



Clinical trial results:

A Multicenter, Follow-Up Study to Assess Long-Term Electrophysiologic and Clinical Outcomes in Subjects Previously Enrolled in Study 215ON201

Summary

EudraCT number	2015-003618-26
Trial protocol	GB HU CZ ES DE BE SE DK
Global end of trial date	23 January 2017

Results information

Result version number	v1 (current)
This version publication date	08 February 2018
First version publication date	08 February 2018

Trial information

Trial identification

Sponsor protocol code	215ON203
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Additional study identifiers

ISRCTN number	-
ClinicalTrials.gov id (NCT number)	NCT02657915
WHO universal trial number (UTN)	-

Notes:

Sponsors

Sponsor organisation name	Biogen
Sponsor organisation address	250 Binney Street, Cambridge, United States, 02142
Public contact	Study Director, Biogen, +1 866-633-4636, clinicaltrials@biogen.com
Scientific contact	Study Director, Biogen, +1 866-633-4636, 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	23 January 2017
Is this the analysis of the primary completion data?	Yes
Primary completion date	23 January 2017
Global end of trial reached?	Yes
Global end of trial date	23 January 2017
Was the trial ended prematurely?	No

Notes:

General information about the trial

Main objective of the trial:

The primary objective of the study was to assess full-field visual evoked potential (FF-VEP) latency in subjects who were enrolled in the parent Study 215ON201 (hereafter referred to as RENEW) at 2 years (+ up to 12 months) after the last study visit.

Protection of trial subjects:

Written informed consent was obtained from each subject prior to evaluations performed for eligibility. Subjects were given adequate time to review the information in the Informed Consent Form (ICF) and were allowed to ask, and have answered, questions concerning all portions of the conduct of the study. Subjects were provided with a copy of the signed and dated ICF.

Background therapy: -

Evidence for comparator: -

Actual start date of recruitment	10 March 2016
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	Belgium: 2
Country: Number of subjects enrolled	Australia: 6
Country: Number of subjects enrolled	Canada: 2
Country: Number of subjects enrolled	Czech Republic: 4
Country: Number of subjects enrolled	Denmark: 3
Country: Number of subjects enrolled	Germany: 14
Country: Number of subjects enrolled	Hungary: 2
Country: Number of subjects enrolled	Italy: 4
Country: Number of subjects enrolled	Spain: 10
Country: Number of subjects enrolled	Sweden: 2
Country: Number of subjects enrolled	United Kingdom: 3
Worldwide total number of subjects	52
EEA total number of subjects	44

Notes:

Subjects enrolled per age group

In utero	0
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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)	52
From 65 to 84 years	0
85 years and over	0

Subject disposition

Recruitment

Recruitment details: -

Pre-assignment

Screening details:

The number of subjects eligible for this study was determined by the number of subjects who participated in RENEW. A total of 82 subjects were enrolled in RENEW and received at least 1 dose of study treatment. A total of 52 subjects participated in this study.

Period 1

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

Blinding implementation details:

This was a follow-up study with no investigational product; however, the allocation method in RENEW was randomised-controlled and to maintain the blind from RENEW, the treatment disclosure for RENEW was not shared with study sites or subjects until the end of this study.

Arms

Are arms mutually exclusive?	Yes
Arm title	Placebo

Arm description:

This was a follow-up study with no investigational product administered. Subjects in the placebo arm had received at least 1 dose of placebo in RENEW.

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

Dosage and administration details:

Administered as specified in the treatment arm

Arm title	BIIB033 100mg/Kg
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Arm description:

This was a follow-up study with no investigational product administered. Subjects in the BIIB033 arm had received at least 1 dose of 100 mg/kg BIIB033 in RENEW.

Arm type	Experimental
Investigational medicinal product name	BIIB033 100 mg/Kg
Investigational medicinal product code	
Other name	Opicinumab
Pharmaceutical forms	Solution for injection
Routes of administration	Intravenous use

Dosage and administration details:

Administered as specified in the treatment arm.

Number of subjects in period 1	Placebo	BIIB033 100mg/Kg
Started	24	28
Completed	24	28

Baseline characteristics

Reporting groups

Reporting group title	Placebo
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Reporting group description:

This was a follow-up study with no investigational product administered. Subjects in the placebo arm had received at least 1 dose of placebo in RENEW.

Reporting group title	BIIB033 100mg/Kg
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Reporting group description:

This was a follow-up study with no investigational product administered. Subjects in the BIIB033 arm had received at least 1 dose of 100 mg/kg BIIB033 in RENEW.

Reporting group values	Placebo	BIIB033 100mg/Kg	Total
Number of subjects	24	28	52
Age Categorical			
Units: Subjects			
In utero	0	0	0
Preterm newborn infants (gestational age < 37 wks)	0	0	0
Newborns (0-27 days)	0	0	0
Infants and toddlers (28 days-23 months)	0	0	0
Children (2-11 years)	0	0	0
Adolescents (12-17 years)	0	0	0
Adults (18-64 years)	24	28	52
From 65-84 years	0	0	0
85 years and over	0	0	0
Age Continuous			
Units: years			
arithmetic mean	35.6	34.6	
standard deviation	± 7.96	± 6.57	-
Gender Categorical			
Units: Subjects			
Female	19	19	38
Male	5	9	14

End points

End points reporting groups

Reporting group title	Placebo
Reporting group description: This was a follow-up study with no investigational product administered. Subjects in the placebo arm had received at least 1 dose of placebo in RENEW.	
Reporting group title	BIIB033 100mg/Kg
Reporting group description: This was a follow-up study with no investigational product administered. Subjects in the BIIB033 arm had received at least 1 dose of 100 mg/kg BIIB033 in RENEW.	

Primary: FF-VEP Latency of the Affected Eye as Compared to the Baseline of the Fellow Eye at 2 Years (+ up to 12 Months) After the Last Study Visit Assessment (Week 32) in Study 215ON201 (RENEW)

End point title	FF-VEP Latency of the Affected Eye as Compared to the Baseline of the Fellow Eye at 2 Years (+ up to 12 Months) After the Last Study Visit Assessment (Week 32) in Study 215ON201 (RENEW)
End point description: A full field visual evoked potential (FF-VEP) is an evoked potential caused by a visual stimulus, such as an alternating checkerboard pattern on a computer screen. Responses are recorded from electrodes that are placed on the back of the head and are observed as a reading on an electroencephalogram (EEG). These responses usually originate from the occipital cortex, the area of the brain involved in receiving and interpreting visual signals. Primary analysis for this endpoint was performed in the Per Protocol (PP) population and data from this population are presented below. The PP population was defined as subjects from the intent-to-treat (ITT) population who completed the study, did not miss more than one dose of BIIB033 or placebo, and did not receive multiple sclerosis (MS) modifying therapies in RENEW. The number of subjects analysed in each arm at each time point is indicated by "n".	
End point type	Primary
End point timeframe: Day 1	

End point values	Placebo	BIIB033 100mg/Kg		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	23	24		
Units: milliseconds (msec)				
arithmetic mean (standard deviation)				
Baseline (n= 22, 24)	100.68 (± 4.854)	102.29 (± 5.507)		
Day 1 (n=21, 23)	119.52 (± 13.395)	114.20 (± 14.235)		

Statistical analyses

Statistical analysis title	Placebo Vs. BIIB033
Comparison groups	BIIB033 100mg/Kg v Placebo

Number of subjects included in analysis	47
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.165
Method	ANCOVA
Parameter estimate	Mean difference (final values)
Point estimate	-6
Confidence interval	
level	95 %
sides	2-sided
lower limit	-14.56
upper limit	2.57

Secondary: Number of Subjects that Developed Clinically Definite Multiple Sclerosis (CDMS) After Enrollment in RENEW

End point title	Number of Subjects that Developed Clinically Definite Multiple Sclerosis (CDMS) After Enrollment in RENEW
End point description: Primary analysis for this endpoint was performed in the Per Protocol (PP) population and data from this population are presented below. The Per Protocol (PP) population was defined as subjects from the intent-to-treat (ITT) population who completed the study, did not miss more than one dose of BIIB033 or placebo, and did not receive multiple sclerosis (MS) modifying therapies in RENEW.	
End point type	Secondary
End point timeframe: Day 1	

End point values	Placebo	BIIB033 100mg/Kg		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	23	24		
Units: Number of Subjects	12	12		

Statistical analyses

No statistical analyses for this end point

Secondary: Time to Diagnosis of CDMS

End point title	Time to Diagnosis of CDMS
End point description: Measured in Days using the Median (50th percentile) for each arm. NOTE: The value of 9999.99 for the max of the inter-quartile range = NA. Data is not reported for this value as it was not observed during this study.	
End point type	Secondary
End point timeframe: Day 1	

End point values	Placebo	BIIB033 100mg/Kg		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	23	24		
Units: Days				
median (inter-quartile range (Q1-Q3))	386.0 (212.0 to 1065.0)	909.5 (281.0 to 9999.99)		

Statistical analyses

No statistical analyses for this end point

Secondary: Severity of Central Nervous System (CNS) Demyelinating Disease as Assessed Using the Expanded Disability Status Scale (EDSS)

End point title	Severity of Central Nervous System (CNS) Demyelinating Disease as Assessed Using the Expanded Disability Status Scale (EDSS)
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End point description:

The EDSS measures disability status on a scale ranging from 0 to 10, with higher scores indicating more disability. Scoring is based on measures of impairment in eight functional systems on examination by a neurologist. originate from the occipital cortex, the area of the brain involved in receiving and interpreting visual signals. Primary analysis for this endpoint was performed in the Per Protocol (PP) population and data from this population are presented below. The Per Protocol (PP) population was defined as subjects from the intent-to-treat (ITT) population who completed the study, did not miss more than one dose of BIIB033 or placebo, and did not receive multiple sclerosis (MS) modifying therapies in RENEW. The number of subjects analysed in each arm is indicated by "n".

End point type	Secondary
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End point timeframe:

Day 1

End point values	Placebo	BIIB033 100mg/Kg		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	23	24		
Units: EDSS Total Score				
arithmetic mean (standard deviation)				
n=23, 21	1.22 (± 0.837)	1.26 (± 1.136)		

Statistical analyses

No statistical analyses for this end point

Secondary: Severity of CNS Demyelinating Disease as Assessed Using the Symbol-Digit Modalities Test (SDMT)

End point title	Severity of CNS Demyelinating Disease as Assessed Using the Symbol-Digit Modalities Test (SDMT)
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End point description:

SDMT is a screening test for cognitive impairment. Subjects are given 90 seconds in which to pair specific numbers with given geometric figures using a key. Scores range from 0 to 110 (best). Originate from the occipital cortex, the area of the brain involved in receiving and interpreting visual signals. Primary analysis for this endpoint was performed in the Per Protocol (PP) population and data from this population are presented below. The Per Protocol (PP) population was defined as subjects from the intent-to-treat (ITT) population who completed the study, did not miss more than one dose of BIIB033 or placebo, and did not receive multiple sclerosis (MS) modifying therapies in RENEW. The number of subjects analysed in each arm is indicated by "n".

End point type	Secondary
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End point timeframe:

Day 1

End point values	Placebo	BIIB033 100mg/Kg		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	23	24		
Units: SDMT Total Score				
arithmetic mean (standard deviation)				
n= 22, 20	56.7 (± 9.91)	58.7 (± 9.01)		

Statistical analyses

No statistical analyses for this end point

Secondary: Severity of CNS Demyelinating Disease as Assessed Using the Multiple Sclerosis Functional Composite (MSFC) Assessment

End point title	Severity of CNS Demyelinating Disease as Assessed Using the Multiple Sclerosis Functional Composite (MSFC) Assessment
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End point description:

The MSFC is a three-part, standardized, quantitative, assessment instrument for use in clinical studies, particularly clinical trials, of MS. The three components of the MSFC are: (1) measure leg function/ambulation, (2) measure arm/hand function, and (3) measure cognitive function. MSFC is reported as a Z-score where higher scores represent better neurological function. Originate from the occipital cortex, the area of the brain involved in receiving and interpreting visual signals. Primary analysis for this endpoint was performed in the Per Protocol (PP) population and data from this population are presented below. The Per Protocol (PP) population was defined as subjects from the intent-to-treat (ITT) population who completed the study, did not miss more than one dose of BIIB033 or placebo, and did not receive multiple sclerosis (MS) modifying therapies in RENEW. The number of subjects analysed in each arm is indicated by "n".

End point type	Secondary
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End point timeframe:

Day 1

End point values	Placebo	BIIB033 100mg/Kg		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	23	24		
Units: Z-score				
arithmetic mean (standard deviation)				
n= 20, 21	-0.82 (\pm 2.883)	-0.06 (\pm 0.804)		

Statistical analyses

No statistical analyses for this end point

Secondary: Change in Number of Gadolinium (Gd)-Enhanced Lesions from Baseline in RENEW to Day 1

End point title	Change in Number of Gadolinium (Gd)-Enhanced Lesions from Baseline in RENEW to Day 1
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End point description:

Number of consensus GD-enhanced lesions as compared to baseline. Primary analysis for this endpoint was performed in the Per Protocol (PP) population and data from this population are presented below. The Per Protocol (PP) population was defined as subjects from the intent-to-treat (ITT) population who completed the study, did not miss more than one dose of BIIB033 or placebo, and did not receive multiple sclerosis (MS) modifying therapies in RENEW. The number of subjects analysed in each arm at each time point is indicated by "n".

End point type	Secondary
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End point timeframe:

Day 1

End point values	Placebo	BIIB033 100mg/Kg		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	23	24		
Units: Number of Lesions				
arithmetic mean (standard deviation)				
Baseline n=22, 24	0.2 (\pm 0.69)	0.1 (\pm 0.41)		
Change from Baseline to Day 1 n= 21, 19	0.2 (\pm 1.54)	-0.1 (\pm 0.46)		

Statistical analyses

No statistical analyses for this end point

Secondary: Change in Volume of T2 Lesions from Baseline in RENEW to Day 1

End point title	Change in Volume of T2 Lesions from Baseline in RENEW to Day 1
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End point description:

Volume of T2 lesions as compared to baseline. Primary analysis for this endpoint was performed in the Per Protocol (PP) population and data from this population are presented below. The Per Protocol (PP)

population was defined as subjects from the intent-to-treat (ITT) population who completed the study, did not miss more than one dose of BIIB033 or placebo, and did not receive multiple sclerosis (MS) modifying therapies in RENEW. The number of subjects analysed in each arm at each time point is indicated by "n".

End point type	Secondary
End point timeframe:	
Day 1	

End point values	Placebo	BIIB033 100mg/Kg		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	23	24		
Units: Millilitres (mL)				
arithmetic mean (standard deviation)				
Baseline n= 22, 24	0.9710 (± 0.93551)	0.7341 (± 1.29222)		
Change from Baseline to Day 1 n= 21, 19	0.5090 (± 1.38861)	0.6244 (± 0.74850)		

Statistical analyses

No statistical analyses for this end point

Adverse events

Adverse events information^[1]

Timeframe for reporting adverse events:

Day 1

Adverse event reporting additional description:

The safety population was defined as all subjects who received at least 1 dose of study treatment in RENEW and completed at least 1 of the 1-day assessments in this study. There were no Adverse Events or Serious Adverse Events observed or reported in this study.

Assessment type	Systematic
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Dictionary used

Dictionary name	MedDRA
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Dictionary version	17.0
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Reporting groups

Reporting group title	BIIB033 100mg/Kg
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Reporting group description: -

Reporting group title	Placebo
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Reporting group description: -

Serious adverse events	BIIB033 100mg/Kg	Placebo	
Total subjects affected by serious adverse events			
subjects affected / exposed	0 / 28 (0.00%)	0 / 24 (0.00%)	
number of deaths (all causes)	0	0	
number of deaths resulting from adverse events	0	0	

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

Non-serious adverse events	BIIB033 100mg/Kg	Placebo	
Total subjects affected by non-serious adverse events			
subjects affected / exposed	0 / 28 (0.00%)	0 / 24 (0.00%)	

Notes:

[1] - There are no non-serious adverse events recorded for these results. It is expected that there will be at least one non-serious adverse event reported.

Justification: There are no non-serious adverse events recorded as none were observed during this study.

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

Date	Amendment
16 November 2015	The primary reason for this amendment is to add adverse event (AE) reporting from the signing of the ICF throughout the study and to specify that AEs and serious AEs (SAEs) will be evaluated as possibly related to prior treatment with investigational drug (administered in Study 215ON201) in addition to those possibly related to study procedure(s).
08 June 2016	The primary reason for this amendment is to extend the length of time that subjects are eligible for study participation following the completion of Study 215ON201 from 2 years (+ 4 months) to 2 years (+ up to 12 months) after the last study visit.

Notes:

Interruptions (globally)

Were there any global interruptions to the trial? No

Limitations and caveats

None reported