



## Clinical trial results:

### A Multicenter Extension Study to Determine the Long-Term Safety and Efficacy of BG00012 in Pediatric Subjects With Relapsing-Remitting Multiple Sclerosis

#### Summary

EudraCT number	2015-003282-29
Trial protocol	DE BE CZ LV BG
Global end of trial date	24 September 2018

#### Results information

Result version number	v1 (current)
This version publication date	11 April 2019
First version publication date	11 April 2019

#### Trial information

##### Trial identification

Sponsor protocol code	109MS311
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##### Additional study identifiers

ISRCTN number	-
ClinicalTrials.gov id (NCT number)	NCT02555215
WHO universal trial number (UTN)	-

Notes:

#### Sponsors

Sponsor organisation name	Biogen
Sponsor organisation address	250 Binney Street, Cambridge, United States, 02142
Public contact	Medical Director, Overall Study Officials, Biogen, clinicaltrials@biogen.com
Scientific contact	Medical Director, Overall Study Officials, 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	27 February 2019
Is this the analysis of the primary completion data?	Yes
Primary completion date	24 September 2018
Global end of trial reached?	Yes
Global end of trial date	24 September 2018
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 evaluate the long-term safety of BG00012 in subjects who completed Study 109MS202 (NCT02410200). Secondary objectives were to evaluate the long-term efficacy of BG00012 and to describe the long-term Multiple Sclerosis (MS) outcomes in subjects who completed Study 109MS202 (NCT02410200).

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 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 informed consent form (ICF).

Background therapy: -

Evidence for comparator: -

Actual start date of recruitment	22 February 2016
Long term follow-up planned	No
Independent data monitoring committee (IDMC) involvement?	Yes

Notes:

## Population of trial subjects

### Subjects enrolled per country

Country: Number of subjects enrolled	Poland: 5
Country: Number of subjects enrolled	Bulgaria: 3
Country: Number of subjects enrolled	Kuwait: 3
Country: Number of subjects enrolled	Germany: 2
Country: Number of subjects enrolled	Lebanon: 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	Turkey: 1
Country: Number of subjects enrolled	United States: 1
Worldwide total number of subjects	20
EEA total number of subjects	13

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)	14
Adults (18-64 years)	6
From 65 to 84 years	0
85 years and over	0

## Subject disposition

### Recruitment

Recruitment details:

The number of subjects who were eligible for this study was determined by the number of subjects who had completed Study 109MS202 as per protocol.

### Pre-assignment

Screening details:

A total of 20 subjects who completed Study 109MS202 were enrolled at 12 study sites in 10 countries.

### Period 1

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

### Arms

<b>Arm title</b>	Dimethyl Fumarate
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Arm description:

Participants received 240 mg dimethyl fumarate oral capsules daily for 96 weeks.

Arm type	Experimental
Investigational medicinal product name	dimethyl fumarate
Investigational medicinal product code	
Other name	Tecfidera, BG000012
Pharmaceutical forms	Capsule
Routes of administration	Oral use

Dosage and administration details:

Participants received 240 mg dimethyl fumarate oral capsules daily for 96 weeks.

Number of subjects in period 1	Dimethyl Fumarate
Started	20
Completed	17
Not completed	3
Not Specified	1
Investigator Decision	2

## Baseline characteristics

### Reporting groups

Reporting group title	Dimethyl Fumarate
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Reporting group description:

Participants received 240 mg dimethyl fumarate oral capsules daily for 96 weeks.

Reporting group values	Dimethyl Fumarate	Total	
Number of subjects	20	20	
Age Categorical			
Units: Subjects			
<=18 years	14	14	
Between 18 and 65 years	6	6	
>=65 years	0	0	
Age Continuous			
Units: years			
arithmetic mean	16.7		
standard deviation	± 1.31	-	
Sex: Female, Male			
Units: Subjects			
Female	13	13	
Male	7	7	
Race/Ethnicity, Customized			
Units: Subjects			
Asian	1	1	
Black or African American	0	0	
White	5	5	
Not Reported Due to Confidentiality Regulations	13	13	
Other	1	1	

## End points

### End points reporting groups

Reporting group title	Dimethyl Fumarate
Reporting group description:	
Participants received 240 mg dimethyl fumarate oral capsules daily for 96 weeks.	

### Primary: 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) <sup>[1]</sup>
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End point description:

An AE is any untoward medical occurrence that does not necessarily have a causal relationship with treatment. An SAE is any untoward medical occurrence that at any dose: results in death; in the view of the Investigator, places the subject 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 subject or may require intervention to prevent one of the other outcomes listed in the definition above.

End point type	Primary
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End point timeframe:

Baseline to Week 96

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	Dimethyl Fumarate			
Subject group type	Reporting group			
Number of subjects analysed	20			
Units: Subjects				
Adverse Event	18			
Serious Adverse Event	2			

### Statistical analyses

No statistical analyses for this end point

### Primary: Number of Subjects Discontinuing Treatment Due to an Adverse Event

End point title	Number of Subjects Discontinuing Treatment Due to an Adverse Event <sup>[2]</sup>
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End point description:

An AE is any untoward medical occurrence that does not necessarily have a causal relationship with treatment.

End point type	Primary
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End point timeframe:

Baseline to Week 96

Notes:

[2] - No statistical analyses have been specified for this primary end point. It is expected there is at least one statistical analysis for each primary end point.

Justification: No statistical analyses are reported for this endpoint.

End point values	Dimethyl Fumarate			
Subject group type	Reporting group			
Number of subjects analysed	20			
Units: Subjects	0			

### Statistical analyses

No statistical analyses for this end point

### Secondary: Total Number of New or Newly Enlarging T2 Hyperintense Lesions from Week 16 to Week 24

End point title	Total Number of New or Newly Enlarging T2 Hyperintense Lesions from Week 16 to Week 24
End point description: T2 hyperintense lesions were measured by MRI brain scans.	
End point type	Secondary
End point timeframe: Week 16 to Week 24	

End point values	Dimethyl Fumarate			
Subject group type	Reporting group			
Number of subjects analysed	17			
Units: Subjects				
0 lesions	12			
1 lesion	2			
2 lesions	1			
3 lesions	1			
4 lesions	0			
5 or more lesions	1			

### Statistical analyses

No statistical analyses for this end point

### Secondary: Total Number of New or Newly Enlarging T2 Hyperintense Lesions from Week 64 to Week 72

End point title	Total Number of New or Newly Enlarging T2 Hyperintense Lesions from Week 64 to Week 72			
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End point description:	
T2 hyperintense lesions were measured by MRI brain scans.	
End point type	Secondary
End point timeframe:	
Week 64 to Week 72	

End point values	Dimethyl Fumarate			
Subject group type	Reporting group			
Number of subjects analysed	10			
Units: Subjects				
0 lesions	8			
1 lesion	1			
2 lesions	1			
3 lesions	0			
4 lesions	0			
5 or more lesions	0			

### Statistical analyses

No statistical analyses for this end point

### Secondary: Average Annualized Relapse Rate (ARR)

End point title	Average Annualized Relapse Rate (ARR)
End point description:	
Relapses were defined as new or recurrent neurologic symptoms not associated with fever or infection, lasting at least 24 hours, and accompanied by new objective neurological findings upon examination by the Investigator. New or recurrent neurologic symptoms that evolved gradually over months were considered disability progression, not an acute relapse, and were not treated with steroids. The ARR was calculated as the total number of relapses that occurred during the previous 12 months and during the 120 weeks on treatment for subjects in Study 109MS202 that continued into Study 109MS311, divided by the total number of person-years followed prior to the study and by the total number of person-years followed during the study, respectively.	
End point type	Secondary
End point timeframe:	
Baseline to Week 96	

End point values	Dimethyl Fumarate			
Subject group type	Reporting group			
Number of subjects analysed	20			
Units: Annualized relapse rate				
number (not applicable)	0.1			



## Statistical analyses

No statistical analyses for this end point

### Secondary: Percentage of Subjects Experiencing One or More Relapses

End point title	Percentage of Subjects Experiencing One or More Relapses
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End point description:

Relapses were defined as new or recurrent neurologic symptoms not associated with fever or infection, lasting at least 24 hours, and accompanied by new objective neurological findings upon examination by the Investigator. New or recurrent neurologic symptoms that evolved gradually over months were considered disability progression, not an acute relapse, and were not treated with steroids.

End point type	Secondary
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End point timeframe:

Baseline to Week 96

End point values	Dimethyl Fumarate			
Subject group type	Reporting group			
Number of subjects analysed	20			
Units: Percentage of subjects	10			

## Statistical analyses

No statistical analyses for this end point

### Secondary: Change from Baseline in the Degree of Disability

End point title	Change from Baseline in the Degree of Disability
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End point description:

The Expanded Disability Status Scale (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.

End point type	Secondary
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End point timeframe:

Baseline to Week 96

End point values	Dimethyl Fumarate			
Subject group type	Reporting group			
Number of subjects analysed	20			
Units: Score on a scale				
arithmetic mean (standard deviation)				
Baseline	1.00 (± 1.026)			
Change from Baseline at Week 12	0.15 (± 0.718)			
Change from Baseline at Week 24	0.29 (± 0.508)			
Change from Baseline at Week 36	0.27 (± 0.832)			
Change from Baseline at Week 48	0.50 (± 0.791)			
Change from Baseline at Week 72	0.71 (± 1.010)			
Change from Baseline at Week 96	0.21 (± 0.964)			

### Statistical analyses

No statistical analyses for this end point

### Secondary: Number of Subjects Experiencing Disability Progression

End point title	Number of Subjects Experiencing Disability Progression
End point description:	
Measured by at least a 1.0-point increase on the EDSS from baseline EDSS ≥1.0 that is sustained for 24 weeks, or at least a 1.5-point increase on the EDSS from baseline EDSS = 0 that is sustained for 24 weeks.	
End point type	Secondary
End point timeframe:	
Baseline to Week 96	

End point values	Dimethyl Fumarate			
Subject group type	Reporting group			
Number of subjects analysed	20			
Units: Subjects	3			

### Statistical analyses

No statistical analyses for this end point

## Adverse events

### Adverse events information

Timeframe for reporting adverse events:

**\*\*Timeframe description needed\*\***

Assessment type	Systematic
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### Dictionary used

Dictionary name	MedDRA
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Dictionary version	20.1
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### Reporting groups

Reporting group title	BG00012
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Reporting group description: -

Serious adverse events	BG00012		
Total subjects affected by serious adverse events			
subjects affected / exposed	2 / 20 (10.00%)		
number of deaths (all causes)	0		
number of deaths resulting from adverse events			
Nervous system disorders			
Multiple sclerosis relapse			
subjects affected / exposed	1 / 20 (5.00%)		
occurrences causally related to treatment / all	0 / 2		
deaths causally related to treatment / all	0 / 0		
Gastrointestinal disorders			
Abdominal pain			
subjects affected / exposed	1 / 20 (5.00%)		
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	18 / 20 (90.00%)		
Vascular disorders			
Flushing			
subjects affected / exposed	5 / 20 (25.00%)		
occurrences (all)	21		

General disorders and administration site conditions			
Fatigue			
subjects affected / exposed	2 / 20 (10.00%)		
occurrences (all)	2		
Influenza like illness			
subjects affected / exposed	1 / 20 (5.00%)		
occurrences (all)	1		
Immune system disorders			
Dust allergy			
subjects affected / exposed	1 / 20 (5.00%)		
occurrences (all)	1		
Seasonal allergy			
subjects affected / exposed	1 / 20 (5.00%)		
occurrences (all)	1		
Smoke sensitivity			
subjects affected / exposed	1 / 20 (5.00%)		
occurrences (all)	1		
Reproductive system and breast disorders			
Dysmenorrhoea			
subjects affected / exposed	3 / 20 (15.00%)		
occurrences (all)	7		
Menstruation irregular			
subjects affected / exposed	1 / 20 (5.00%)		
occurrences (all)	1		
Ovarian cyst			
subjects affected / exposed	1 / 20 (5.00%)		
occurrences (all)	1		
Uterine inflammation			
subjects affected / exposed	1 / 20 (5.00%)		
occurrences (all)	1		
Respiratory, thoracic and mediastinal disorders			
Cough			
subjects affected / exposed	3 / 20 (15.00%)		
occurrences (all)	3		
Hyperventilation			

subjects affected / exposed	1 / 20 (5.00%)		
occurrences (all)	1		
Oropharyngeal pain			
subjects affected / exposed	2 / 20 (10.00%)		
occurrences (all)	7		
Paranasal cyst			
subjects affected / exposed	1 / 20 (5.00%)		
occurrences (all)	1		
Productive cough			
subjects affected / exposed	1 / 20 (5.00%)		
occurrences (all)	1		
Rhinorrhoea			
subjects affected / exposed	2 / 20 (10.00%)		
occurrences (all)	3		
Upper-airway cough syndrome			
subjects affected / exposed	1 / 20 (5.00%)		
occurrences (all)	1		
Psychiatric disorders			
Irritability			
subjects affected / exposed	1 / 20 (5.00%)		
occurrences (all)	1		
Somatic symptom disorder			
subjects affected / exposed	1 / 20 (5.00%)		
occurrences (all)	1		
Injury, poisoning and procedural complications			
Burns second degree			
subjects affected / exposed	1 / 20 (5.00%)		
occurrences (all)	1		
Fall			
subjects affected / exposed	1 / 20 (5.00%)		
occurrences (all)	1		
Ligament sprain			
subjects affected / exposed	1 / 20 (5.00%)		
occurrences (all)	1		
Limb injury			

subjects affected / exposed occurrences (all)	1 / 20 (5.00%) 1		
Cardiac disorders Wolff-parkinson-white syndrome subjects affected / exposed occurrences (all)	1 / 20 (5.00%) 1		
Nervous system disorders Demyelination subjects affected / exposed occurrences (all)  Headache subjects affected / exposed occurrences (all)  Hypoaesthesia subjects affected / exposed occurrences (all)  Migraine subjects affected / exposed occurrences (all)  Multiple sclerosis relapse subjects affected / exposed occurrences (all)  Paraesthesia subjects affected / exposed occurrences (all)  Presyncope subjects affected / exposed occurrences (all)  Syncope subjects affected / exposed occurrences (all)	1 / 20 (5.00%) 1  3 / 20 (15.00%) 12  2 / 20 (10.00%) 2  1 / 20 (5.00%) 1  4 / 20 (20.00%) 5  1 / 20 (5.00%) 2  1 / 20 (5.00%) 1  1 / 20 (5.00%) 1		
Ear and labyrinth disorders Vertigo subjects affected / exposed occurrences (all)	2 / 20 (10.00%) 2		
Eye disorders			

Eye irritation			
subjects affected / exposed	1 / 20 (5.00%)		
occurrences (all)	1		
Vision blurred			
subjects affected / exposed	1 / 20 (5.00%)		
occurrences (all)	1		
Gastrointestinal disorders			
Abdominal discomfort			
subjects affected / exposed	1 / 20 (5.00%)		
occurrences (all)	2		
Abdominal pain			
subjects affected / exposed	3 / 20 (15.00%)		
occurrences (all)	6		
Abdominal pain upper			
subjects affected / exposed	2 / 20 (10.00%)		
occurrences (all)	2		
Diarrhoea			
subjects affected / exposed	1 / 20 (5.00%)		
occurrences (all)	1		
Dry mouth			
subjects affected / exposed	1 / 20 (5.00%)		
occurrences (all)	1		
Mouth ulceration			
subjects affected / exposed	1 / 20 (5.00%)		
occurrences (all)	1		
Nausea			
subjects affected / exposed	1 / 20 (5.00%)		
occurrences (all)	4		
Vomiting			
subjects affected / exposed	1 / 20 (5.00%)		
occurrences (all)	1		
Skin and subcutaneous tissue disorders			
Acne			
subjects affected / exposed	2 / 20 (10.00%)		
occurrences (all)	2		
Alopecia			

subjects affected / exposed	1 / 20 (5.00%)		
occurrences (all)	1		
Alopecia areata			
subjects affected / exposed	1 / 20 (5.00%)		
occurrences (all)	1		
Dermatitis allergic			
subjects affected / exposed	1 / 20 (5.00%)		
occurrences (all)	1		
Dry skin			
subjects affected / exposed	1 / 20 (5.00%)		
occurrences (all)	1		
Renal and urinary disorders			
Dysuria			
subjects affected / exposed	1 / 20 (5.00%)		
occurrences (all)	3		
Hypertonic bladder			
subjects affected / exposed	1 / 20 (5.00%)		
occurrences (all)	1		
Micturition urgency			
subjects affected / exposed	1 / 20 (5.00%)		
occurrences (all)	1		
Urinary retention			
subjects affected / exposed	1 / 20 (5.00%)		
occurrences (all)	1		
Musculoskeletal and connective tissue disorders			
Arthralgia			
subjects affected / exposed	1 / 20 (5.00%)		
occurrences (all)	1		
Back pain			
subjects affected / exposed	1 / 20 (5.00%)		
occurrences (all)	1		
Limb discomfort			
subjects affected / exposed	1 / 20 (5.00%)		
occurrences (all)	1		
Muscle spasms			



subjects affected / exposed	2 / 20 (10.00%)		
occurrences (all)	2		
Musculoskeletal pain			
subjects affected / exposed	1 / 20 (5.00%)		
occurrences (all)	1		
Infections and infestations			
Cystitis			
subjects affected / exposed	1 / 20 (5.00%)		
occurrences (all)	1		
Gastroenteritis			
subjects affected / exposed	2 / 20 (10.00%)		
occurrences (all)	2		
Herpes zoster			
subjects affected / exposed	1 / 20 (5.00%)		
occurrences (all)	1		
Mastoiditis			
subjects affected / exposed	1 / 20 (5.00%)		
occurrences (all)	1		
Nasopharyngitis			
subjects affected / exposed	2 / 20 (10.00%)		
occurrences (all)	2		
Pharyngitis			
subjects affected / exposed	2 / 20 (10.00%)		
occurrences (all)	3		
Respiratory tract infection viral			
subjects affected / exposed	1 / 20 (5.00%)		
occurrences (all)	1		
Root canal infection			
subjects affected / exposed	1 / 20 (5.00%)		
occurrences (all)	1		
Salpingo-oophoritis			
subjects affected / exposed	1 / 20 (5.00%)		
occurrences (all)	1		
Sinusitis			
subjects affected / exposed	1 / 20 (5.00%)		
occurrences (all)	1		

Tonsillitis			
subjects affected / exposed	1 / 20 (5.00%)		
occurrences (all)	2		
Upper respiratory tract infection			
subjects affected / exposed	3 / 20 (15.00%)		
occurrences (all)	3		
Viral upper respiratory tract infection			
subjects affected / exposed	3 / 20 (15.00%)		
occurrences (all)	6		

## More information

### Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

Date	Amendment
08 January 2016	Removed the paragraph on resumption of study treatment for subjects with <LLN; Removed the section on central assessment of MRI scans.
24 April 2018	There were no major changes to the protocol.

Notes:

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### Interruptions (globally)

Were there any global interruptions to the trial? No

### Limitations and caveats

None reported