Clinical trial results:
Open-Label, Multicenter, Multiple-Dose Study of the Effect of BG00012 on MRI Lesions and Pharmacokinetics in Pediatric Subjects With Relapsing-Remitting Multiple Sclerosis Aged 10 to 17 Years

Summary

EudraCT number	2014-005003-24
Trial protocol	LV DE CZ BG PL BE
Global end of trial date	23 September 2016

Results information

Result version number	v1
This version publication date	05 April 2017
First version publication date	05 April 2017

Trial information

Trial identification

Sponsor protocol code	109MS202

Additional study identifiers

ISRCTN number	-
ClinicalTrials.gov id (NCT number)	NCT02410200
WHO universal trial number (UTN)	-

Notes:

Sponsors

Sponsor organisation name	Biogen
Sponsor organisation address	225 Binney Street, Cambridge, Massachusetts, 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?	Yes

Notes:

Results analysis stage

Analysis stage	Final
Date of interim/final analysis	23 September 2016
Is this the analysis of the primary completion data?	No

Global end of trial reached?	Yes
Global end of trial date	23 September 2016
Was the trial ended prematurely?	No

Notes:

General information about the trial

Main objective of the trial:

The primary objective of this study is to evaluate the effect of BG00012 (dimethyl fumarate) on brain magnetic resonance imaging (MRI) lesions in pediatric participants with relapsing-remitting multiple sclerosis (RRMS). The secondary objectives of this study are to characterize the pharmacokinetics of BG00012 in pediatric participants with RRMS and to evaluate the safety and tolerability of BG00012 in pediatric participants with RRMS.

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: -

Evidence for comparator: -

Actual start date of recruitment	07 September 2015
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: 5
Country: Number of subjects enrolled	Bulgaria: 3
Country: Number of subjects enrolled	Germany: 3
Country: Number of subjects enrolled	Kuwait: 3
Country: Number of subjects enrolled	Lebanon: 2
Country: Number of subjects enrolled	Turkey: 2
Country: Number of subjects enrolled	Belgium: 1
Country: Number of subjects enrolled	Czech Republic: 1
Country: Number of subjects enrolled	Latvia: 1
Country: Number of subjects enrolled	United States: 1
Worldwide total number of subjects	22
EEA total number of subjects	14

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)	22
Adults (18-64 years)	0
From 65 to 84 years	0
85 years and over	0

Subject disposition

Recruitment

Recruitment details: -

Pre-assignment

Screening details:

Subject eligibility for the study was determined within 4 weeks prior to the Baseline Period.

Period 1

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

Arms

Arm title	BG00012

Arm description:

BG00012 taken orally at a dose of 120 mg twice daily (BID) for the first 7 days and at a dose of 240 mg BID thereafter for 24 weeks.

Arm type	Experimental
Investigational medicinal product name	BG00012
Investigational medicinal product code	
Other name	dimethyl fumarate DMF
Pharmaceutical forms	Gastro-resistant capsule, hard
Routes of administration	Oral use

Dosage and administration details:

Directions for Handling and Administration were followed.

Number of subjects in period 1	BG00012
Started	22
Completed	20
Not completed	2
Adverse event, non-fatal	2

Baseline characteristics

Reporting groups	
Reporting group title	BG00012
Reporting group description:	
BG00012 taken orally at a dose of 120 mg twice daily (BID) for the first 7 days and at a dose of 240 mg BID thereafter for 24 weeks.	

Reporting group values	BG00012	Total	
Number of subjects	22	22	
Age categorical Units: Subjects			
Adolescents (12-17 years)	22	22	
Age Continuous Units: years			
arithmetic mean	15.8		
standard deviation	± 1.18	-	
Gender, Male/Female Units: Subjects			
Female	14	14	
Male	8	8	

End points

End points reporting groups

Reporting group title	BG00012

Reporting group description:

BG00012 taken orally at a dose of 120 mg twice daily (BID) for the first 7 days and at a dose of 240 mg BID thereafter for 24 weeks.

Primary: Change in the Number of New or Newly Enlarging T2 Hyperintense Lesions on Brain Magnetic Resonance Imaging (MRI) Scans From the Baseline Period to On-Treatment Assessment Period

End point title	Change in the Number of New or Newly Enlarging T2 Hyperintense Lesions on Brain Magnetic Resonance Imaging (MRI) Scans From the Baseline Period to On-Treatment Assessment Period[1]

End point description:

End point type	Primary

End point timeframe:

Baseline Period (Week -8 to Day 0), On-Treatment Assessment Period (Week 16 to Week 24)

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: Statistical analysis is provided in the document attached to this endpoint presentation. (Analysis could not be entered into EudraCT due to system limitations.)

End point values	BG00012			
Subject group type	Reporting group			
Number of subjects analysed	15			
Units: lesions				
arithmetic mean (standard deviation)	-7.9 (± 16.23)			

Attachments (see zip file)	Statistical Analysis for Primary Endpoint.docx

Statistical analyses

No statistical analyses for this end point

Secondary: Maximum Observed Plasma Concentration (Cmax)

End point title	Maximum Observed Plasma Concentration (Cmax)

End point description:

End point type	Secondary

End point timeframe:

Day 8

End point values	BG00012			
Subject group type	Reporting group			
Number of subjects analysed	21			
Units: ng/mL				
arithmetic mean (standard deviation)	1998.62 (± 1286.467)			

Statistical analyses

No statistical analyses for this end point

Secondary: Time to Reach Maximum Observed Plasma Concentration (Tmax)

End point title	Time to Reach Maximum Observed Plasma Concentration (Tmax)

End point description:

End point type	Secondary

End point timeframe:

Day 8

End point values	BG00012			
Subject group type	Reporting group			
Number of subjects analysed	21			
Units: hours				
arithmetic mean (standard deviation)	4.2 (± 1.543)			

Statistical analyses

No statistical analyses for this end point

Secondary: Apparent Clearance (CL/F)

End point title	Apparent Clearance (CL/F)

End point description:

End point type	Secondary

End point timeframe:

Day 8

End point values	BG00012			
Subject group type	Reporting group			
Number of subjects analysed	17			
Units: L/h				
arithmetic mean (standard deviation)	74.45 (± 30.185)			

Statistical analyses

No statistical analyses for this end point

Secondary: Apparent Volume of Distribution (V/F)

End point title	Apparent Volume of Distribution (V/F)

End point description:

End point type	Secondary

End point timeframe:

Day 8

End point values	BG00012			
Subject group type	Reporting group			
Number of subjects analysed	14			
Units: liters				
arithmetic mean (standard deviation)	98.19 (± 91.679)			

Statistical analyses

No statistical analyses for this end point

Secondary: Half-Life Lambda z

End point title	Half-Life Lambda z

End point description:

End point type	Secondary

End point timeframe:

Day 8

End point values	BG00012			
Subject group type	Reporting group			
Number of subjects analysed	14			
Units: hours				
arithmetic mean (standard deviation)	0.84 (± 0.408)			

Statistical analyses

No statistical analyses for this end point

Secondary: Area Under the Concentration-Time Curve from Time 0 to Infinity (AUC0-inf)

End point title	Area Under the Concentration-Time Curve from Time 0 to Infinity (AUC0-inf)

End point description:

End point type	Secondary

End point timeframe:

Day 8

End point values	BG00012			
Subject group type	Reporting group			
Number of subjects analysed	14			
Units: h*mcg/mL				
arithmetic mean (standard deviation)	3630.52 (± 1153.768)			

Statistical analyses

No statistical analyses for this end point

Secondary: Number of Participants Who Experienced Treatment-Emergent Adverse Events (AEs) and Serious Adverse events (SAEs)

End point title	Number of Participants Who Experienced Treatment-Emergent Adverse Events (AEs) and Serious Adverse events (SAEs)

End point description:

AE: any untoward medical occurrence that does not necessarily have a causal relationship with treatment. SAE: any untoward medical occurrence that at any dose: results in death; in the view of the Investigator, places the participant at immediate risk of death (a life-threatening event); requires inpatient hospitalization or prolongation of existing hospitalization; results in persistent or significant disability/incapacity; results in a congenital anomaly/birth defect; any other medically important event that, in the opinion of the Investigator, may jeopardize the participant or may require intervention to

prevent one of the other outcomes listed in the definition above.

End point type	Secondary

End point timeframe:

Up to Week 28

End point values	BG00012			
Subject group type	Reporting group			
Number of subjects analysed	22			
Units: participants				
Any event	20			
Moderate or severe event	7			
Severe event	1			
Event related to BG00012	16			
Serious event	5			
Serious event related to BG00012	0			
Discontinued treatment due to an event	2			
Withdrew from study due to an event	2			

Statistical analyses

No statistical analyses for this end point

Adverse events

Adverse events information	
Timeframe for reporting adverse events:	
From first dose of study drug through end of treatment period (Week 24 ±7 days) plus 4 weeks follow-up.	
Adverse event reporting additional description:	
Treatment-emergent events are presented.	
Assessment type	Systematic

Dictionary used	
Dictionary name	MedDRA
Dictionary version	19

Reporting groups	
Reporting group title	BG00012
Reporting group description:	
BG00012 taken orally at a dose of 120 mg BID for the first 7 days and at a dose of 240 mg BID thereafter for 24 weeks.	

Serious adverse events	BG00012		
Total subjects affected by serious adverse events			
subjects affected / exposed	5 / 22 (22.73%)		
number of deaths (all causes)	0		
number of deaths resulting from adverse events			
Nervous system disorders			
Multiple sclerosis relapse			
subjects affected / exposed	4 / 22 (18.18%)		
occurrences causally related to treatment / all	0 / 4		
deaths causally related to treatment / all	0 / 0		
Ear and labyrinth disorders			
Vertigo			
subjects affected / exposed	1 / 22 (4.55%)		
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	BG00012		
Total subjects affected by non-serious adverse events			
subjects affected / exposed	19 / 22 (86.36%)		
Investigations			
Lymphocyte count decreased			
subjects affected / exposed	2 / 22 (9.09%)		
occurrences (all)	3		
Vascular disorders			
Flushing			
subjects affected / exposed	10 / 22 (45.45%)		
occurrences (all)	51		
Nervous system disorders			
Headache			
subjects affected / exposed	4 / 22 (18.18%)		
occurrences (all)	5		
Multiple sclerosis relapse			
subjects affected / exposed	7 / 22 (31.82%)		
occurrences (all)	8		
General disorders and administration site conditions			
Fatigue			
subjects affected / exposed	3 / 22 (13.64%)		
occurrences (all)	3		
Ear and labyrinth disorders			
Vertigo			
subjects affected / exposed	2 / 22 (9.09%)		
occurrences (all)	3		
Gastrointestinal disorders			
Abdominal pain			
subjects affected / exposed	6 / 22 (27.27%)		
occurrences (all)	6		
Abdominal pain upper			
subjects affected / exposed	4 / 22 (18.18%)		
occurrences (all)	4		
Nausea			
subjects affected / exposed	4 / 22 (18.18%)		
occurrences (all)	5		
Vomiting			

subjects affected / exposed occurrences (all)	3 / 22 (13.64%) 5		
Reproductive system and breast disorders Dysmenorrhoea subjects affected / exposed occurrences (all)	 2 / 22 (9.09%) 4		
Respiratory, thoracic and mediastinal disorders Cough subjects affected / exposed occurrences (all) Oropharyngeal pain subjects affected / exposed occurrences (all)	 3 / 22 (13.64%) 3 2 / 22 (9.09%) 2		
Skin and subcutaneous tissue disorders Alopecia subjects affected / exposed occurrences (all)	 2 / 22 (9.09%) 2		
Infections and infestations Nasopharyngitis subjects affected / exposed occurrences (all) Upper respiratory tract infection subjects affected / exposed occurrences (all) Viral upper respiratory tract infection subjects affected / exposed occurrences (all)	 2 / 22 (9.09%) 2 2 / 22 (9.09%) 2 2 / 22 (9.09%) 2		

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

Date	Amendment
04 September 2015	The primary reasons for this amendment to Protocol 109MS202 are as follows: - As a safety measure, management of lymphocyte count is revised to decrease the likelihood of potential serious infections, including multifocal leukoencephalopathy. If the lymphocyte count is <500/mm3 for more than 6 months, study treatment will be permanently discontinued rather than temporarily withheld. - Conditions under which subjects not initially meeting eligibility criteria may be rescreened are specified. - Based on toxicology data obtained after finalization of the initial protocol, the requirement that male subjects must agree to abstain from sperm donation is removed. - Clarification is provided that while human immunodeficiency virus (HIV) infection is exclusionary, HIV testing is not required at Screening. - Clarification is provided that subjects with immunity to hepatitis B virus arising from immunization (and not just subjects with immunity arising from natural infection) are eligible to participate in the study. - Clarification is provided that subjects who temporarily reduce dosage for tolerability issues should resume the standard dosage within 4 weeks after dose reduction rather than at exactly 4 weeks after dose reduction. - Clarification is provided that an MRI obtained during the Baseline period will be centrally read to ensure consistency with the brain MRI criteria. - Clarification is provided that only subjects who received at least 1 dose of BG00012 and had new or newly enlarging T2 lesions during the Baseline period will be included in the population for analysis of the primary endpoint. - Clarification is provided that subjects who become of childbearing potential during the study should receive study contraception information and may need to re-consent to the study.

Notes:

Interruptions (globally)

Were there any global interruptions to the trial? No

Limitations and caveats

None reported