Clinical trial results:
A Multicenter, Randomized, Double-Blind, Placebo-Controlled, Efficacy and Safety Study of BG00012 in Subjects From the Asia Pacific Region and Other Countries With Relapsing-Remitting Multiple Sclerosis

Summary

EudraCT number	2013-004533-32
Trial protocol	CZ PL
Global end of trial date	

Results information

Result version number	v1
This version publication date	19 June 2016
First version publication date	19 June 2016

Trial information

Trial identification

Sponsor protocol code	109MS305

Additional study identifiers

ISRCTN number	-
ClinicalTrials.gov id (NCT number)	NCT01838668
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	Interim
Date of interim/final analysis	16 June 2015
Is this the analysis of the primary completion data?	Yes
Primary completion date	16 June 2015
Global end of trial reached?	No

Notes:

General information about the trial

Main objective of the trial:

The primary objective of Part I of the study is to determine the efficacy of BG00012 on inflammatory brain magnetic resonance imaging (MRI) lesion activity (gadolinium [Gd]-enhancing lesions) when compared with placebo from 4 scans performed at Weeks 12, 16, 20, and 24 in subjects with relapsing-remitting multiple sclerosis (RRMS) including subjects from the Asia-Pacific region.

The primary objective of Part II of this study is to evaluate the long-term safety profile of BG00012 in eligible subjects from Part I.

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	28 March 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	Poland: 40
Country: Number of subjects enrolled	Czech Republic: 42
Country: Number of subjects enrolled	Japan: 115
Country: Number of subjects enrolled	Korea, Republic of: 20
Country: Number of subjects enrolled	Taiwan: 8
Worldwide total number of subjects	225
EEA total number of subjects	82

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)	225
From 65 to 84 years	0
85 years and over	0

Subject disposition

Recruitment

Recruitment details: -

Pre-assignment

Screening details:

This study included a Screening Period (maximum of 28 days). A total of 225 subjects were randomized; however, 1 subject in the BG00012 240 mg BID arm was not dosed.

Pre-assignment period milestones

Number of subjects started	225
Number of subjects completed	224

Pre-assignment subject non-completion reasons

Reason: Number of subjects	Randomized but not dosed: 1

Period 1

Period 1 title	Part I (Double-blind Treatment Period) (overall period)
Is this the baseline period?	Yes
Allocation method	Randomised - controlled
Blinding used	Double blind
Roles blinded	Investigator, Subject

Blinding implementation details:

BG00012 and placebo administration was double-blind. Placebo capsules matched BG00012 capsules in size, shape, color, and taste. Additionally, all subjects (including those receiving placebo) were dosed with the same number of capsules BID.

Arms

Are arms mutually exclusive?	Yes
Arm title	Part I Placebo

Arm description:

Subjects randomized to placebo BID began dosing at 1 placebo capsule orally BID for the first 7 days and escalated to 2 placebo capsules orally BID from Day 8 through Week 24 (end of Part I).

Arm type	Placebo
Investigational medicinal product name	Placebo
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Capsule
Routes of administration	Oral use

Dosage and administration details:

The pharmacist or designee dispensed at least a 4-week supply of study treatment to subjects at Baseline (Day 1/Enrollment Visit) and at each subsequent study visit through Week 24. Study treatment was not to be dispensed at Week 24 (except in the case of subjects continuing to Part II Extension Period) or at any Unscheduled Relapse Assessment Visit.

Arm title	Part I BG00012 240 mg BID

Arm description:

Subjects randomized to BG00012 began dosing at 120 mg BG00012 (1 capsule orally BID) for the first 7 days and escalated to 240 mg BG00012 (2 capsules orally BID) from Day 8 through Week 24 (end of Part I).

Arm type	Experimental

Investigational medicinal product name	BG00012
Investigational medicinal product code	BG00012
Other name	dimethyl fumarate, DMF, Tecfidera
Pharmaceutical forms	Capsule
Routes of administration	Oral use

Dosage and administration details:

The pharmacist or designee dispensed at least a 4-week supply of study treatment to subjects at Baseline (Day 1/Enrollment Visit) and at each subsequent study visit through Week 24. Study treatment was not to be dispensed at Week 24 (except in the case of subjects continuing to Part II Extension Period) or at any Unscheduled Relapse Assessment Visit.

Number of subjects in period 1[1]	Part I Placebo	Part I BG00012 240 mg BID
Started	113	111
Subjects dosed in Part I	113	111
Completed study drug in Part I	107 [2]	105
Completed study in Part I	108	105
Completed	108	105
Not completed	5	6
Consent withdrawn by subject	3	1
Not specified	-	4
Adverse event	2	1

Notes:

[1] - The number of subjects reported to be in the baseline period are not the same as the worldwide number enrolled in the trial. It is expected that these numbers will be the same.
Justification: 1 subject was enrolled and randomized but was not treated.

[2] - The number of subjects at this milestone seems inconsistent with the number of subjects in the arm. It is expected that the number of subjects will be greater than, or equal to the number that completed, minus those who left.
Justification: 1 subject who did not complete treatment with study drug did not withdraw prematurely from Part I of the study .

Baseline characteristics

Reporting groups	
Reporting group title	Part I Placebo
Reporting group description:	
Subjects randomized to placebo BID began dosing at 1 placebo capsule orally BID for the first 7 days and escalated to 2 placebo capsules orally BID from Day 8 through Week 24 (end of Part I).	
Reporting group title	Part I BG00012 240 mg BID
Reporting group description:	
Subjects randomized to BG00012 began dosing at 120 mg BG00012 (1 capsule orally BID) for the first 7 days and escalated to 240 mg BG00012 (2 capsules orally BID) from Day 8 through Week 24 (end of Part I).	

Reporting group values	Part I Placebo	Part I BG00012 240 mg BID	Total
Number of subjects	113	111	224
Age categorical Units: Subjects			
18 to 19 years	0	0	0
20 to 29 years	23	20	43
30 to 39 years	57	45	102
40 to 49 years	29	37	66
50 to 55 years	3	9	12
> 55 years	1	0	1
Age continuous Units: years			
arithmetic mean	36	37.3	
standard deviation	± 7.46	± 8.27	-
Gender categorical Units: Subjects			
Female	84	78	162
Male	29	33	62

End points

End points reporting groups

Reporting group title	Part I Placebo
Reporting group description:	
Subjects randomized to placebo BID began dosing at 1 placebo capsule orally BID for the first 7 days and escalated to 2 placebo capsules orally BID from Day 8 through Week 24 (end of Part I).	
Reporting group title	Part I BG00012 240 mg BID
Reporting group description:	
Subjects randomized to BG00012 began dosing at 120 mg BG00012 (1 capsule orally BID) for the first 7 days and escalated to 240 mg BG00012 (2 capsules orally BID) from Day 8 through Week 24 (end of Part I).	
Subject analysis set title	ITT Population: Placebo
Subject analysis set type	Intention-to-treat
Subject analysis set description:	
ITT Population: subjects who were randomized to placebo and received at least 1 dose of study treatment.	
Subject analysis set title	ITT Population: BG00012 240 mg BID
Subject analysis set type	Intention-to-treat
Subject analysis set description:	
ITT Population: subjects who were randomized to BG00012 and received at least 1 dose of study treatment.	

Primary: MRI: Total Number of New Gd-Enhancing Lesions From Scans at Week 12 to 24: Part I

End point title	MRI: Total Number of New Gd-Enhancing Lesions From Scans at Week 12 to 24: Part I
End point description:	
The total number of new Gd-enhancing lesions from qualified MRI scans at Weeks 12, 16, 20, and 24, calculated as the sum of new Gd-enhancing lesions from these four scans. Gd-enhancing lesions are detected when Gd leaks into the perivascular space due to local breakdown of the blood-brain barrier, indicating the presence of active inflammation in periventricular lesions.	
End point type	Primary
End point timeframe:	
Week 12 to Week 24	

End point values	ITT Population: Placebo	ITT Population: BG00012 240 mg BID		
Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed	113	111		
Units: lesions				
arithmetic mean (standard deviation)	4.3 (± 8.2)	1.1 (± 5.46)		

Statistical analyses

Statistical analysis title	Statistical Analysis 1
Statistical analysis description:	
Percentage change, 95% CI and p-value for comparison between the active and placebo groups, based	

on negative binomial regression, adjusted for region (Japan/Non-Japan) and baseline number of Gd lesions.

Comparison groups	ITT Population: Placebo v ITT Population: BG00012 240 mg BID
Number of subjects included in analysis	224
Analysis specification	Pre-specified
Analysis type	superiority
Parameter estimate	lesion mean ratio
Point estimate	0.164
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.101
upper limit	0.266

Statistical analysis title	Statistical Analysis 2

Statistical analysis description:

Percentage change, 95% CI and p-value for comparison between the active and placebo groups, based on negative binomial regression, adjusted for region (Japan/Non-Japan) and baseline number of Gd lesions.

Comparison groups	ITT Population: Placebo v ITT Population: BG00012 240 mg BID
Number of subjects included in analysis	224
Analysis specification	Pre-specified
Analysis type	superiority
P-value	< 0.0001
Method	negative binomial regression
Parameter estimate	percentage reduction (vs. placebo)
Point estimate	83.6
Confidence interval	
level	95 %
sides	2-sided
lower limit	73.4
upper limit	89.9

Statistical analysis title	Sensitivity Analysis 1
Comparison groups	ITT Population: Placebo v ITT Population: BG00012 240 mg BID
Number of subjects included in analysis	224
Analysis specification	Pre-specified
Analysis type	superiority
P-value	< 0.0001
Method	Wilcoxon rank sum test

Statistical analysis title	Sensitivity Analysis 2
Comparison groups	ITT Population: Placebo v ITT Population: BG00012 240 mg

	BID
Number of subjects included in analysis	224
Analysis specification	Pre-specified
Analysis type	superiority
P-value	< 0.0001 [1]
Method	see footnote

Notes:

[1] - Based on exclusion of 1 subject with outlier values and subjects who tested positive for anti-aquaporin 4 (AQP4) antibody.

Statistical analysis title	Sensitivity Analysis 3
Comparison groups	ITT Population: Placebo v ITT Population: BG00012 240 mg BID
Number of subjects included in analysis	224
Analysis specification	Pre-specified
Analysis type	superiority
P-value	< 0.0001 [2]
Method	see footnote

Notes:

[2] - Based on imputation with interpolation for missing values at a visit that has valid readings at the visits immediately prior and after the visit with the missing value.

Secondary: MRI: Total Number of New Gd-Enhancing Lesions From Scans at Weeks 4 to 24: Part I

End point title	MRI: Total Number of New Gd-Enhancing Lesions From Scans at Weeks 4 to 24: Part I

End point description:

The cumulative number of new Gd-enhancing lesions over the six MRI scans in the placebo-controlled phase was calculated as the sum of the new Gd-enhancing lesions from the Week 4 to Week 24 scans.

End point type	Secondary

End point timeframe:

Week 4 to Week 24

End point values	ITT Population: Placebo	ITT Population: BG00012 240 mg BID		
Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed	113	111		
Units: lesions				
arithmetic mean (standard deviation)	6.5 (± 10.7)	2.6 (± 12.57)		

Statistical analyses

Statistical analysis title	Statistical Analysis 1

Statistical analysis description:

Percentage change, 95% CI and p-value for comparison between the active and placebo groups, based on negative binomial regression, adjusted for region (Japan/Non-Japan) and baseline number of Gd lesions.

Comparison groups	ITT Population: Placebo v ITT Population: BG00012 240 mg BID

Number of subjects included in analysis	224
Analysis specification	Pre-specified
Analysis type	superiority
Parameter estimate	lesion mean ratio
Point estimate	0.247
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.167
upper limit	0.366

Statistical analysis title	Statistical Analysis 2

Statistical analysis description:

Percentage change, 95% CI and p-value for comparison between the active and placebo groups, based on negative binomial regression, adjusted for region (Japan/Non-Japan) and baseline number of Gd lesions.

Comparison groups	ITT Population: Placebo v ITT Population: BG00012 240 mg BID
Number of subjects included in analysis	224
Analysis specification	Pre-specified
Analysis type	superiority
P-value	< 0.0001
Method	negative binomial regression
Parameter estimate	percentage reduction (vs. placebo)
Point estimate	75.3
Confidence interval	
level	95 %
sides	2-sided
lower limit	63.4
upper limit	83.3

Secondary: MRI: Total Number of New or Newly Enlarging T2 Lesions at Week 24 Compared to Baseline: Part I

End point title	MRI: Total Number of New or Newly Enlarging T2 Lesions at Week 24 Compared to Baseline: Part I

End point description:

The total number of new or newly-enlarging T2 hyperintense lesions at Week 24 compared to baseline. Lesions detected on T2-weighted sequences have been shown to represent a range of histopathology related to MS, including edema, inflammation, demyelination, gliosis, and axon loss.

End point type	Secondary

End point timeframe:

Baseline, Week 24

End point values	ITT Population: Placebo	ITT Population: BG00012 240 mg BID		
Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed	113	111		
Units: lesions				
arithmetic mean (standard deviation)	4.9 (± 6.23)	1.9 (± 3.42)		

Statistical analyses

Statistical analysis title	Statistical Analysis 1
Statistical analysis description:	
Percentage change, 95% CI and p-value for comparison between the active and placebo groups, based on negative binomial regression, adjusted for region (Japan/Non-Japan) and baseline volume of T2 lesions.	
Comparison groups	ITT Population: Placebo v ITT Population: BG00012 240 mg BID
Number of subjects included in analysis	224
Analysis specification	Pre-specified
Analysis type	superiority
Parameter estimate	lesion mean ratio
Point estimate	0.368
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.258
upper limit	0.525

Statistical analysis title	Statistical Analysis 2
Statistical analysis description:	
Percentage change, 95% CI and p-value for comparison between the active and placebo groups, based on negative binomial regression, adjusted for region (Japan/Non-Japan) and baseline volume of T2 lesions.	
Comparison groups	ITT Population: Placebo v ITT Population: BG00012 240 mg BID
Number of subjects included in analysis	224
Analysis specification	Pre-specified
Analysis type	superiority
P-value	< 0.0001
Method	negative binomial regression
Parameter estimate	percentage reduction (vs. placebo)
Point estimate	63.2
Confidence interval	
level	95 %
sides	2-sided
lower limit	47.5
upper limit	74.2

Adverse events

Adverse events information

Timeframe for reporting adverse events:

AE monitoring was from the administration of the first dose of study treatment to Week 24 or premature withdrawal (end of Part I). SAE monitoring was from signing of the informed consent to Week 24 or premature withdrawal (end of Part I).

Assessment type	Systematic

Dictionary used

Dictionary name	MedDRA
Dictionary version	13.1

Reporting groups

Reporting group title	Placebo

Reporting group description:

Subjects randomized to placebo BID began dosing at 1 placebo capsule orally BID for the first 7 days and escalated to 2 placebo capsules orally BID from Day 8 through Week 24 (end of Part I).

Reporting group title	BG00012 240 mg BID

Reporting group description:

Subjects randomized to BG00012 began dosing at 120 mg BG00012 (1 capsule orally BID) for the first 7 days and escalated to 240 mg BG00012 (2 capsules orally BID) from Day 8 through Week 24 (end of Part I).

Serious adverse events	Placebo	BG00012 240 mg BID	
Total subjects affected by serious adverse events			
subjects affected / exposed	16 / 113 (14.16%)	15 / 111 (13.51%)	
number of deaths (all causes)	0	0	
number of deaths resulting from adverse events			
Neoplasms benign, malignant and unspecified (incl cysts and polyps)			
Fallopian tube cancer			
subjects affected / exposed	1 / 113 (0.88%)	0 / 111 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Injury, poisoning and procedural complications			
Humerus fracture			
subjects affected / exposed	0 / 113 (0.00%)	1 / 111 (0.90%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Road traffic accident			

subjects affected / exposed	0 / 113 (0.00%)	1 / 111 (0.90%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Tibia fracture			
subjects affected / exposed	0 / 113 (0.00%)	1 / 111 (0.90%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Nervous system disorders			
Multiple sclerosis relapse			
subjects affected / exposed	16 / 113 (14.16%)	12 / 111 (10.81%)	
occurrences causally related to treatment / all	2 / 23	1 / 17	
deaths causally related to treatment / all	0 / 0	0 / 0	
Psychiatric disorders			
Anxiety			
subjects affected / exposed	0 / 113 (0.00%)	1 / 111 (0.90%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Infections and infestations			
Pyelonephritis			
subjects affected / exposed	0 / 113 (0.00%)	1 / 111 (0.90%)	
occurrences causally related to treatment / all	0 / 0	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	

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

Non-serious adverse events	Placebo	BG00012 240 mg BID	
Total subjects affected by non-serious adverse events			
subjects affected / exposed	65 / 113 (57.52%)	78 / 111 (70.27%)	
Investigations			
Alanine aminotransferase increased			
subjects affected / exposed	2 / 113 (1.77%)	7 / 111 (6.31%)	
occurrences (all)	2	8	
Vascular disorders			
Flushing			

subjects affected / exposed	9 / 113 (7.96%)	24 / 111 (21.62%)	
occurrences (all)	11	26	
Hot flush			
subjects affected / exposed	1 / 113 (0.88%)	7 / 111 (6.31%)	
occurrences (all)	1	7	
Nervous system disorders			
Multiple sclerosis relapse			
subjects affected / exposed	31 / 113 (27.43%)	23 / 111 (20.72%)	
occurrences (all)	42	31	
Gastrointestinal disorders			
Abdominal pain			
subjects affected / exposed	0 / 113 (0.00%)	8 / 111 (7.21%)	
occurrences (all)	0	11	
Abdominal pain upper			
subjects affected / exposed	6 / 113 (5.31%)	5 / 111 (4.50%)	
occurrences (all)	8	5	
Diarrhoea			
subjects affected / exposed	6 / 113 (5.31%)	11 / 111 (9.91%)	
occurrences (all)	6	12	
Nausea			
subjects affected / exposed	6 / 113 (5.31%)	11 / 111 (9.91%)	
occurrences (all)	7	11	
Skin and subcutaneous tissue disorders			
Pruritus			
subjects affected / exposed	2 / 113 (1.77%)	8 / 111 (7.21%)	
occurrences (all)	7	9	
Infections and infestations			
Nasopharyngitis			
subjects affected / exposed	28 / 113 (24.78%)	26 / 111 (23.42%)	
occurrences (all)	45	29	
Upper respiratory tract infection			
subjects affected / exposed	11 / 113 (9.73%)	5 / 111 (4.50%)	
occurrences (all)	17	7	

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

Date	Amendment
19 November 2012	The primary reason for this amendment was to extend the contraception requirement from 30 days after the last dose of study treatment through the Final Safety Follow-Up Visit 12 weeks after the last dose of study treatment.
22 November 2013	The primary reasons for this amendment were to: - Open the study in the Czech Republic and Poland in addition to Japan, South Korea, and Taiwan. Although China was originally included, the study was withdrawn from China prior to study approval in that country. The title of the study was updated to reflect these changes. - Recommend that visits for female subjects be scheduled when the subject was not menstruating as a precaution against contamination of urine samples. - Anti-APQ4 antibody testing was to occur at the first Relapse Assessment Visit but was not required at any subsequent Relapse Assessment Visit. - Weight was added as an assessment at the End of Study/Premature Withdrawal/Final Safety Follow-Up Visit. - Clarify that MRI was not to be performed within 28 days after completing a course of steroids. - Clarify that if a subject had positive urinalysis test at Screening and the etiology was known (e.g., due to menses or urinary tract infection in the case of hematuria, or due to recent steroid use or elevated serum glucose in the case of glycosuria), a repeat test was not required.
10 December 2014	The primary reasons for this amendment were to: - Enable the early identification of subjects in Parts I or II who are at risk for developing severe, prolonged lymphopenia, and to provide additional guidance on the management of such subjects. In addition, lymphocyte and subset counts have been supplemented as an exploratory endpoint with the objective to study the impact of BG00012 treatment on lymphocytes and the recovery of lymphocyte count in patients with lymphopenia. - Extend the duration of study participation from 28 or 40 weeks to 28 to 52 weeks to reflect the additional safety follow-up for subjects with abnormally low lymphocyte counts. Subjects who completed Part I and did not enroll in Part II of the study or subjects who permanently discontinued study treatment for any reason and had a lymphocyte count <LLN were to be followed until the lymphocyte count was ≥LLN or until 24 weeks after the last dose (whichever was sooner). - Clarify that the use of alternative MS therapies was allowed only after the Investigators had contacted Biogen or its designee to determine their necessity in subjects who completed Part I and did not enroll in Part II of the study or subjects who permanently discontinued study treatment. - Country was added as a covariate for the statistical modelling of additional endpoints to be consistent with the analysis of the primary and secondary endpoints. - If lymphocyte count remains <500/mm3 for ≥24 weeks consecutively, study treatment will be permanently discontinued, and recovery of lymphocytes will be followed.

Notes:

Interruptions (globally)

Were there any global interruptions to the trial? No

Limitations and caveats

None reported