Clinical trial results:
A Multicenter, Randomized, Double-Blind, Placebo-Controlled Study of the Efficacy and Safety of BG00012 in Delaying Disability Progression in Subjects With Secondary Progressive Multiple Sclerosis

Summary

EudraCT number	2014-003021-18
Trial protocol	SE IT SK NL CZ BE DE PL AT DK FI
Global end of trial date	05 January 2016

Results information

Result version number	v1 (current)
This version publication date	28 December 2016
First version publication date	28 December 2016

Trial information

Trial identification

Sponsor protocol code	109MS308

Additional study identifiers

ISRCTN number	-
ClinicalTrials.gov id (NCT number)	NCT02430532
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?	No

Notes:

Results analysis stage

Analysis stage	Final
Date of interim/final analysis	05 January 2016
Is this the analysis of the primary completion data?	No

Global end of trial reached?	Yes
Global end of trial date	05 January 2016
Was the trial ended prematurely?	Yes

Notes:

General information about the trial

Main objective of the trial:

The primary objective of the study is to investigate whether treatment with BG00012 (dimethyl fumarate) compared with placebo slows the accumulation of disability not related to relapses in participants with secondary progressive multiple sclerosis (SPMS). The secondary objective of the study is to assess the effect of BG00012 compared with placebo on patient-reported outcomes, brain atrophy, and cognitive function.

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	14 May 2015
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: 44
Country: Number of subjects enrolled	United States: 9
Country: Number of subjects enrolled	Czech Republic: 2
Country: Number of subjects enrolled	Belgium: 1
Country: Number of subjects enrolled	Netherlands: 1
Country: Number of subjects enrolled	Slovakia: 1
Worldwide total number of subjects	58
EEA total number of subjects	49

Notes:

Subjects enrolled per age group

In utero	0
Preterm newborn - gestational age < 37	0

wk	
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)	58
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 study entry.

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

Blinding implementation details:

Protocol-specified measures were put in place to maintain the study blind. Sites were selected based on their ability to comply with these requirements.

Arms

Are arms mutually exclusive?	Yes
Arm title	Placebo

Arm description:

BG00012 120 mg capsule orally once a day (QD) supplemented with matching placebo capsules for the first 4 weeks of treatment. Matched placebo capsules only thereafter for up to 108 weeks.

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

Dosage and administration details:

Subjects in the Placebo Group received BG00012 120 mg QD randomly in the morning or evening for the first 4 weeks of treatment as an additional blinding measure, and matched placebo only thereafter.

Investigational medicinal product name	Placebo
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Capsule, hard
Routes of administration	Oral use

Dosage and administration details:

Subjects in the Placebo Group received 1 BG00012 120 mg capsule+1 matching placebo capsule in the morning AND 2 matching placebo capsules in the evening; or, 2 matching placebo capsules in the morning AND 1 BG00012 120 mg capsule+1 matching placebo capsule in the evening for Weeks 1-4. Subjects received 2 matching placebo capsules BID thereafter.

Arm title	Tecfidera 240 mg BID

Arm description:

BG00012 120 mg (1 BG00012 120 mg capsule + 1 matching placebo capsule) orally twice daily (BID) for 1 week, followed by BG00012 240 mg orally BID thereafter.

Arm type	Experimental

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

Dosage and administration details:

Subjects in the BG00012 Treatment Group received BG00012 120 mg BID for 1 week, and an increased dose of BG00012 240 mg BID beginning on Day 8.

Investigational medicinal product name	Placebo
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Capsule, hard
Routes of administration	Oral use

Dosage and administration details:

Subjects in the Tecfidera 240 mg Group received 1 matching placebo capsule BID during Week 1 only.

Number of subjects in period 1	Placebo	Tecfidera 240 mg BID
Started	30	28
Completed	0	0
Not completed	30	28
Sponsor Decision to Stop Study Early	30	25
Adverse event, non-fatal	-	1
Consent Withdrawn	-	2

Baseline characteristics

Reporting groups	
Reporting group title	Placebo
Reporting group description:	
BG00012 120 mg capsule orally once a day (QD) supplemented with matching placebo capsules for the first 4 weeks of treatment. Matched placebo capsules only thereafter for up to 108 weeks.	
Reporting group title	Tecfidera 240 mg BID
Reporting group description:	
BG00012 120 mg (1 BG00012 120 mg capsule + 1 matching placebo capsule) orally twice daily (BID) for 1 week, followed by BG00012 240 mg orally BID thereafter.	

