Clinical trial results:
A Randomized, Double-Blind, Placebo-Controlled, Parallel-Group, Dose-Ranging Study to Assess the Efficacy, Safety, Tolerability, and Pharmacokinetics of BIIB033 in Subjects With Relapsing Forms of Multiple Sclerosis When Used Concurrently With Avonex®

Summary

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

Results information

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

Trial information

Trial identification

Sponsor protocol code	215MS201

Additional study identifiers

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

Notes:

Sponsors

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

Notes:

Paediatric regulatory details

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

Notes:

Results analysis stage

Analysis stage	Final
Date of interim/final analysis	29 March 2016
Is this the analysis of the primary completion data?	No

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

Notes:

General information about the trial

Main objective of the trial:

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

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

Protection of trial subjects:

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

Background therapy:

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

Evidence for comparator: -

Actual start date of recruitment	13 August 2013
Long term follow-up planned	No
Independent data monitoring committee (IDMC) involvement?	No

Notes:

Population of trial subjects

Subjects enrolled per country

Country: Number of subjects enrolled	Poland: 118
Country: Number of subjects enrolled	Serbia: 75
Country: Number of subjects enrolled	United States: 52
Country: Number of subjects enrolled	Czech Republic: 48
Country: Number of subjects enrolled	Russian Federation: 35
Country: Number of subjects enrolled	Spain: 23
Country: Number of subjects enrolled	Italy: 18
Country: Number of subjects enrolled	Netherlands: 12
Country: Number of subjects enrolled	Canada: 11
Country: Number of subjects enrolled	United Kingdom: 11
Country: Number of subjects enrolled	France: 9
Country: Number of subjects enrolled	Hungary: 7

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

Notes:

Subjects enrolled per age group

In utero	0
Preterm newborn - gestational age < 37 wk	0
Newborns (0-27 days)	0
Infants and toddlers (28 days-23 months)	0
Children (2-11 years)	0
Adolescents (12-17 years)	0
Adults (18-64 years)	419
From 65 to 84 years	0
85 years and over	0

Subject disposition

Recruitment

Recruitment details: -

Pre-assignment

Screening details:

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

Pre-assignment period milestones

Number of subjects started	419
Number of subjects completed	418

Pre-assignment subject non-completion reasons

Reason: Number of subjects	randomized and not dosed: 1

Period 1

Period 1 title	Overall Study (overall period)
Is this the baseline period?	Yes
Allocation method	Randomised - controlled
Blinding used	Double blind
Roles blinded	Subject, Investigator, Carer

Blinding implementation details:

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

Arms

Are arms mutually exclusive?	Yes
Arm title	Placebo

Arm description:

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

Arm type	Placebo
Investigational medicinal product name	sterile normal saline (0.9% sodium chloride)
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Solution for infusion
Routes of administration	Intravenous use

Dosage and administration details:

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

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

Dosage and administration details:

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

Arm title	BIIB033, 3 mg/kg

Arm description:

BIIB033 3 mg/kg once every 4 weeks IV infusion up to Week 72. Avonex once-weekly IM injection up to Week 84.

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

Dosage and administration details:

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

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

Dosage and administration details:

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

Arm title	BIIB033, 10 mg/kg

Arm description:

BIIB033 10 mg/kg once every 4 weeks IV infusion up to Week 72. Avonex once-weekly IM injection up to Week 84.

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

Dosage and administration details:

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

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

Dosage and administration details:

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

Arm title	BIIB033, 30 mg/kg

Arm description:

BIIB033 30 mg/kg once every 4 weeks IV infusion up to Week 72. Avonex once-weekly IM injection up to Week 84.

Arm type	Experimental

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

Dosage and administration details:

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

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

Dosage and administration details:

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

Arm title	BIIB033, 100 mg/kg

Arm description:

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

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

Dosage and administration details:

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

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

Dosage and administration details:

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

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

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

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

Notes:

[1] - The number of subjects reported to be in the baseline period are not the same as the worldwide number enrolled in the trial. It is expected that these numbers will be the same.
Justification: One subject in the BIIB033 30 mg/kg arm was randomized and not dosed.

Baseline characteristics

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

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

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

Male	32	26	141

End points

End points reporting groups

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

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

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

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

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

Statistical analyses

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

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

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

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

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

Secondary: Proportion of Participants Confirmed as Worsening Responders for

Primary Multicomponent Endpoint

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

End point description:

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

End point type	Secondary

End point timeframe:

72 weeks

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

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

Statistical analyses

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

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

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

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

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

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

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

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

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

End point description:

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

End point type	Secondary

End point timeframe:

Up to 84 weeks

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

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

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

Statistical analyses

No statistical analyses for this end point

Secondary: Pharmacokinetics: BIIB033 Plasma Concentrations up to Week 84

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

End point description:

End point type	Secondary

End point timeframe:

Up to 84 weeks

Notes:

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

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

Statistical analyses

No statistical analyses for this end point

Adverse events

Adverse events information	
Timeframe for reporting adverse events:	
From first dosing of study treatment through end of study (Week 84)	
Assessment type	Systematic
Dictionary used	
Dictionary name	MedDRA
Dictionary version	18.1
Reporting groups	
Reporting group title	BIIB033 3 mg/kg
Reporting group description: -	
Reporting group title	Placebo
Reporting group description: -	
Reporting group title	BIIB033 30 mg/kg
Reporting group description: -	
Reporting group title	BIIB033 100 mg/kg
Reporting group description: -	
Reporting group title	BIIB033 10 mg/kg
Reporting group description: -	

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

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

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

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

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

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

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

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

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

subjects affected / exposed	0 / 92 (0.00%)	0 / 95 (0.00%)	
occurrences causally related to treatment / all	0 / 0	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Femur fracture			
subjects affected / exposed	0 / 92 (0.00%)	0 / 95 (0.00%)	
occurrences causally related to treatment / all	0 / 0	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Intentional overdose			
subjects affected / exposed	0 / 92 (0.00%)	0 / 95 (0.00%)	
occurrences causally related to treatment / all	0 / 0	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Road traffic accident			
subjects affected / exposed	0 / 92 (0.00%)	0 / 95 (0.00%)	
occurrences causally related to treatment / all	0 / 0	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cardiac disorders			
Acute myocardial infarction			
subjects affected / exposed	0 / 92 (0.00%)	0 / 95 (0.00%)	
occurrences causally related to treatment / all	0 / 0	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Myocardial infarction			
subjects affected / exposed	0 / 92 (0.00%)	1 / 95 (1.05%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Myocardial ischaemia			
subjects affected / exposed	0 / 92 (0.00%)	0 / 95 (0.00%)	
occurrences causally related to treatment / all	0 / 0	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Nervous system disorders			
Multiple sclerosis			
subjects affected / exposed	0 / 92 (0.00%)	1 / 95 (1.05%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Multiple sclerosis relapse			

subjects affected / exposed	6 / 92 (6.52%)	6 / 95 (6.32%)	
occurrences causally related to treatment / all	0 / 6	0 / 11	
deaths causally related to treatment / all	0 / 0	0 / 0	
Radicular syndrome			
subjects affected / exposed	0 / 92 (0.00%)	0 / 95 (0.00%)	
occurrences causally related to treatment / all	0 / 0	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Secondary progressive multiple sclerosis			
subjects affected / exposed	0 / 92 (0.00%)	0 / 95 (0.00%)	
occurrences causally related to treatment / all	0 / 0	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Seizure			
subjects affected / exposed	0 / 92 (0.00%)	0 / 95 (0.00%)	
occurrences causally related to treatment / all	0 / 0	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Trigeminal neuralgia			
subjects affected / exposed	0 / 92 (0.00%)	0 / 95 (0.00%)	
occurrences causally related to treatment / all	0 / 0	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Blood and lymphatic system disorders			
Hypochromic anaemia			
subjects affected / exposed	0 / 92 (0.00%)	0 / 95 (0.00%)	
occurrences causally related to treatment / all	0 / 0	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Gastrointestinal disorders			
Ileus			
subjects affected / exposed	0 / 92 (0.00%)	1 / 95 (1.05%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pancreatitis			
subjects affected / exposed	1 / 92 (1.09%)	0 / 95 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	

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

subjects affected / exposed	0 / 92 (0.00%)	0 / 95 (0.00%)	
occurrences causally related to treatment / all	0 / 0	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	

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

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

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

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

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

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

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

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

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

Date	Amendment
19 December 2012	The primary reasons for the first global amendment (Version 2), dated 19 December 2012, were to change the information for the conrtact research organization associated with this study, change the use of the Avonex Prefilled Syringe to only Weeks 0 to 3, add the use of the Avonex Pen for the weeks after Week 3, make it mandatory that subjects titrate Avonex in Month 1 using the Avostartgrip Titration Kit and Prefilled Syringes, and define the DSRC and its members.
10 March 2015	The primary reason for the second global amendment (Version 3), dated 10 March 2015, was to include Avonex assignment during the 3-month safety Follow-Up Period (Weeks 72 to 84).
18 August 2015	The primary reason for the third global amendment (Version 4) was to omit the interim analysis. Additionally, the following 4 MRI endpoints for pre-existing brain lesions were made optional and ultimately were not measured in this study: - Change in magnetization transfer ratio (MTR) from Baseline for abnormal T1 volume. - Change in MTR from Baseline for abnormal T2 volume not associated with T1 hypointensity. - Change in diffusion tensor imaging (DTI) from Baseline for abnormal T1 volume. - Change in DTI from Baseline for abnormal T2 volume not associated with T1 hypointensity.

Notes:

Interruptions (globally)

Were there any global interruptions to the trial? No

Limitations and caveats

None reported