Clinical trial results:
Single Country Study Assessing Cognition in Relapsing Remitting Multiple Sclerosis Patients Treated with BG00012

Summary

EudraCT number	2013-001422-25
Trial protocol	IT
Global end of trial date	21 December 2016

Results information

Result version number	v1 (current)
This version publication date	21 September 2018
First version publication date	21 September 2018

Trial information

Trial identification

Sponsor protocol code	ITA-BGT-12-10389

Additional study identifiers

ISRCTN number	-
ClinicalTrials.gov id (NCT number)	NCT02579681
WHO universal trial number (UTN)	-
Other trial identifiers	109MS410: Biogen

Notes:

Sponsors

Sponsor organisation name	Biogen Italia S.R.L.
Sponsor organisation address	Centro Leoni, Via Spadolini 5, Milan, Italy, 20141
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	30 March 2018
Is this the analysis of the primary completion data?	Yes
Primary completion date	21 December 2016
Global end of trial reached?	Yes
Global end of trial date	21 December 2016
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 assess the BG00012 treatment effect on cognition over a 2 year period in subjects with relapsing remitting multiple sclerosis (RRMS). The secondary objectives were to further assess BG00012 treatment effect on cognition, predictors of cognitive impairment, clinical efficacy, and patient reported outcomes (PRO): depression, fatigue, quality of life, and work and social life activity.

Protection of trial subjects:

All study subjects were required to read and sign an informed consent form (ICF).

Background therapy: -

Evidence for comparator: -

Actual start date of recruitment	08 April 2014
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	Italy: 232
Worldwide total number of subjects	232
EEA total number of subjects	232

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)	232
From 65 to 84 years	0
85 years and over	0

Subject disposition

Recruitment

Recruitment details:

Subjects were recruited from 24 sites in Italy.

Pre-assignment

Screening details:

Prior to performing any study-related activities under this protocol, including screening tests and assessments, written informed consent with the approved informed consent form (ICF) was to be obtained from the subject or subject's legally authorized representative, as applicable, in accordance with local practice and regulations.

Period 1

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

Arms

Arm title	BG00012

Arm description:

Subjects with RRMS received 240 milligrams (mg) BG00012 twice daily for 24 months.

Arm type	Experimental
Investigational medicinal product name	BG00012
Investigational medicinal product code	
Other name	Tecfidera
Pharmaceutical forms	Capsule
Routes of administration	Oral use

Dosage and administration details:

240 mg BG00012 twice daily for 24 months.

Number of subjects in period 1	BG00012
Started	232
Enrolled (ENR) Set	232
Intent to Treat (ITT) Set	217
Safety Analysis (SAF) Set	217
Completed	156
Not completed	76
Patient not treated	3
Not specified	6
Adverse event	31
Investigator Decision	1
Eligibility criteria violated	8
Lost to follow-up	1

Clinical worsening	9
Withdrawal of informed consent	17

Baseline characteristics

Reporting groups	
Reporting group title	BG00012
Reporting group description:	
Subjects with RRMS received 240 milligrams (mg) BG00012 twice daily for 24 months.	

Reporting group values	BG00012	Total	
Number of subjects	232	232	
Age Categorical Units: Subjects			
In utero	0	0	
Preterm newborn infants (gestational age < 37 wks)	0	0	
Newborns (0-27 days)	0	0	
Infants and toddlers (28 days-23 months)	0	0	
Children (2-11 years)	0	0	
Adolescents (12-17 years)	0	0	
Adults (18-64 years)	232	232	
From 65-84 years	0	0	
85 years and over	0	0	
Age Continuous Units: years			
arithmetic mean	37.14		
standard deviation	± 9.75	-	
Gender Categorical Units: Subjects			
Female	172	172	
Male	60	60	

End points

End points reporting groups

Reporting group title	BG00012
Reporting group description:	
Subjects with RRMS received 240 milligrams (mg) BG00012 twice daily for 24 months.	
Subject analysis set title	BG00012 Intent to Treat (ITT)
Subject analysis set type	Intention-to-treat
Subject analysis set description:	
All subjects in the ENR set who received at least 1 dose of study treatment.	
Subject analysis set title	BG00012 Safety
Subject analysis set type	Safety analysis
Subject analysis set description:	
All enrolled subjects who received at least 1 dose of study treatment.	