Reporting group values	Placebo	Tecfidera 240 mg BID	Total
Number of subjects	30	28	58
Age Categorical Units: Subjects			
< 20 years	0	0	0
20 to 29 years	0	0	0
30 to 39 years	1	4	5
40 to 49 years	10	8	18
>= 50 years	19	16	35
Age Continuous Units: years			
arithmetic mean	50.7	49.6	
standard deviation	± 6.67	± 8.05	-
Gender, Male/Female Units: Subjects			
Female	19	17	36
Male	11	11	22

End points

End points reporting groups

Reporting group title	Placebo
Reporting group description:	
BG00012 120 mg capsule orally once a day (QD) supplemented with matching placebo capsules for the first 4 weeks of treatment. Matched placebo capsules only thereafter for up to 108 weeks.	
Reporting group title	Tecfidera 240 mg BID
Reporting group description:	
BG00012 120 mg (1 BG00012 120 mg capsule + 1 matching placebo capsule) orally twice daily (BID) for 1 week, followed by BG00012 240 mg orally BID thereafter.	

Primary: Time to Disability Progression Independent of Relapse

End point title	Time to Disability Progression Independent of Relapse[1]
End point description:	
Time to onset of confirmed progression of disability is defined as 1 or more of the following criteria, confirmed at ≥ 6 months after start of treatment and at Week 108 using 1 or more of the following assessments: Expanded Disability Status Scale (EDSS) score increased from Baseline of ≥ 1 point if baseline EDSS ≤ 5.5, or ≥ 0.5 point if Baseline EDSS ≥ 6.0; Timed 25-Foot Walk (T25FW) ≥ 20% increase from Baseline in the time taken for the 25-foot walk; worsening on the 9-Hole Peg Test (9HPT; ≥ 20% increase from Baseline in the time taken for the 9HPT, confirmed in the same hand). The EDSS measures disability status on a scale ranging from 0 to 10, with higher scores indicating more disability. The T25FW is a quantitative mobility and leg function performance test where the participant is timed while walking for 25 feet. The 9HPT is a quantitative test of upper extremity function that measures the time it takes to place 9 pegs into 9 holes and then remove the pegs.	
End point type	Primary
End point timeframe:	
Up to 108 weeks	

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: The endpoint was not analyzed due to early study termination.

End point values	Placebo	Tecfidera 240 mg BID		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	0[2]	0[3]		
Units: days				
arithmetic mean (standard deviation)	()	()		

Notes:

[2] - These data were not analyzed due to early study termination.

[3] - These data were not analyzed due to early study termination.

Statistical analyses

No statistical analyses for this end point

Secondary: Change from Baseline to 2 Years on the 12-Item Multiple Sclerosis Walking Scale (MSWS-12)

End point title	Change from Baseline to 2 Years on the 12-Item Multiple Sclerosis Walking Scale (MSWS-12)
End point description:	
MSWS-12 is a participant self-assessment of walking limitations due to multiple sclerosis (MS) during	

the past 2 weeks. It contains 12 items that measure the impact of MS on walking. Items are summed to generate a total score and transformed to a scale with a range of 0 to 100, where high scores indicate greater negative impact on walking.

End point type	Secondary

End point timeframe:

Baseline, 2 years

End point values	Placebo	Tecfidera 240 mg BID		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	0[4]	0[5]		
Units: units on a scale				
arithmetic mean (standard deviation)	()	()		

Notes:

[4] - These data were not analyzed due to early study termination.

[5] - These data were not analyzed due to early study termination.

Statistical analyses

No statistical analyses for this end point

Secondary: Change from Baseline to Week 108 in ABILHAND Questionnaire Score

End point title	Change from Baseline to Week 108 in ABILHAND Questionnaire Score

End point description:

The ABILHAND Questionnaire measures the participant's perceived difficulty in performing everyday manual activities in the last 3 months. Participants fill in the 56-item questionnaire by estimating their own difficulty or ease in performing each of the 56 activities. Items are summed to generate a total score and transformed to a scale with a range of 0 to 100, where high scores indicate greater impact on manual ability.

End point type	Secondary

End point timeframe:

Baseline, Week 108

End point values	Placebo	Tecfidera 240 mg BID		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	0[6]	0[7]		
Units: units on a scale				
arithmetic mean (standard deviation)	()	()		

Notes:

[6] - These data were not analyzed due to early study termination.

[7] - These data were not analyzed due to early study termination.

Statistical analyses

No statistical analyses for this end point

Secondary: Percentage Change from Baseline to Week 108 in Whole Brain Volume

End point title	Percentage Change from Baseline to Week 108 in Whole Brain Volume

End point description:

Whole brain volume is measured by magnetic resonance imaging (MRI).

End point type	Secondary

End point timeframe:

Baseline, Week 108

End point values	Placebo	Tecfidera 240 mg BID		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	0[8]	0[9]		
Units: percentage change				

Notes:

[8] - These data were not analyzed due to early study termination.

[9] - These data were not analyzed due to early study termination.

