	Part 1: BIIB033 750 mg		
Total subjects affected by non-serious adverse events			
subjects affected / exposed	93 / 132 (70.45%)		
Investigations			
Weight increased			
subjects affected / exposed	8 / 132 (6.06%)		
occurrences (all)	8		
Injury, poisoning and procedural complications			
Fall			
subjects affected / exposed	17 / 132 (12.88%)		
occurrences (all)	23		
Nervous system disorders			
Dizziness			
subjects affected / exposed	5 / 132 (3.79%)		
occurrences (all)	6		
Headache			
subjects affected / exposed	19 / 132 (14.39%)		
occurrences (all)	29		
Multiple sclerosis relapse			
subjects affected / exposed	23 / 132 (17.42%)		
occurrences (all)	29		
Paraesthesia			
subjects affected / exposed	7 / 132 (5.30%)		
occurrences (all)	8		

General disorders and administration site conditions			
Fatigue			
subjects affected / exposed	14 / 132 (10.61%)		
occurrences (all)	15		
Gastrointestinal disorders			
Diarrhoea			
subjects affected / exposed	6 / 132 (4.55%)		
occurrences (all)	6		
Nausea			
subjects affected / exposed	11 / 132 (8.33%)		
occurrences (all)	14		
Vomiting			
subjects affected / exposed	4 / 132 (3.03%)		
occurrences (all)	5		
Respiratory, thoracic and mediastinal disorders			
Cough			
subjects affected / exposed	9 / 132 (6.82%)		
occurrences (all)	10		
Musculoskeletal and connective tissue disorders			
Arthralgia			
subjects affected / exposed	8 / 132 (6.06%)		
occurrences (all)	8		
Back pain			
subjects affected / exposed	8 / 132 (6.06%)		
occurrences (all)	10		
Muscle spasms			
subjects affected / exposed	2 / 132 (1.52%)		
occurrences (all)	2		
Pain in extremity			
subjects affected / exposed	10 / 132 (7.58%)		
occurrences (all)	16		
Infections and infestations			
Bronchitis			
subjects affected / exposed	10 / 132 (7.58%)		
occurrences (all)	12		
Nasopharyngitis			

subjects affected / exposed	26 / 132 (19.70%)		
occurrences (all)	37		
Sinusitis			
subjects affected / exposed	9 / 132 (6.82%)		
occurrences (all)	9		
Upper respiratory tract infection			
subjects affected / exposed	31 / 132 (23.48%)		
occurrences (all)	42		
Urinary tract infection			
subjects affected / exposed	18 / 132 (13.64%)		
occurrences (all)	29		

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: