Clinical trial results:
A Phase 3b, 12-month, Open-label, Multicenter Study to Evaluate the Efficacy and Safety of BIIB019, Daclizumab, in Subjects with Relapsing-Remitting Multiple Sclerosis (RRMS) Switching from Natalizumab (SUSTAIN)

Summary

EudraCT number	2016-002820-10
Trial protocol	GB DE IT
Global end of trial date	12 September 2018

Results information

Result version number	v1 (current)
This version publication date	22 September 2019
First version publication date	22 September 2019

Trial information

Trial identification

Sponsor protocol code	205MS305

Additional study identifiers

ISRCTN number	-
ClinicalTrials.gov id (NCT number)	NCT02881567
WHO universal trial number (UTN)	-

Notes:

Sponsors

Sponsor organisation name	Biogen
Sponsor organisation address	250 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 September 2018
Is this the analysis of the primary completion data?	No

Global end of trial reached?	Yes
Global end of trial date	12 September 2018
Was the trial ended prematurely?	Yes

Notes:

General information about the trial

Main objective of the trial:

The primary objective of the study was to evaluate the effects of treatment with daclizumab on the proportion of subjects relapse-free at 6 months in RRMS subjects, who switched from treatment with natalizumab to daclizumab due to safety concerns. The secondary objectives of this study in this study population were to evaluate the effects of daclizumab on the following: 1) Multiple Sclerosis (MS) relapse activity including the annualized relapse rate (ARR) and the proportion of subjects experiencing relapses requiring hospitalization and/or steroid treatment 2) MS-related outcomes measured using magnetic resonance imaging (MRI) 3) Safety and tolerability in subjects previously treated with natalizumab.

Protection of trial subjects:

Written informed consent was obtained from each subject or subject's legally authorised representative (e.g., parent or legal guardian), as applicable, prior to evaluations performed for eligibility. Subjects or the subject's legally authorised 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: -

Evidence for comparator: -

Actual start date of recruitment	18 April 2017
Long term follow-up planned	Yes
Long term follow-up rationale	Safety
Long term follow-up duration	6 Months
Independent data monitoring committee (IDMC) involvement?	No

Notes:

Population of trial subjects

Subjects enrolled per country

Country: Number of subjects enrolled	Canada: 1
Country: Number of subjects enrolled	Germany: 10
Country: Number of subjects enrolled	Italy: 17
Country: Number of subjects enrolled	United States: 13
Worldwide total number of subjects	41
EEA total number of subjects	27

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)	41
From 65 to 84 years	0
85 years and over	0

Subject disposition

Recruitment

Recruitment details:

Subjects enrolled in the study at 11 investigative sites in Canada, Germany, Italy, and the United States from 05 April 2017 to 12 September 2018.

Pre-assignment

Screening details:

Subjects who discontinued treatment with natalizumab due to safety concerns were enrolled to receive daclizumab 150 milligrams (mg) per 1.0 millilitre (mL).

Period 1

Period 1 title	Overall Study (overall period)
Is this the baseline period?	Yes
Allocation method	Non-randomised - controlled
Blinding used	Not blinded

Arms

Arm title	Daclizumab

Arm description:

Subjects previously treated with natalizumab for at least 12 months and who discontinued treatment, received daclizumab 150 mg per 1.0 mL administered subcutaneously once a month for up to 11 months.

Arm type	Experimental
Investigational medicinal product name	Daclizumab
Investigational medicinal product code	
Other name	Zinbryta
Pharmaceutical forms	Solution for injection
Routes of administration	Subcutaneous use

Dosage and administration details:

Daclizumab was administered as 150 mg per 1.0 mL subcutaneously, once a month for up to 11 months.

Number of subjects in period 1	Daclizumab
Started	41
Completed	23
Not completed	18
Adverse event	1
Investigator decision	1
Study terminated by sponsor	9
Lost to follow-up	3
Consent withdrawn	1
Reason not Specified	3

Baseline characteristics

Reporting groups	
Reporting group title	Daclizumab
Reporting group description:	
Subjects previously treated with natalizumab for at least 12 months and who discontinued treatment, received daclizumab 150 mg per 1.0 mL administered subcutaneously once a month for up to 11 months.	

Reporting group values	Daclizumab	Total	
Number of subjects	41	41	
Age Categorical Units: Subjects			
Adults (18-64 years)	41	41	
Age Continuous Units: years			
arithmetic mean	36.9		
standard deviation	± 9.71	-	
Gender Categorical Units: Subjects			
Female	28	28	
Male	13	13	
Race Units: Subjects			
White	9	9	
Black or African American	4	4	
Not Reported Due to Confidentiality Regulation	27	27	
Other (Aboriginal)	1	1	

End points

End points reporting groups

Reporting group title	Daclizumab

Reporting group description:

Subjects previously treated with natalizumab for at least 12 months and who discontinued treatment, received daclizumab 150 mg per 1.0 mL administered subcutaneously once a month for up to 11 months.

Primary: Percentage of Subjects Relapse-free at Month 6

End point title	Percentage of Subjects Relapse-free at Month 6[1]

End point description:

Relapses were defined as new or recurrent neurological symptoms not associated with fever or infection, lasting at least 24 hours, and accompanied by new objective neurological findings upon examination by the Examining Neurologist. The Kaplan-Meier estimate of the percentage of subjects relapse-free at Month 6 is reported. FAS included all subjects enrolled in the study.

End point type	Primary

End point timeframe:

Month 6

Notes:

[1] - 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 analyses are reported for this endpoint.

End point values	Daclizumab			
Subject group type	Reporting group			
Number of subjects analysed	41			
Units: percentage of subjects				
number (not applicable)	66.615			

Statistical analyses

No statistical analyses for this end point

Secondary: Percentage of Subjects Experiencing Relapse Requiring Hospitalization and/or Steroid Treatment at Month 12

End point title	Percentage of Subjects Experiencing Relapse Requiring Hospitalization and/or Steroid Treatment at Month 12

End point description:

Relapses were defined as new or recurrent neurological symptoms not associated with fever or infection, lasting at least 24 hours, and accompanied by new objective neurological findings upon examination by the Examining Neurologist.

End point type	Secondary

End point timeframe:

Month 12

End point values	Daclizumab			
Subject group type	Reporting group			
Number of subjects analysed	0[2]			
Units: percentage of subjects				
number (not applicable)				

Notes:

[2] - The study was terminated. No subjects reached the 12-month time point.

Statistical analyses

No statistical analyses for this end point

Secondary: Percentage of Subjects Relapse-free at Month 12

End point title	Percentage of Subjects Relapse-free at Month 12

End point description:

Relapses were defined as new or recurrent neurological symptoms not associated with fever or infection, lasting at least 24 hours, and accompanied by new objective neurological findings upon examination by the Examining Neurologist.

End point type	Secondary

End point timeframe:

Month 12

End point values	Daclizumab			
Subject group type	Reporting group			
Number of subjects analysed	0[3]			
Units: percentage of subjects				
number (not applicable)				

Notes:

[3] - The study was terminated. No subjects reached the 12-month time point.

Statistical analyses

No statistical analyses for this end point

Secondary: Annualised Relapse Rate (ARR) at Month 12

End point title	Annualised Relapse Rate (ARR) at Month 12

End point description:

Relapses were defined as new or recurrent neurological symptoms not associated with fever or infection, lasting at least 24 hours, and accompanied by new objective neurological findings upon examination by the Examining Neurologist. The ARR was calculated by tabulating the total number of relapses experienced in the group divided by the number of days up to the end of Month 12, and the ratio then multiplied by 365.

End point type	Secondary

End point timeframe:

Month 12

End point values	Daclizumab			
Subject group type	Reporting group			
Number of subjects analysed	0[4]			
Units: relapses per year				
arithmetic mean (confidence interval 95%)	(to)			

Notes:

[4] - The study was terminated. No subjects reached the 12-month time point.

Statistical analyses

No statistical analyses for this end point

Secondary: Number of Subjects with New Gadolinium-Enhanced (Gd+) and T1 Hypointense Lesions at Months 6 and 12

End point title	Number of Subjects with New Gadolinium-Enhanced (Gd+) and T1 Hypointense Lesions at Months 6 and 12

End point description:

New Gadolinium-Enhanced (Gd+) and T1 Hypointense Lesions were assessed using magnetic resonance imaging (MRI). FAS included all subjects enrolled in the study. Number of Subjects Analyzed is the number of subjects with available assessment. 'n' signifies the number of subjects analysed at specified time point. '99999' for Month 6, T1 Hypointense Lesions indicates that no data was collected. '99999' for Month 12, Gd+ and Month 12, T1 Hypointense Lesions indicates that the study was terminated and no subjects reached the 12-month time point.

End point type	Secondary

End point timeframe:

Months 6 and 12

End point values	Daclizumab			
Subject group type	Reporting group			
Number of subjects analysed	11			
Units: subjects				
Month 6, Gd+ Lesions (n= 11)	3			
Month 6, T1 Hypointense Lesions (n=0)	99999			
Month 12, Gd+ Lesions (n= 0)	99999			
Month 12, T1 Hypointense Lesions (n= 0)	99999			

Statistical analyses

No statistical analyses for this end point

Secondary: Number of Subjects with New and Newly Enlarged T2 Hypointense Lesions at Months 6 and 12

End point title	Number of Subjects with New and Newly Enlarged T2 Hypointense Lesions at Months 6 and 12

End point description:

New and newly enlarged T2 Hypointense Lesions were measured by MRI. FAS included all subjects enrolled in the study. Number of Subjects Analyzed is the number of subjects with available assessment. 'n' signifies the number of subjects analysed at specified time point. '99999' indicates that the study was terminated and no subjects reached the 12-month time point.

End point type	Secondary

End point timeframe:

Months 6 and 12

End point values	Daclizumab			
Subject group type	Reporting group			
Number of subjects analysed	11			
Units: subjects				
Month 6 (n=11) Month 12 (n= 0)	3 99999			

Statistical analyses

No statistical analyses for this end point

Secondary: Permanent Discontinuation Rate of Daclizumab at Month 12

End point title	Permanent Discontinuation Rate of Daclizumab at Month 12

End point description:

Permanent Discontinuation Rate was calculated as the ratio of number of subjects who had permanently discontinued daclizumab prior to Month 12 over the total number of subjects who received at least 1 dose of daclizumab in the study.

End point type	Secondary

End point timeframe:

Month 12

End point values	Daclizumab			
Subject group type	Reporting group			
Number of subjects analysed	0[5]			
Units: ratio				
arithmetic mean (confidence interval 95%)	(to)			

Notes:

[5] - The study was terminated. No subjects reached the 12-month time point

Statistical analyses

No statistical analyses for this end point

Secondary: Number of Subjects with Adverse Events (AEs) and Serious Adverse Events (SAEs)

End point title	Number of Subjects with Adverse Events (AEs) and Serious Adverse Events (SAEs)

End point description:

An AE can be any unfavourable 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. An SAE is any untoward medical occurrence that at any dose results in death or in the view of the Investigator, places the subject at immediate risk of death or requires inpatient hospitalisation or prolongation of existing hospitalisation or results in persistent or significant disability or results in a birth defect. Safety Population included all enrolled subjects who received at least 1 dose of study drug.

End point type	Secondary

End point timeframe:

The first dose of study drug to within 30 days of last dose (up to 11 months)

End point values	Daclizumab			
Subject group type	Reporting group			
Number of subjects analysed	41			
Units: subjects				
Subjects with AEs	27			
Subjects with SAEs	9			

Statistical analyses

No statistical analyses for this end point

Secondary: Number of Subjects with Clinically Relevant Shifts in Laboratory Assessments

End point title	Number of Subjects with Clinically Relevant Shifts in Laboratory Assessments

End point description:

Clinical Laboratory assessments were tests of Chemistry and Hematology. The investigator determined if any of the laboratory results were clinically relevant shifts from Baseline. Safety Population included all enrolled subjects who received at least 1 dose of study drug.

End point type	Secondary

End point timeframe:

First dose of study drug to within 30 days of last dose (up to 11 months)

End point values	Daclizumab			
Subject group type	Reporting group			
Number of subjects analysed	41			
Units: subjects	0			

Statistical analyses

No statistical analyses for this end point

Adverse events

Adverse events information	
Timeframe for reporting adverse events:	
First dose of study drug to within 30 days of last dose (up to 11 months)	
Assessment type	Systematic

Dictionary used	
Dictionary name	MedDRA
Dictionary version	21.1

Reporting groups	
Reporting group title	Daclizumab

Reporting group description:

Subjects previously treated with natalizumab for at least 12 months and who discontinued treatment received daclizumab 150 mg per 1.0 mL administered subcutaneously once a month for up to 11 months.

Serious adverse events	Daclizumab		
Total subjects affected by serious adverse events			
subjects affected / exposed	9 / 41 (21.95%)		
number of deaths (all causes)	0		
number of deaths resulting from adverse events			
Nervous system disorders			
Multiple sclerosis relapse			
subjects affected / exposed	2 / 41 (4.88%)		
occurrences causally related to treatment / all	0 / 2		
deaths causally related to treatment / all	0 / 0		
Blood and lymphatic system disorders			
Lymphadenopathy			
subjects affected / exposed	1 / 41 (2.44%)		
occurrences causally related to treatment / all	1 / 1		
deaths causally related to treatment / all	0 / 0		
Gastrointestinal disorders			
Gastrointestinal ulcer			
subjects affected / exposed	1 / 41 (2.44%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Hepatobiliary disorders			
Cholelithiasis			

subjects affected / exposed	1 / 41 (2.44%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Skin and subcutaneous tissue disorders			
Drug reaction with eosinophilia and systemic symptoms			
subjects affected / exposed	1 / 41 (2.44%)		
occurrences causally related to treatment / all	1 / 1		
deaths causally related to treatment / all	0 / 0		
Musculoskeletal and connective tissue disorders			
Rhabdomyolysis			
subjects affected / exposed	1 / 41 (2.44%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Infections and infestations			
Encephalitis			
subjects affected / exposed	1 / 41 (2.44%)		
occurrences causally related to treatment / all	1 / 1		
deaths causally related to treatment / all	0 / 0		
Influenza			
subjects affected / exposed	1 / 41 (2.44%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Oesophageal candidiasis			
subjects affected / exposed	1 / 41 (2.44%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Subcutaneous abscess			
subjects affected / exposed	1 / 41 (2.44%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		

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

Non-serious adverse events	Daclizumab		
Total subjects affected by non-serious adverse events			
subjects affected / exposed	23 / 41 (56.10%)		
Nervous system disorders			
Migraine			
subjects affected / exposed	3 / 41 (7.32%)		
occurrences (all)	3		
Multiple sclerosis relapse			
subjects affected / exposed	7 / 41 (17.07%)		
occurrences (all)	7		
Blood and lymphatic system disorders			
Lymphadenopathy			
subjects affected / exposed	3 / 41 (7.32%)		
occurrences (all)	4		
General disorders and administration site conditions			
Injection site pain			
subjects affected / exposed	7 / 41 (17.07%)		
occurrences (all)	11		
Gastrointestinal disorders			
Nausea			
subjects affected / exposed	5 / 41 (12.20%)		
occurrences (all)	5		
Vomiting			
subjects affected / exposed	3 / 41 (7.32%)		
occurrences (all)	4		
Psychiatric disorders			
Depression			
subjects affected / exposed	4 / 41 (9.76%)		
occurrences (all)	4		
Infections and infestations			
Influenza			
subjects affected / exposed	9 / 41 (21.95%)		
occurrences (all)	11		
Nasopharyngitis			
subjects affected / exposed	4 / 41 (9.76%)		
occurrences (all)	4		

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? No

Interruptions (globally)

Were there any global interruptions to the trial? Yes

Date	Interruption	Restart date
02 March 2018	The study was terminated and enrollment closed due to the Sponsor's decision to discontinue the daclizumab clinical development program. This was concurrent with the announcement of the voluntary worldwide withdrawal of Zinbryta (daclizumab) for relapsing MS.	-

Notes:

Limitations and caveats

None reported