Statistical analyses

No statistical analyses for this end point

Secondary: Change from Baseline to Week 108 in Cognitive Function as Measured by the Symbol Digit Modalities Test (SDMT)

End point title	Change from Baseline to Week 108 in Cognitive Function as Measured by the Symbol Digit Modalities Test (SDMT)

End point description:

The SDMT measures the time to pair abstract geometric symbols with specific numbers. The score is the number of correctly coded items from 0-110 in 90 seconds. A higher score indicates a better outcome.

End point type	Secondary

End point timeframe:

Baseline, Week 108

End point values	Placebo	Tecfidera 240 mg BID		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	0[10]	0[11]		
Units: units on a scale				
arithmetic mean (standard deviation)	()	()		

Notes:

[10] - These data were not analyzed due to early study termination.

[11] - These data were not analyzed due to early study termination.

Statistical analyses

No statistical analyses for this end point

Adverse events

Adverse events information

Timeframe for reporting adverse events:

Up to approximately 24 weeks (overall mean time on study of 14.34, with an overall mean time on study treatment of 9.58 weeks).

Adverse event reporting additional description:

Data summaries of adverse events are descriptive in nature and the comparison between treatment groups might not be appropriate due to the small number of participants and limited study follow-up duration.

Assessment type	Systematic

Dictionary used

Dictionary name	MedDRA
Dictionary version	15.0

Reporting groups

Reporting group title	Tecfidera 240 mg BID

Reporting group description:

BG00012 120 mg orally twice daily (BID) for 1 week, followed by BG00012 240 mg orally BID beginning on Day 8 for up to 108 weeks.

Reporting group title	Placebo

Reporting group description:

BG00012 120 mg capsule orally once a day (QD) supplemented with matching placebo capsules for the first 4 weeks of treatment. Matched placebo capsules only thereafter for up to 108 weeks.

Serious adverse events	Tecfidera 240 mg BID	Placebo	
Total subjects affected by serious adverse events			
subjects affected / exposed	5 / 28 (17.86%)	0 / 30 (0.00%)	
number of deaths (all causes)	0	0	
number of deaths resulting from adverse events			
Injury, poisoning and procedural complications			
Fall			
subjects affected / exposed	1 / 28 (3.57%)	0 / 30 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Femur fracture			
subjects affected / exposed	1 / 28 (3.57%)	0 / 30 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Nervous system disorders			
Multiple sclerosis relapse			

subjects affected / exposed	1 / 28 (3.57%)	0 / 30 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Trigeminal neuralgia			
subjects affected / exposed	1 / 28 (3.57%)	0 / 30 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Gastrointestinal disorders			
Enteritis			
subjects affected / exposed	1 / 28 (3.57%)	0 / 30 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Respiratory, thoracic and mediastinal disorders			
Dyspnoea			
subjects affected / exposed	1 / 28 (3.57%)	0 / 30 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Renal and urinary disorders			
Calculus ureteric			
subjects affected / exposed	1 / 28 (3.57%)	0 / 30 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Nephrolithiasis			
subjects affected / exposed	1 / 28 (3.57%)	0 / 30 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Renal colic			
subjects affected / exposed	1 / 28 (3.57%)	0 / 30 (0.00%)	
occurrences causally related to treatment / all	0 / 1	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	Tecfidera 240 mg BID	Placebo	
Total subjects affected by non-serious adverse events			
subjects affected / exposed	9 / 28 (32.14%)	9 / 30 (30.00%)	
Vascular disorders			
Flushing			
subjects affected / exposed	5 / 28 (17.86%)	5 / 30 (16.67%)	
occurrences (all)	5	5	
Nervous system disorders			
Multiple sclerosis relapse			
subjects affected / exposed	2 / 28 (7.14%)	0 / 30 (0.00%)	
occurrences (all)	2	0	
Gastrointestinal disorders			
Diarrhoea			
subjects affected / exposed	2 / 28 (7.14%)	0 / 30 (0.00%)	
occurrences (all)	2	0	
Nausea			
subjects affected / exposed	2 / 28 (7.14%)	0 / 30 (0.00%)	
occurrences (all)	3	0	
Vomiting			
subjects affected / exposed	2 / 28 (7.14%)	0 / 30 (0.00%)	
occurrences (all)	2	0	
Infections and infestations			
Upper respiratory tract infection			
subjects affected / exposed	0 / 28 (0.00%)	2 / 30 (6.67%)	
occurrences (all)	0	2	
Urinary tract infection			
subjects affected / exposed	2 / 28 (7.14%)	3 / 30 (10.00%)	
occurrences (all)	2	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? No

Limitations and caveats

Limitations of the trial such as small numbers of subjects analysed or technical problems leading to unreliable data.

The study was terminated early by the sponsor for business reasons. Efficacy, patient-reported outcomes, and pharmacodynamic data were not analyzed.

Notes: