Clinical trial results:
A Multicenter, Open-Label Study Evaluating the Effectiveness of Oral Tecfidera® (Dimethyl Fumarate) on Multiple Sclerosis Disease Activity and Patient-Reported Outcomes in Subjects with Relapsing-Remitting Multiple Sclerosis in the Real-World Setting (PROTEC)

Summary

EudraCT number	2013-001656-35
Trial protocol	AT HU BE PT IT CZ SK ES SI FR
Global end of trial date	09 January 2020

Results information

Result version number	v1 (current)
This version publication date	24 January 2021
First version publication date	24 January 2021

Trial information

Trial identification

Sponsor protocol code	109MS408

Additional study identifiers

ISRCTN number	-
ClinicalTrials.gov id (NCT number)	NCT01930708
WHO universal trial number (UTN)	-

Notes:

Sponsors

Sponsor organisation name	Biogen MA Inc.
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	09 January 2020
Is this the analysis of the primary completion data?	No

Global end of trial reached?	Yes
Global end of trial date	09 January 2020
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 estimate the annualised relapse rate (ARR) in subjects with relapsing-remitting multiple sclerosis (RRMS) who were treated with dimethyl fumarate (DMF) over a 12-month period.

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	31 October 2013
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	Austria: 114
Country: Number of subjects enrolled	Belgium: 47
Country: Number of subjects enrolled	Canada: 109
Country: Number of subjects enrolled	Czechia: 86
Country: Number of subjects enrolled	France: 199
Country: Number of subjects enrolled	Hungary: 54
Country: Number of subjects enrolled	Italy: 208
Country: Number of subjects enrolled	Portugal: 134
Country: Number of subjects enrolled	Slovakia: 21
Country: Number of subjects enrolled	Slovenia: 21
Country: Number of subjects enrolled	Spain: 121
Worldwide total number of subjects	1114
EEA total number of subjects	1005

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)	1107
From 65 to 84 years	7
85 years and over	0

Subject disposition

Recruitment

Recruitment details:

Subjects were enrolled at 93 investigational sites in Australia, Austria, Belgium, Czech Republic, France, Hungary, Italy, Portugal, Slovakia, Slovenia, Spain, and Canada from 31 October 2013 to 20 March 2015.

Pre-assignment

Screening details:

A total of 1114 subjects with Relapsing-Remitting Multiple Sclerosis (RRMS) were enrolled in this study. Of which, 1106 subjects received at least 1 dose of study drug (Dimethyl Fumarate {DMF}). Subjects started were subjects who were enrolled in study. Subjects treated were subjects who received at least 1 dose of DMF.

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 240 mg BID

Arm description:

Subjects received BG00012 capsules, 120 milligrams (mg), orally, twice daily (BID) on Days 1 through 7 followed by BG00012 capsules, 240 mg, orally, BID, thereafter for up to 12 months.

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:

BG00012 was administered as capsules, 120 mg, orally, BID on Day 1 through 7 followed by BG00012 capsules, 240 mg, orally, BID thereafter up to 12 months.

Number of subjects in period 1	BG00012 240 mg BID
Started	1114
Treated	1106
Completed	925
Not completed	189
Adverse Event	129
Reason Not Specified	19
Investigator Decision	7
Lost to follow-up	8
Consent Withdrawn	18

Baseline characteristics

Reporting groups	
Reporting group title	Overall Study

Reporting group description:

Subjects received BG00012 capsules, 120 milligrams (mg), orally, twice daily (BID) on Days 1 through 7 followed by BG00012 capsules, 240 mg, orally, BID, thereafter up to 12 months.

Reporting group values	Overall Study	Total	
Number of subjects	1114	1114	
Age Categorical Units: subjects			
Age Continuous Units: years			
arithmetic mean	38.81		
standard deviation	± 10.02	-	
Gender Categorical Units: subjects			
Female	805	805	
Male	309	309	
Race Units: Subjects			
Not reported due to confidentiality regulations	1008	1008	
White	95	95	
Asian	1	1	
Black or African American	2	2	
Other	8	8	
Ethnicity Units: Subjects			
Hispanic or Latino	3	3	
Not Hispanic or Latino	106	106	
Not Specified	1005	1005	

End points

End points reporting groups

Reporting group title	BG00012 240 mg BID

Reporting group description:

Subjects received BG00012 capsules, 120 milligrams (mg), orally, twice daily (BID) on Days 1 through 7 followed by BG00012 capsules, 240 mg, orally, BID, thereafter for up to 12 months.

Primary: Annualised Relapse Rate (ARR) at Month 12

End point title	Annualised Relapse Rate (ARR) at Month 12[1]

End point description:

A multiple sclerosis (MS) relapse was defined as new or recurrent neurologic symptoms not associated with fever or infection, lasting for at least 24 hours, and accompanied by new objective neurologic findings upon examination by the investigator, and followed by a period of 30 days of stability or improvement. The annualised relapse rate for a period was calculated as the total number of relapses that occurred during the period for all subjects, divided by the total number of subject-years followed in that period. Relapses and follow-up times that occurred after treatment discontinuation were excluded from the calculations. Primary analysis population included all subjects who were eligible, signed informed consent, enrolled, and took at least 1 dose of DMF.

End point type	Primary

End point timeframe:

Month 12

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 statistical analysis is not added to the primary endpoint as the study is single arm study and per EudraCT format only statistical analysis between two comparison arms can be added to the database.

End point values	BG00012 240 mg BID			
Subject group type	Reporting group			
Number of subjects analysed	1105			
Units: relapses per year				
number (confidence interval 95%)	0.161 (0.136 to 0.191)			

Statistical analyses

No statistical analyses for this end point

Secondary: Change from Baseline to Month 12 in Multiple Sclerosis Impact Scale (MSIS-29) Score

End point title	Change from Baseline to Month 12 in Multiple Sclerosis Impact Scale (MSIS-29) Score

End point description:

MSIS-29 was a validated, 29-item, MS-specific HRQoL scale which included 2 sub-scales that measured the physical and psychological impact of MS on the subject's day-to-day life: the 20-item physical impact scale and the 9-item psychological impact scale. For each item, the subject was asked to circle the number that best described his or her situation. The numbers for each item ranged from 1 (not at all) to 5 (extremely). The total score range ranged from 0-100, where lower scores indicated a better outcome. Primary analysis population included all subjects who were eligible, signed informed consent,

enrolled, and took at least 1 dose of DMF. A negative number of change from baseline (CFB) value indicates an improvement in MSIS-29. Here, 'n' signifies the number of subjects analysed at specified time point.

End point type	Secondary

End point timeframe:

Baseline, Month 12

End point values	BG00012 240 mg BID			
Subject group type	Reporting group			
Number of subjects analysed	1105			
Units: score on scale				
arithmetic mean (standard deviation)				
Physical Impact Score:Baseline (n=1069)	22.78 (± 21.520)			
Physical Impact Score:CFB at Month 12 (n= 868)	-3.04 (± 14.135)			
Psychological Impact Score:Baseline (n=1064)	34.77 (± 23.666)			
Psychological Impact Score:CFB at Month 12 (n=860)	-8.01 (± 18.582)			

Statistical analyses

No statistical analyses for this end point

Secondary: Change from Baseline to Month 12 in Modified Fatigue Impact Scale-5 Item (MFIS-5) Score

End point title	Change from Baseline to Month 12 in Modified Fatigue Impact Scale-5 Item (MFIS-5) Score

End point description:

MFIS-5 scale consisted of 5 statements that described how fatigue affected a person. It assessed the effects of fatigue on physical, cognitive, and psychosocial functioning. For each statement, the subject was asked to circle the number that best indicated how often fatigue had affected him or her during the previous 4 weeks. The numbers for each question ranged from 0 (never) to 4 (almost always). The total scores ranged from 0 to 20. A lower MFIS-5 score indicated a lower impact of fatigue and therefore a better outcome. Primary analysis population included all subjects who were eligible, signed informed consent, enrolled, and took at least 1 dose of DMF. A negative number of CFB value indicates an improvement in MFIS-5. Here, 'n' signifies the number of subjects analysed at specified time point.

End point type	Secondary

End point timeframe:

Baseline, Month 12

End point values	BG00012 240 mg BID			
Subject group type	Reporting group			
Number of subjects analysed	1105			
Units: score on scale				
arithmetic mean (standard deviation)				
Baseline (n= 1074)	8.17 (± 4.962)			
CFB at Month 12 (n= 867)	-1.66 (± 3.813)			

Statistical analyses

No statistical analyses for this end point

Secondary: Change from Baseline to Month 12 in Treatment Satisfaction Questionnaire for Medication (TSQM) Score

End point title	Change from Baseline to Month 12 in Treatment Satisfaction Questionnaire for Medication (TSQM) Score

End point description:

TSQM was a validated, 14-item questionnaire that measured a subject's level of satisfaction/dissatisfaction with medication. It consisted of four scales: effectiveness scale (questions 1 to 3), side effects scale (questions 4 to 8), convenience scale (questions 9 to 11) and global satisfaction scale (questions 12 to 14). The scores were computed by adding items for each domain. The lowest possible score was subtracted from this composite score and divided by the greatest possible score minus the lowest possible score. This provided a transformed score between 0 and 1 that was then multiplied by 100. The total score ranged from 0 to 100, where a higher TSQM score indicated greater satisfaction with medication. Primary analysis population included all subjects who were eligible, signed informed consent, enrolled, and took at least 1 dose of DMF. A positive number of CFB value indicates an improvement in TSQM. Here, 'n' signifies the number of subjects analysed at specified time point.

End point type	Secondary

End point timeframe:

Baseline, Month 12

End point values	BG00012 240 mg BID			
Subject group type	Reporting group			
Number of subjects analysed	1105			
Units: score on scale				
arithmetic mean (standard deviation)				
Effectiveness Summary Score (SS): Baseline (n=596)	54.29 (± 21.707)			
Effectiveness SS: CFB at Month 12 (n= 492)	14.35 (± 29.490)			
Side Effects SS: Baseline (n= 611)	60.09 (± 30.559)			
Side Effects SS: CFB at Month 12 (n= 500)	25.36 (± 31.370)			
Convenience SS: Baseline (n= 612)	52.41 (± 21.202)			
Convenience SS: CFB at Month 12 (n= 505)	33.43 (± 25.651)			
Global SS: Baseline (n= 616)	51.39 (± 22.475)			

Global SS: CFB at Month 12 (n= 511)	21.82 (± 26.894)			

Statistical analyses

No statistical analyses for this end point

Secondary: Change from Baseline to Month 12 in EuroQol 5-Dimension 5-Level (EQ-5D-5L) Index Score

End point title	Change from Baseline to Month 12 in EuroQol 5-Dimension 5-Level (EQ-5D-5L) Index Score

End point description:

EQ-5D-5L include 2 components, EuroQol-5D (EQ-5D) descriptive system and EuroQol visual analogue scale (EQ VAS). EQ-5D descriptive system provided a profile of the subject's health state in 5 dimensions (mobility, selfcare, usual activities, pain/discomfort, and anxiety/depression). For each dimension, the subject was instructed to indicate whether they had "no problems" (level 1), "slight problems" (level 2), "moderate problems" (level 3), "severe problems (level 4), or "extreme problems/inability" (level 5) on that day. EQ-5D-5L scores were derived based on value sets for England. EQ-5D descriptive system score had a possible range from -0.109 to 1.00, with higher scores indicating a better outcome. Primary analysis population included all subjects who were eligible, signed informed consent, enrolled, and took at least 1 dose of DMF. Positive number of CFB value indicates an improvement in EQ-5D descriptive system. 'n' signifies number of subjects analysed at specified time point.

End point type	Secondary

End point timeframe:

Baseline, Month 12

End point values	BG00012 240 mg BID			
Subject group type	Reporting group			
Number of subjects analysed	1105			
Units: score on scale				
arithmetic mean (standard deviation)				
EQ-5D Index Score: Baseline (n= 1068)	0.83 (± 0.160)			
EQ-5D Index Score: CFB at Month 12 (n= 792)	0.02 (± 0.127)			

Statistical analyses

No statistical analyses for this end point

Secondary: Change from Baseline to Month 12 in EuroQol Visual Analogue Scale (EQ VAS) Score

End point title	Change from Baseline to Month 12 in EuroQol Visual Analogue Scale (EQ VAS) Score

End point description:

EQ-5D-5L included 2 components, the EuroQol-5D (EQ-5D) descriptive system and the EuroQol visual

analogue scale (EQ VAS). For the EQ VAS, the subject was instructed to mark an “x” on a vertical scale at the point that best described his or her own health on that day, where 0 represented the “worst health” he or she could imagine and 100 the “best health” he or she could imagine. Higher scores indicated a better outcome. Primary analysis population included all subjects who were eligible, signed informed consent, enrolled, and took at least 1 dose of DMF. Positive number of CFB value indicates an improvement in EQ-5D VAS. Here, 'n' signifies the number of subjects analysed at specified time point.

End point type	Secondary

End point timeframe:

Baseline, Month 12

End point values	BG00012 240 mg BID			
Subject group type	Reporting group			
Number of subjects analysed	1105			
Units: score on a scale				
arithmetic mean (standard deviation)				
EQ-5D VAS Score: Baseline (n= 1076)	74.05 (± 18.669)			
EQ-5D VAS Score: CFB at Month 12 (n= 803)	3.69 (± 15.859)			

Statistical analyses

No statistical analyses for this end point

Secondary: Change from Baseline to Month 12 in Patient-Reported Indices for Multiple Sclerosis-Activity Limitations (PRIMUS-Activity Limitations) Score

End point title	Change from Baseline to Month 12 in Patient-Reported Indices for Multiple Sclerosis-Activity Limitations (PRIMUS-Activity Limitations) Score

End point description:

This 15-item component of the PRIMUS assessed a subject's ability to carry out various activities of daily living during the previous week without the use of aids (e.g., cane, walker, or wheelchair) or assistance. For each item, the subject was asked whether he or she could perform the activity without difficulty (scoring 0) or with difficulty (scoring 1), or was unable to perform the activity (scoring 2). The possible total scores ranged from 0 to 30. Higher scores indicated a worse outcome. Primary analysis population included all subjects who were eligible, signed informed consent, enrolled, and took at least 1 dose of DMF. A negative number of CFB value indicates an improvement in PRIMUS. Here, 'n' signifies the number of subjects analysed at specified time point.

End point type	Secondary

End point timeframe:

Baseline, Month 12

End point values	BG00012 240 mg BID			
Subject group type	Reporting group			
Number of subjects analysed	1105			
Units: score on scale				
arithmetic mean (standard deviation)				
Baseline (n= 689)	3.10 (± 4.623)			
CFB at Month 12 (n= 545)	-0.14 (± 3.200)			

Statistical analyses

No statistical analyses for this end point

Secondary: Work Productivity and Activity Impairment-Multiple Sclerosis Version (WPAI-MS): Change from Baseline to Month 12 in Number of Subjects Who Were Employed

End point title	Work Productivity and Activity Impairment-Multiple Sclerosis Version (WPAI-MS): Change from Baseline to Month 12 in Number of Subjects Who Were Employed

End point description:

This 6-item instrument assesses employment status, and, during the previous 7 days, hours of missed work due to MS or other reasons, hours worked (if employed), effect on productivity due to MS while working, and activity impairment attributable to health problems. Primary analysis population included all subjects who were eligible, signed informed consent, enrolled, and took at least 1 dose of DMF. Here, 'n' signifies the number of subjects analysed at specified time point.

End point type	Secondary

End point timeframe:

Baseline, Month 12

End point values	BG00012 240 mg BID			
Subject group type	Reporting group			
Number of subjects analysed	1105			
Units: subjects				
Baseline (n= 1075)	693			
Month 12 (n= 878)	593			

Statistical analyses

No statistical analyses for this end point

Secondary: Change from Baseline to Month 12 in WPAI-MS Scores

End point title	Change from Baseline to Month 12 in WPAI-MS Scores

End point description:

The WPAI measured impairments in work and activities due to MS. It included 1. work time missed, 2. impairment while working, 3. overall work impairment, and 4. activity impairment. The scores were

reported as percentage. A higher score indicates higher impairment and lower productivity. A negative number of CFB value indicates an improvement in WPAI-MS. Here, 'n' signifies the number of subjects analysed at specified time point.

End point type	Secondary

End point timeframe:

Baseline, Month 12

End point values	BG00012 240 mg BID			
Subject group type	Reporting group			
Number of subjects analysed	1105			
Units: percentage of impairment				
arithmetic mean (standard deviation)				
Percent (%) Work Time Missed:Baseline(n=555)	9.74 (± 25.203)			
% Work Time Missed:CFB at Month 12(n=351)	-0.43 (± 19.322)			
% Impairment While Working:Baseline(n=628)	21.70 (± 25.096)			
% Impairment While Working:CFB at Month 12(n=443)	-3.23 (± 19.067)			
% Overall Work Impairment:Baseline(n=515)	23.65 (± 27.056)			
% Overall Work Impairment:CFB at Month 12(n=327)	-2.21 (± 19.485)			
% Activity Impairment: Baseline(n=1067)	28.45 (± 27.795)			
% Activity Impairment:CFB at Month 12(n=851)	-4.21 (± 22.301)			

Statistical analyses

No statistical analyses for this end point

Secondary: Change from Baseline to Month 12 in Beck Depression Inventory-Fast Screen (BDI-Fast Screen) Score

End point title	Change from Baseline to Month 12 in Beck Depression Inventory-Fast Screen (BDI-Fast Screen) Score

End point description:

This was a 7-item scale that evaluated depression in subjects with medical illness during the prior 2 weeks. It had been validated in subjects with MS. It assessed depressive symptoms, and possible scores ranged from 0 to 21, where 0 to 3 = minimal depression symptoms, 4 to 6 = mild depression symptoms, 7 to 9 = moderate depression symptoms, and 10 or higher = severe depression symptoms. A lower BDI-Fast Screen score indicated fewer depressive symptoms and therefore a better outcome. Primary analysis population included all subjects who were eligible, signed informed consent, enrolled, and took at least 1 dose of DMF. A negative number of CFB value indicates an improvement in BDI-Fast Screen. Here, 'n' signifies the number of subjects analysed at specified time point.

End point type	Secondary

End point timeframe:

Baseline, Month 12

End point values	BG00012 240 mg BID			
Subject group type	Reporting group			
Number of subjects analysed	1105			
Units: score on scale				
arithmetic mean (standard deviation)				
Baseline (n= 1063) CFB at Month 12 (n= 854)	2.79 (± 3.181) -0.78 (± 2.538)			

Statistical analyses

No statistical analyses for this end point

Secondary: Percentage of Subjects with Confirmed (24-week) Expanded Disability Status Scale (EDSS) Progression at Month 12

End point title	Percentage of Subjects with Confirmed (24-week) Expanded Disability Status Scale (EDSS) Progression at Month 12

End point description:

Confirmed EDSS disability progression was defined as at least a 1.0 point increase in EDSS from a baseline EDSS >=1.0 or at least a 1.5 point increase from a baseline EDSS of 0 or at least 0.5 point increase from a baseline EDSS >= 6 and confirmed at 6 months (154 days) after initial progression. Progression could start at a scheduled assessment or relapse assessment during the treatment period but could be confirmed at during either the treatment and/or follow up 24-week period. EDSS assessments during relapse assessments were not used for confirmation. Primary analysis population included all subjects who were eligible, signed informed consent, enrolled, and took at least 1 dose of DMF.

End point type	Secondary

End point timeframe:

Month 12

End point values	BG00012 240 mg BID			
Subject group type	Reporting group			
Number of subjects analysed	1105			
Units: percentage of subjects				
number (not applicable)	1.9			

Statistical analyses

No statistical analyses for this end point

Secondary: ARR at Baseline and Month 6

End point title	ARR at Baseline and Month 6

End point description:

An MS relapse was defined as new or recurrent neurologic symptoms not associated with fever or infection, lasting for at least 24 hours, and accompanied by new objective neurologic findings upon examination by the investigator, and followed by a period of 30 days of stability or improvement. The annualised relapse rate for a period was calculated as the total number of relapses that occurred during the period for all subjects, divided by the total number of subject-years followed in that period. Relapses and follow-up times that occurred after treatment discontinuation were excluded from the calculations. Primary analysis population included all subjects who were eligible, signed informed consent, enrolled, and took at least 1 dose of DMF.

End point type	Secondary

End point timeframe:

Baseline and Month 6

End point values	BG00012 240 mg BID			
Subject group type	Reporting group			
Number of subjects analysed	1105			
Units: relapses per year				
number (confidence interval 95%)				
Baseline	0.643 (0.602 to 0.686)			
Month 6	0.201 (0.164 to 0.247)			

Statistical analyses

No statistical analyses for this end point

Secondary: Percentage of Subjects Relapsed at Month 12

End point title	Percentage of Subjects Relapsed at Month 12

End point description:

An MS relapse was defined as new or recurrent neurologic symptoms not associated with fever or infection, lasting for at least 24 hours, and accompanied by new objective neurologic findings upon examination by the investigator, and followed by a period of 30 days of stability or improvement. Relapses and follow-up times that occurred after treatment discontinuation were excluded from the calculations. Primary analysis population included all subjects who were eligible, signed informed consent, enrolled, and took at least 1 dose of DMF.

End point type	Secondary

End point timeframe:

Month 12

End point values	BG00012 240 mg BID			
Subject group type	Reporting group			
Number of subjects analysed	1105			
Units: percentage of subjects				
number (not applicable)	12.2			

Statistical analyses

No statistical analyses for this end point

Secondary: Number of Subjects Who Are Hospitalised Due to MS Relapses

End point title	Number of Subjects Who Are Hospitalised Due to MS Relapses

End point description:

Primary analysis population included all subjects who were eligible, signed informed consent, enrolled, and took at least 1 dose of DMF.

End point type	Secondary

End point timeframe:

Up to Month 12

End point values	BG00012 240 mg BID			
Subject group type	Reporting group			
Number of subjects analysed	1105			
Units: subjects	19			

Statistical analyses

No statistical analyses for this end point

Secondary: Number of Subjects Who Have Emergency Room Visits due to MS Relapses

End point title	Number of Subjects Who Have Emergency Room Visits due to MS Relapses

End point description:

Primary analysis population included all subjects who were eligible, signed informed consent, enrolled, and took at least 1 dose of DMF.

End point type	Secondary

End point timeframe:

Up to Month 12

End point values	BG00012 240 mg BID			
Subject group type	Reporting group			
Number of subjects analysed	0[2]			
Units: subjects				

Notes:

[2] - Data on emergency room visits was not collected in the study.

Statistical analyses

No statistical analyses for this end point

Secondary: Number of Subjects Who Have Relapses Requiring Intravenous (IV) Steroid Treatment During the Study

End point title	Number of Subjects Who Have Relapses Requiring Intravenous (IV) Steroid Treatment During the Study

End point description:

The rate of relapses requiring IV steroid therapy is calculated as the total number of relapses requiring IV therapy divided by number of subject-years followed within 12 months. Primary analysis population included all subjects who were eligible, signed informed consent, enrolled, and took at least 1 dose of DMF.

End point type	Secondary

End point timeframe:

Up to Month 12

End point values	BG00012 240 mg BID			
Subject group type	Reporting group			
Number of subjects analysed	1105			
Units: subjects				
0 Relapse	996			
1 Relapse	97			
2 Relapses	11			
3 Relapses	1			
>=4 Relapses	0			

Statistical analyses

No statistical analyses for this end point

Secondary: Number of Subjects Who Make Visits to Neurologists or Other Specialists Due to MS Over a 12-Month Period

End point title	Number of Subjects Who Make Visits to Neurologists or Other Specialists Due to MS Over a 12-Month Period

End point description:

Enrolled population included all subjects who were eligible, signed informed consent and were enrolled in the study.

End point type	Secondary

End point timeframe:

Up to Month 12

End point values	BG00012 240 mg BID			
Subject group type	Reporting group			
Number of subjects analysed	1114			
Units: subjects	1040			

Statistical analyses

No statistical analyses for this end point

Secondary: Percentage of Subjects Who Reported Not Taking the Full Prescribed DMF Dose

End point title	Percentage of Subjects Who Reported Not Taking the Full Prescribed DMF Dose

End point description:

Primary analysis population included all subjects who were eligible, signed informed consent, enrolled, and took at least 1 dose of DMF.

End point type	Secondary

End point timeframe:

Up to Month 12

End point values	BG00012 240 mg BID			
Subject group type	Reporting group			
Number of subjects analysed	1105			
Units: percentage of subjects				
number (not applicable)	71			

Statistical analyses

No statistical analyses for this end point

Secondary: Percentage of Overall Adherence

End point title	Percentage of Overall Adherence

End point description:

Primary analysis population included all subjects who were eligible, signed informed consent, enrolled, and took at least 1 dose of DMF. Here, 'number of subjects analysed' are subjects assessed in this endpoint.

End point type	Secondary

End point timeframe:

Up to Month 12

End point values	BG00012 240 mg BID			
Subject group type	Reporting group			
Number of subjects analysed	1049			
Units: percentage of overall adherence				
arithmetic mean (standard deviation)	80.23 (± 20.648)			

Statistical analyses

No statistical analyses for this end point

Secondary: Number of Subjects Who Had Reasons for Not Taking Full Dose Over a 12-Month Period

End point title	Number of Subjects Who Had Reasons for Not Taking Full Dose Over a 12-Month Period

End point description:

Primary analysis population included all subjects who were eligible, signed informed consent, enrolled, and took at least 1 dose of DMF.

End point type	Secondary

End point timeframe:

Up to Month 12

End point values	BG00012 240 mg BID			
Subject group type	Reporting group			
Number of subjects analysed	1105			
Units: subjects				
Feel/felt better	41			
Forgot to take the medication	623			
Cognitive issues (difficult remembering)	25			
Mobility issues (difficulty accessing medication)	7			
Afraid of side effects	90			
Experienced side effects	174			
Experienced relapse(s)	14			
Dosing regimen (twice a day)	51			
Other	297			

Statistical analyses

No statistical analyses for this end point

Adverse events

Adverse events information	
Timeframe for reporting adverse events:	
From Baseline (Day 1) up to end of treatment (Month 12)	
Adverse event reporting additional description:	
The safety population is defined as all subjects who received at least 1 dose of DMF.	
Assessment type	Systematic

Dictionary used	
Dictionary name	MedDRA
Dictionary version	20.0

Reporting groups	
Reporting group title	BG00012 240 mg BID
Reporting group description:	
Subjects received BG00012 capsules, 120 milligrams (mg), orally, twice daily (BID) on Days 1 through 7 followed by BG00012 capsules, 240 mg, orally, BID, thereafter up to 12 months.	

Serious adverse events	BG00012 240 mg BID		
Total subjects affected by serious adverse events			
subjects affected / exposed	44 / 1106 (3.98%)		
number of deaths (all causes)	1		
number of deaths resulting from adverse events			
Neoplasms benign, malignant and unspecified (incl cysts and polyps)			
Breast cancer			
subjects affected / exposed	3 / 1106 (0.27%)		
occurrences causally related to treatment / all	0 / 3		
deaths causally related to treatment / all	0 / 0		
Inflammatory pseudotumour			
subjects affected / exposed	1 / 1106 (0.09%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Ovarian cancer			
subjects affected / exposed	1 / 1106 (0.09%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Vascular disorders			
Lymphoedema			

subjects affected / exposed	1 / 1106 (0.09%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Phlebitis			
subjects affected / exposed	1 / 1106 (0.09%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
General disorders and administration site conditions			
Pyrexia			
subjects affected / exposed	1 / 1106 (0.09%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Immune system disorders			
Anaphylactic reaction			
subjects affected / exposed	1 / 1106 (0.09%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Reproductive system and breast disorders			
Colpocele			
subjects affected / exposed	1 / 1106 (0.09%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Metrorrhagia			
subjects affected / exposed	1 / 1106 (0.09%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Ovarian cyst			
subjects affected / exposed	1 / 1106 (0.09%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Uterine prolapse			

subjects affected / exposed	1 / 1106 (0.09%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Respiratory, thoracic and mediastinal disorders			
Dyspnoea			
subjects affected / exposed	1 / 1106 (0.09%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Psychiatric disorders			
Bipolar disorder			
subjects affected / exposed	1 / 1106 (0.09%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Delirium			
subjects affected / exposed	1 / 1106 (0.09%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Depression			
subjects affected / exposed	1 / 1106 (0.09%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Major depression			
subjects affected / exposed	1 / 1106 (0.09%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Panic attack			
subjects affected / exposed	1 / 1106 (0.09%)		
occurrences causally related to treatment / all	0 / 3		
deaths causally related to treatment / all	0 / 0		
Investigations			
Alanine aminotransferase increased			
subjects affected / exposed	1 / 1106 (0.09%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		

Aspartate aminotransferase increased				
subjects affected / exposed	1 / 1106 (0.09%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Injury, poisoning and procedural complications				
Ankle fracture				
subjects affected / exposed	1 / 1106 (0.09%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Concussion				
subjects affected / exposed	1 / 1106 (0.09%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Fall				
subjects affected / exposed	4 / 1106 (0.36%)			
occurrences causally related to treatment / all	0 / 4			
deaths causally related to treatment / all	0 / 0			
Intentional overdose				
subjects affected / exposed	1 / 1106 (0.09%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Skin wound				
subjects affected / exposed	1 / 1106 (0.09%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Tendon rupture				
subjects affected / exposed	1 / 1106 (0.09%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Vaccination complication				
subjects affected / exposed	1 / 1106 (0.09%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			

Cardiac disorders			
Angina unstable			
subjects affected / exposed	1 / 1106 (0.09%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Nervous system disorders			
Multiple sclerosis relapse			
subjects affected / exposed	2 / 1106 (0.18%)		
occurrences causally related to treatment / all	0 / 2		
deaths causally related to treatment / all	0 / 0		
Neuralgia			
subjects affected / exposed	1 / 1106 (0.09%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Blood and lymphatic system disorders			
Lymphopenia			
subjects affected / exposed	3 / 1106 (0.27%)		
occurrences causally related to treatment / all	0 / 3		
deaths causally related to treatment / all	0 / 0		
Gastrointestinal disorders			
Abdominal pain			
subjects affected / exposed	1 / 1106 (0.09%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Enteritis			
subjects affected / exposed	1 / 1106 (0.09%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Gastrooesophageal reflux disease			
subjects affected / exposed	1 / 1106 (0.09%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Subileus			

subjects affected / exposed	1 / 1106 (0.09%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Vomiting			
subjects affected / exposed	1 / 1106 (0.09%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Skin and subcutaneous tissue disorders			
Drug eruption			
subjects affected / exposed	1 / 1106 (0.09%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Erythema			
subjects affected / exposed	1 / 1106 (0.09%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Endocrine disorders			
Goitre			
subjects affected / exposed	1 / 1106 (0.09%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Musculoskeletal and connective tissue disorders			
Back pain			
subjects affected / exposed	1 / 1106 (0.09%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Osteoarthritis			
subjects affected / exposed	1 / 1106 (0.09%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Infections and infestations			
Chikungunya virus infection			

subjects affected / exposed	1 / 1106 (0.09%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Gastroenteritis cryptosporidial			
subjects affected / exposed	1 / 1106 (0.09%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Herpes zoster			
subjects affected / exposed	1 / 1106 (0.09%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Ophthalmic herpes zoster			
subjects affected / exposed	1 / 1106 (0.09%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Pneumonia			
subjects affected / exposed	1 / 1106 (0.09%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Salpingitis			
subjects affected / exposed	1 / 1106 (0.09%)		
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 240 mg BID		
Total subjects affected by non-serious adverse events			
subjects affected / exposed	731 / 1106 (66.09%)		
Vascular disorders			
Flushing			
subjects affected / exposed	512 / 1106 (46.29%)		
occurrences (all)	626		

Nervous system disorders			
Headache			
subjects affected / exposed	60 / 1106 (5.42%)		
occurrences (all)	95		
Gastrointestinal disorders			
Abdominal pain			
subjects affected / exposed	120 / 1106 (10.85%)		
occurrences (all)	142		
Abdominal pain upper			
subjects affected / exposed	125 / 1106 (11.30%)		
occurrences (all)	143		
Diarrhoea			
subjects affected / exposed	185 / 1106 (16.73%)		
occurrences (all)	195		
Nausea			
subjects affected / exposed	107 / 1106 (9.67%)		
occurrences (all)	117		
Vomiting			
subjects affected / exposed	82 / 1106 (7.41%)		
occurrences (all)	94		
Skin and subcutaneous tissue disorders			
Pruritus			
subjects affected / exposed	47 / 1106 (4.25%)		
occurrences (all)	57		
Infections and infestations			
Nasopharyngitis			
subjects affected / exposed	47 / 1106 (4.25%)		
occurrences (all)	61		
Urinary tract infection			
subjects affected / exposed	50 / 1106 (4.52%)		
occurrences (all)	63		

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

Date	Amendment
20 June 2013	The primary reason for this amendment is to address the following: 1) Validated translations for the Patient-Reported Indices for Multiple Sclerosis (PRIMUS) Activity Limitations instrument were not available for all languages. As a result, this instrument was administered only in countries where translations were available (Austria, Canada, France, Italy, and Spain). 2) Austrian Drug Law allows clinical trials to be conducted in women of childbearing potential only if it is confirmed that they are not pregnant. Therefore, pregnancy tests must be performed on a monthly basis during the study (including 4 to 5 half-life times after the last dose) by a physician who is not necessarily the investigator.

Notes:

Interruptions (globally)

Were there any global interruptions to the trial? No

Limitations and caveats

None reported