Primary: Percentage of Subjects With Worsened Cognitive Impairment (CI) Over Two Years

End point title	Percentage of Subjects With Worsened Cognitive Impairment (CI) Over Two Years[1]
End point description:	
CI was defined as a subject's failure,at any testing session,on 2 tests that were part of the Rao's Brief Repeatable Battery of Neuropsychological Tests(BRB-N) or as failure on the 100-item version of the Stroop test.A subject failed any item of the BRB-N and Stroop Test if the normalized score was at least 2 standard deviations (SD) below the Italian normative score.The BRB-N was a measure of CI in subjects with MS that incorporates tests of verbal memory acquisition, visual memory acquisition,delayed recall,attention,concentration and speed of information processing and verbal fluency on semantic stimulus.The Stroop Test was used to measure a person's sustained attention for word reading and color naming with and without interference. Percentages were calculated relative to the total number of subjects in the ITT set with a preexisiting cognitive impairment at baseline assessment and available post baseline values.	
End point type	Primary
End point timeframe:	
Baseline, End of Study (24 months)	
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 were performed for this single-arm study.	

End point values	BG00012 Intent to Treat (ITT)			
Subject group type	Subject analysis set			
Number of subjects analysed	34			
Units: percentage of subjects				
number (confidence interval 95%)	44.1 (28.9 to 60.6)			

Statistical analyses

No statistical analyses for this end point

Secondary: Change From Baseline in the Cognitive Impairment Index (CII) Score

Over Two Years

End point title	Change From Baseline in the Cognitive Impairment Index (CII) Score Over Two Years

End point description:

CII was calculated to assess the amount and direction of cognitive changes over time for each subject between year 0 and year 1, and year 0 and year 2. CII was derived from the subject's performance on the BRB-N and the 100-item Stroop Test. For CII, the mean and SD for each cognitive variable was derived from the matched control normative data obtained from a study by Amato et al (2006) conducted on 200 healthy subjects. For each test, all subjects were graded as Grade 0 if the subject scored at or above the normative data, Grade 1 if below the normative data but within 1 SD of that mean, and Grade 2 if at least 1 but not more than 2 SD below the normative data. The grades were summed across all neuropsychological variables to give one overall score of cognitive dysfunction. Scores on the CII range from 0 (less CI) to 100 (more CI). A negative change from Baseline indicates a decrease in CI. Here, 'n' signifies those subjects who were evaluable at the specified time point.

End point type	Secondary

End point timeframe:

Baseline, Visit 4 (12 months), End of Study (24 months or Early Termination [ET])

End point values	BG00012 Intent to Treat (ITT)			
Subject group type	Subject analysis set			
Number of subjects analysed	217			
Units: score on a scale				
arithmetic mean (standard deviation)				
Baseline (n=200)	10.5 (± 6.79)			
Change from Baseline at Visit 4 (n=148)	0.3 (± 4.72)			
Change from Baseline at EOS/ET (n=125)	-2.3 (± 3.96)			

Statistical analyses

No statistical analyses for this end point

Secondary: Annualized Relapse Rate (ARR) at Year One

End point title	Annualized Relapse Rate (ARR) at Year One

End point description:

The ARR was calculated as the total number of relapses during year 1 for all subjects, divided by the total number of patient-years followed in year 1. Relapse was 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 treating neurologist. New or recurrent neurologic symptoms that occurred less than 30 days following the onset of a protocol-defined relapse were considered part of the same relapse.

End point type	Secondary

End point timeframe:

Visit 4 (12 months)

End point values	BG00012 Intent to Treat (ITT)			
Subject group type	Subject analysis set			
Number of subjects analysed	217			
Units: relapses/year				
number (not applicable)	0.265			

Statistical analyses

No statistical analyses for this end point

Secondary: ARR at Year Two

End point title	ARR at Year Two

End point description:

The ARR was calculated as the total number of relapses during years 1 and 2 for all subjects, divided by the total number of patient-years followed in years 1 and 2. Relapse was 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 treating neurologist. New or recurrent neurologic symptoms that occurred less than 30 days following the onset of a protocol-defined relapse were considered part of the same relapse.

End point type	Secondary

End point timeframe:

End of Study (24 months)

End point values	BG00012 Intent to Treat (ITT)			
Subject group type	Subject analysis set			
Number of subjects analysed	217			
Units: relapses/year				
number (not applicable)	0.19			

Statistical analyses

No statistical analyses for this end point

Secondary: Percentage of Subjects Who Relapsed Over Two Years

End point title	Percentage of Subjects Who Relapsed Over Two Years

End point description:

Relapse was 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 treating neurologist. New or recurrent neurologic symptoms that occurred less than 30 days following the onset of a protocol-defined relapse were considered part of the same relapse.

End point type	Secondary

End point timeframe:

Visit 4 (12 months) and End of Study (24 months)

End point values	BG00012 Intent to Treat (ITT)			
Subject group type	Subject analysis set			
Number of subjects analysed	217			
Units: percentage of subjects				
number (not applicable)				
Year 1	15.7			
Year 2	19.4			

Statistical analyses

No statistical analyses for this end point

Secondary: Median Time to First Relapse Over Two Years

End point title	Median Time to First Relapse Over Two Years

End point description:

Time to first relapse was defined as the time from the date of the screening visit to the date when the first relapse occurred during the study period. Subjects without relapse were censored at the date of the last assessment performed. Time to first relapse was estimated by using the Kaplan-Meier method.

End point type	Secondary

End point timeframe:

End of Study (24 months)

End point values	BG00012 Intent to Treat (ITT)			
Subject group type	Subject analysis set			
Number of subjects analysed	0[2]			
Units: days				
median (confidence interval 95%)	(to)			

Notes:

[2] - The median time to first relapse was not estimable because of the low number of events (< 20%).

Statistical analyses

No statistical analyses for this end point

Secondary: Percentage of Subjects Experiencing 6-Month Sustained Progression of Disability as Measured by the Expanded Disability Status Scale (EDSS)

End point title	Percentage of Subjects Experiencing 6-Month Sustained Progression of Disability as Measured by the Expanded Disability Status Scale (EDSS)

End point description:

Progression of disability was defined as either a ≥ 1.0 point increase on the EDSS from a baseline score ≥1.0 that was sustained for 24 weeks or a ≥ 1.5 point increase on the EDSS from a baseline score = 0 that was sustained for 24 weeks (2 consecutive assessments). EDSS is based on a standardized neurological exam and focuses on symptoms that commonly occur in MS. Total scores range from 0.0 (normal) to 10.0 (death due to MS). Percentages are calculated relative to the total number of subjects in the ITT Set with data.

End point type	Secondary

End point timeframe:

Baseline, End of Study (24 months)

End point values	BG00012 Intent to Treat (ITT)			
Subject group type	Subject analysis set			
Number of subjects analysed	188			
Units: percentage of subjects				
number (not applicable)	5.9			

Statistical analyses

No statistical analyses for this end point

Secondary: Change From Baseline Over Two Years in EDSS Total Score

End point title	Change From Baseline Over Two Years in EDSS Total Score

End point description:

EDSS was based on a standardized neurological exam and focuses on symptoms that commonly occur in MS. Total scores range from 0.0 (normal) to 10.0 (death due to MS). A negative change from Baseline indicates a decrease in disability. Here, 'n' signifies those subjects who were evaluable at the specified time point.

End point type	Secondary

End point timeframe:

Baseline, Visit 2 (6 months) Visit 4 (12 months), Visit 6 (18 months), End of Study (24 months or ET)

End point values	BG00012 Safety			
Subject group type	Subject analysis set			
Number of subjects analysed	217			
Units: score on a scale				
arithmetic mean (standard deviation)				
Baseline (n=217)	1.98 (± 1.17)			
Change from Baseline at Visit 2 (n=195)	-0.01 (± 0.50)			
Change from Baseline at Visit 4 (n=184)	-0.09 (± 0.60)			
Change from Baseline at Visit 6 (n=167)	-0.11 (± 0.63)			
Change from Baseline at End of study/ET (n=196)	-0.04 (± 0.68)			

Statistical analyses

No statistical analyses for this end point

Secondary: Median Time to 6-Month Sustained Progression of Disability Over Two Years

End point title	Median Time to 6-Month Sustained Progression of Disability Over Two Years

End point description:

Time to disability progression was defined as the time from the date of the screening visit to the date of 6-month sustained progression of disability evaluated by the EDSS. EDSS is based on a standardized neurological exam and focuses on symptoms that commonly occur in MS. Total scores range from 0.0 (normal) to 10.0 (death due to MS). Subjects without disability progression were considered censored at the date of the last assessment performed.

End point type	Secondary

End point timeframe:

Baseline, End of Study (24 months)

End point values	BG00012 Intent to Treat (ITT)			
Subject group type	Subject analysis set			
Number of subjects analysed	0[3]			
Units: days				
median (confidence interval 95%)	(to)			

Notes:

[3] - The median time to first relapse was not estimable because of the low number of events (< 10%)..

Statistical analyses

No statistical analyses for this end point

Secondary: Correlation Between Age and Demographic and Clinical Characteristics (Spearman Rank Order Correlation Coefficient) at Two Years

End point title	Correlation Between Age and Demographic and Clinical Characteristics (Spearman Rank Order Correlation Coefficient) at Two Years

End point description:

The Spearman Correlation Coefficient (CC) is a non-parametric measure of the correlation between 2 variables, giving a value between +1 (total positive correlation) and −1 (total negative correlation). CCs were determined for demographic characteristics including age (in years) and the number of years of schooling; clinical characteristics including the number of relapses in the year preceding enrollment in the study, time (in months) from MS diagnosis to study enrollment, EDSS total score at baseline; and patient reported outcomes at the time of initiation of BG00012 including total scores on Modified Fatigue Impact Scale (MFIS), Montgomery and Asberg Depression Rating Scale (MADRS), Environmental Status Scale (ESS) at baseline, and the EQ-5D Health Survey Visual Analog Scale (VAS) score (in millimeters). Here, 'n' signifies those subjects who were evaluable for that characteristic.

End point type	Secondary

End point timeframe:

End of Study (24 months)

End point values	BG00012 Intent to Treat (ITT)			
Subject group type	Subject analysis set			
Number of subjects analysed	217			
Units: correlation coefficient				
number (not applicable)				
Years of schooling (n=215)	-0.02391			
Number of relapses preceding enrollment (n=217)	-0.12023			
Months from MS diagnosis to enrollment (n=217)	0.44149			
MFIS total score at baseline (n=210)	0.26667			
MADRS total score at baseline (n=211)	0.13773			
ESS total score at baseline (n=211)	0.17740			
EDSS total score at baseline (n=217)	0.31757			
EQ-5D Health Survey VAS score (n=211)	-0.22583			

Statistical analyses

No statistical analyses for this end point

Secondary: Correlation Between Number of Years of Schooling and Demographic and Clinical Characteristics (Spearman Rank Order Correlation Coefficient) at Two Years

End point title	Correlation Between Number of Years of Schooling and Demographic and Clinical Characteristics (Spearman Rank Order Correlation Coefficient) at Two Years

End point description:

The Spearman correlation coefficient (CC) is a non-parametric measure of the correlation (dependence) between 2 variables, giving a value between +1 (total positive correlation) and −1 (total negative correlation). CCs were determined for demographic characteristics including age (in years) and the number of years of schooling; clinical characteristics including the number of relapses in the year preceding enrollment in the study, time (in months) from MS diagnosis to study enrollment, and EDSS total score at baseline; and patient reported outcomes at the time of initiation of BG00012 including total scores on the MFIS, the MADRS, and the ESS at baseline and the EQ-5D Health Survey VAS score (in millimeters). Here, 'n' signifies those subjects who were evaluable for that characteristic.

End point type	Secondary

End point timeframe:

End of Study (24 months)

End point values	BG00012 Intent to Treat (ITT)			
Subject group type	Subject analysis set			
Number of subjects analysed	215			
Units: correlation coefficient				
number (not applicable)				
Age (n=215)	-0.02391			
Number of relapses preceding enrollment (n=215)	0.11535			
Months from MS diagnosis to enrollment (n=215)	-0.03985			
MFIS total score at baseline (n=209)	-0.15274			
MADRS total score at baseline (n=210)	-0.08234			
ESS total score at baseline (n=210)	-0.10690			
EDSS total score at baseline (n=215)	-0.18921			
EQ-5D Health Survey VAS score (n=210)	0.06991			

Statistical analyses

No statistical analyses for this end point

Secondary: Correlation Between Number of Relapses in the Year Preceding Study Enrollment and Demographic and Clinical Characteristics (Spearman Rank Order Correlation Coefficient) at Two Years

End point title	Correlation Between Number of Relapses in the Year Preceding Study Enrollment and Demographic and Clinical Characteristics (Spearman Rank Order Correlation Coefficient) at Two Years

End point description:

The Spearman correlation coefficient (CC) is a non-parametric measure of the correlation (dependence) between 2 variables, giving a value between +1 (total positive correlation) and −1 (total negative correlation). CCs were determined for demographic characteristics including age (in years) and the number of years of schooling; clinical characteristics including the number of relapses in the year preceding enrollment in the study, time (in months) from MS diagnosis to study enrollment, and EDSS total score at baseline; and patient reported outcomes at the time of initiation of BG00012 including total scores on the MFIS, the MADRS, and the ESS at baseline and the EQ-5D Health Survey VAS score (in millimeters). Here, 'n' signifies those subjects who were evaluable for that characteristic.

End point type	Secondary

End point timeframe:

End of Study (24 months)

End point values	BG00012 Intent to Treat (ITT)			
Subject group type	Subject analysis set			
Number of subjects analysed	217			
Units: correlation coefficient				
number (not applicable)				
Age (n=217)	-0.12023			
Years of schooling (n=215)	0.11535			

Months from MS diagnosis to enrollment (n=217)	-0.01703			
MFIS total score at baseline (n=210)	0.07876			
MADRS total score at baseline (n=211)	-0.04768			
ESS total score at baseline (n=211)	0.02373			
EDSS total score at baseline (n=217)	0.10473			
EQ-5D Health Survey VAS score (n=211)	-0.08656			

Statistical analyses

No statistical analyses for this end point

Secondary: Correlation Between Time From MS Diagnosis to Study Enrollment and Demographic and Clinical Characteristics (Spearman Rank Order Correlation Coefficient) at Two Years

End point title	Correlation Between Time From MS Diagnosis to Study Enrollment and Demographic and Clinical Characteristics (Spearman Rank Order Correlation Coefficient) at Two Years

End point description:

The Spearman correlation coefficient (CC) is a non-parametric measure of the correlation (dependence) between 2 variables, giving a value between +1 (total positive correlation) and −1 (total negative correlation). CCs were determined for demographic characteristics including age (in years) and the number of years of schooling; clinical characteristics including the number of relapses in the year preceding enrollment in the study, time (in months) from MS diagnosis to study enrollment, and EDSS total score at baseline; and patient reported outcomes at the time of initiation of BG00012 including total scores on the MFIS, the MADRS, and the ESS at baseline and the EQ-5D Health Survey VAS score (in millimeters). Here, 'n' signifies those subjects who were evaluable for that characteristic.

End point type	Secondary

End point timeframe:

End of Study (24 months)

End point values	BG00012 Intent to Treat (ITT)			
Subject group type	Subject analysis set			
Number of subjects analysed	217			
Units: correlation coefficient				
number (not applicable)				
Age (n=217)	0.44149			
Years of schooling (n=215)	-0.03985			
Number of relapses preceding enrollment (n=217)	-0.01703			
MFIS total score at baseline (n=210)	0.22082			
MADRS total score at baseline (n=211)	0.05382			
ESS total score at baseline (n=211)	0.16246			
EDSS total score at baseline (n=217)	0.23126			
EQ-5D Health Survey VAS score (n=211)	-0.28059			

Statistical analyses

No statistical analyses for this end point

Secondary: Correlation Between MFIS Total Score at Baseline and Demographic and Clinical Characteristics (Spearman Rank Order Correlation Coefficient) at Two Years

End point title	Correlation Between MFIS Total Score at Baseline and Demographic and Clinical Characteristics (Spearman Rank Order Correlation Coefficient) at Two Years

End point description:

The Spearman correlation coefficient (CC) is a non-parametric measure of the correlation (dependence) between 2 variables, giving a value between +1 (total positive correlation) and −1 (total negative correlation). CCs were determined for demographic characteristics including age (in years) and the number of years of schooling; clinical characteristics including the number of relapses in the year preceding enrollment in the study, time (in months) from MS diagnosis to study enrollment, and EDSS total score at baseline; and patient reported outcomes at the time of initiation of BG00012 including total scores on the MFIS, the MADRS, and the ESS at baseline and the EQ-5D Health Survey VAS score (in millimeters). Here, 'n' signifies those subjects who were evaluable for that characteristic.

End point type	Secondary

End point timeframe:

End of Study (24 months)

End point values	BG00012 Intent to Treat (ITT)			
Subject group type	Subject analysis set			
Number of subjects analysed	210			
Units: correlation coefficient				
number (not applicable)				
Age (n=210)	0.26667			
Years of schooling (n=209)	-0.15274			
Number of relapses preceding enrollment (n=210)	0.07876			
Months from MS diagnosis to enrollment (n=210)	0.22082			
MADRS total score at baseline (n=210)	0.57165			
ESS total score at baseline (n=210)	0.66357			
EDSS total score at baseline (n=210)	0.43232			
EQ-5D Health Survey VAS score (n=210)	-0.56370			

Statistical analyses

No statistical analyses for this end point

Secondary: Correlation Between MADRS Total Score at Baseline and Demographic and Clinical Characteristics (Spearman Rank Order Correlation Coefficient) at Two Years

End point title	Correlation Between MADRS Total Score at Baseline and Demographic and Clinical Characteristics (Spearman Rank Order Correlation Coefficient) at Two Years

End point description:

The Spearman correlation coefficient (CC) is a non-parametric measure of the correlation (dependence) between 2 variables, giving a value between +1 (total positive correlation) and −1 (total negative correlation). CCs were determined for demographic characteristics including age (in years) and the number of years of schooling; clinical characteristics including the number of relapses in the year preceding enrollment in the study, time (in months) from MS diagnosis to study enrollment, and EDSS total score at baseline; and patient reported outcomes at the time of initiation of BG00012 including total scores on the MFIS, the MADRS, and the ESS at baseline and the EQ-5D Health Survey VAS score (in millimeters). Here, 'n' signifies those subjects who were evaluable for that characteristic.

End point type	Secondary

End point timeframe:

End of Study (24 months)

End point values	BG00012 Intent to Treat (ITT)			
Subject group type	Subject analysis set			
Number of subjects analysed	211			
Units: correlation coefficient				
number (not applicable)				
Age (n=211)	0.13773			
Years of schooling (n=210)	-0.08234			
Number of relapses preceding enrollment (n=211)	-0.04768			
Months from MS diagnosis to enrollment (n=211)	0.05382			
MFIS total score at baseline (n=210)	0.57165			
ESS total score at baseline (n=211)	0.46093			
EDSS total score at baseline (n=211)	0.33939			
EQ-5D Health Survey VAS score (n=211)	-0.35464			

Statistical analyses

No statistical analyses for this end point

Secondary: Correlation Between ESS Total Score at Baseline and Demographic and Clinical Characteristics (Spearman Rank Order Correlation Coefficient) at Two Years

End point title	Correlation Between ESS Total Score at Baseline and Demographic and Clinical Characteristics (Spearman Rank Order Correlation Coefficient) at Two Years

End point description:

The Spearman correlation coefficient (CC) is a non-parametric measure of the correlation (dependence)

between 2 variables, giving a value between +1 (total positive correlation) and −1 (total negative correlation). CCs were determined for demographic characteristics including age (in years) and the number of years of schooling; clinical characteristics including the number of relapses in the year preceding enrollment in the study, time (in months) from MS diagnosis to study enrollment, and EDSS total score at baseline; and patient reported outcomes at the time of initiation of BG00012 including total scores on the MFIS, the MADRS, and the ESS at baseline and the EQ-5D Health Survey VAS score (in millimeters). Here, 'n' signifies those subjects who were evaluable for that characteristic.

End point type	Secondary

End point timeframe:

End of Study (24 months)

End point values	BG00012 Intent to Treat (ITT)			
Subject group type	Subject analysis set			
Number of subjects analysed	211			
Units: correlation coefficient				
number (not applicable)				
Age (n=211)	0.17740			
Years of schooling (n=210)	-0.10690			
Number of relapses preceding enrollment (n=211)	0.02373			
Months from MS diagnosis to enrollment (n=211)	0.16246			
MFIS total score at baseline (n=210)	0.66357			
MADRS total score at baseline (n=211)	0.46093			
EDSS total score at baseline (n=211)	0.43068			
EQ-5D Health Survey VAS score (n=211)	-0.42919			

Statistical analyses

No statistical analyses for this end point

Secondary: Correlation Between EDSS Total Score at Baseline and Demographic and Clinical Characteristics (Spearman Rank Order Correlation Coefficient) at Two Years

End point title	Correlation Between EDSS Total Score at Baseline and Demographic and Clinical Characteristics (Spearman Rank Order Correlation Coefficient) at Two Years

End point description:

The Spearman correlation coefficient (CC) is a non-parametric measure of the correlation (dependence) between 2 variables, giving a value between +1 (total positive correlation) and −1 (total negative correlation). CCs were determined for demographic characteristics including age (in years) and the number of years of schooling; clinical characteristics including the number of relapses in the year preceding enrollment in the study, time (in months) from MS diagnosis to study enrollment, and EDSS total score at baseline; and patient reported outcomes at the time of initiation of BG00012 including total scores on the MFIS, the MADRS, and the ESS at baseline and the EQ-5D Health Survey VAS score (in millimeters). Here, 'n' signifies those subjects who were evaluable for that characteristic.

End point type	Secondary

End point timeframe:

End of Study (24 months)

End point values	BG00012 Intent to Treat (ITT)			
Subject group type	Subject analysis set			
Number of subjects analysed	211			
Units: correlation coefficient				
number (not applicable)				
Age (n=217)	0.31757			
Years of schooling (n=215)	-0.18921			
Number of relapses preceding enrollment (n=217)	0.10473			
Months from MS diagnosis to enrollment (n=217)	0.23126			
MFIS total score at baseline (n=210)	0.43232			
MADRS total score at baseline (n=211)	0.33939			
ESS total score at baseline (n=211)	0.43068			
EQ-5D Health Survey VAS score (n=211)	-0.30822			

Statistical analyses

No statistical analyses for this end point

Secondary: Correlation Between EQ-5D Health Survey VAS Score at Baseline and Demographic and Clinical Characteristics (Spearman Rank Order Correlation Coefficient) at Two Years

End point title	Correlation Between EQ-5D Health Survey VAS Score at Baseline and Demographic and Clinical Characteristics (Spearman Rank Order Correlation Coefficient) at Two Years

End point description:

The Spearman Correlation Coefficient (CC) is a non-parametric measure of the correlation between 2 variables, giving a value between +1 (total positive correlation) and −1 (total negative correlation). CCs were determined for demographic characteristics including age (in years) and the number of years of schooling; clinical characteristics including the number of relapses in the year preceding enrollment in the study, time (in months) from MS diagnosis to study enrollment, EDSS total score at baseline; and patient reported outcomes at the time of initiation of BG00012 including total scores on the MFIS, the MADRS, and the ESS at baseline, and the EQ-5D Health Survey VAS score (in millimeters). Here, 'n' signifies those subjects who were evaluable for that characteristic.

End point type	Secondary

End point timeframe:

End of Study (24 months)

End point values	BG00012 Intent to Treat (ITT)			
Subject group type	Subject analysis set			
Number of subjects analysed	211			
Units: correlation coefficient				
number (not applicable)				
Age (n=211)	-0.22583			
Years of schooling (n=210)	0.06991			
Number of relapses preceding enrollment (n=211)	-0.08656			
Months from MS diagnosis to enrollment (n=211)	-0.28059			
MFIS total score at baseline (n=210)	-0.56370			
MADRS total score at baseline (n=211)	-0.35464			
ESS total score at baseline (n=211)	-0.42919			
EDSS total score at baseline (n=211)	-0.30822			

Statistical analyses

No statistical analyses for this end point

Secondary: Change From Baseline in Fatigue Over Two Years as Measured by the MFIS

End point title	Change From Baseline in Fatigue Over Two Years as Measured by the MFIS

End point description:

The MFIS was a modified form of the Fatigue Impact Scale based on items derived from interviews with subjects with MS concerning how fatigue impacts their lives. This instrument provided an assessment of the effects of fatigue in terms of physical, cognitive, and psychosocial functioning. The full-length MFIS consisted of 21 items scored 0-4 for a total score between 0 (no fatigue) and 84 (severe fatigue). A negative change from Baseline indicates a decrease in fatigue. Here, 'n' signifies those subjects who were evaluable at the specified time point.

End point type	Secondary

End point timeframe:

Baseline, Visit 2 (6 months), Visit 4 (12 months), Visit 6 (18 months), End of Study (24 months or ET)

End point values	BG00012 Intent to Treat (ITT)			
Subject group type	Subject analysis set			
Number of subjects analysed	217			
Units: score on a scale				
least squares mean (confidence interval 95%)				
Baseline	23.5893 (20.3217 to 26.8570)			
Change from Baseline at Visit 2	-3.3243 (-4.9106 to -1.7379)			

Change from Baseline at Visit 4	-3.7791 (-5.3739 to -2.1842)			
Change from Baseline at Visit 6	-3.6647 (-5.3241 to -2.0053)			
Change from Baseline at End of Study/ET	-3.3377 (-4.9588 to -1.7167)			

Statistical analyses

No statistical analyses for this end point

Secondary: Change From Baseline in Depression Over Two Years as Measured by the Self-rating MADRS

End point title	Change From Baseline in Depression Over Two Years as Measured by the Self-rating MADRS

End point description:

The self-rating MADRS instrument had nine questions that assessed a subject's mood, feelings of unease, sleep, appetite, ability to concentrate, initiative, emotional involvement, pessimism, and zest for life. Each question was rated on a 0 to 3 scale, with the total score ranging from 0 points (no depression) to 27 points (severe depression). A negative change from Baseline indicates a decrease in depression. Here, 'n' signifies those subjects who were evaluable at the specified time point.

End point type	Secondary

End point timeframe:

Baseline, Visit 2 (6 months), Visit 4 (12 months), Visit 6 (18 months), End of Study (24 months or ET)

End point values	BG00012 Intent to Treat (ITT)			
Subject group type	Subject analysis set			
Number of subjects analysed	217			
Units: score on a scale				
least squares mean (confidence interval 95%)				
Baseline	7.8522 (6.5035 to 9.2008)			
Change from Baseline at Visit 2	0.1298 (-0.6277 to 0.8873)			
Change from Baseline at Visit 4	-0.9336 (-1.7026 to -0.1646)			
Change from Baseline at Visit 6	-1.0239 (-1.8236 to -0.2242)			
Change from Baseline at End of Study/ET	-1.3024 (-2.0807 to -0.5240)			

Statistical analyses

No statistical analyses for this end point

Secondary: Change From Baseline in Handicap Over Two Years as Measured by the ESS

End point title	Change From Baseline in Handicap Over Two Years as Measured by the ESS

End point description:

The ESS is used to quickly evaluate a subject for handicap. It was derived from a measure of socio-economic status. It consists of seven parameters: (1) actual work status, (2) financial and economic status, (3) personal residence or home, (4) personal assistance required, (5) transportation, (6) community services, (7) social activity. Each parameter has a single score from minimum 0 to maximum 5. The ESS total score is the sum of the points for all 7 parameters: minimum score: 0 (no handicap); maximum score: 35 (maximum handicap). A negative change from Baseline indicates a decrease in handicap. Here, 'n' signifies those subjects who were evaluable at the specified time point.

End point type	Secondary

End point timeframe:

Baseline, Visit 2 (6 months), Visit 4 (12 months), Visit 6 (18 months), End of Study (24 months or ET)

End point values	BG00012 Intent to Treat (ITT)			
Subject group type	Subject analysis set			
Number of subjects analysed	217			
Units: score on a scale				
least squares mean (confidence interval 95%)				
Baseline	2.2908 (1.6278 to 2.9538)			
Change from Baseline at Visit 2	-0.2500 (-0.5892 to 0.08910)			
Change from Baseline at Visit 4	-0.4500 (-0.7937 to -0.1063)			
Change from Baseline at Visit 6	-0.4065 (-0.7677 to -0.04535)			
Change from Baseline at End of Study/ET	-0.5736 (-0.9242 to -0.2231)			

Statistical analyses

No statistical analyses for this end point

Secondary: Change From Baseline in Quality of Life (QoL) Over Two Years as Measured by the EQ-5D Health Survey

End point title	Change From Baseline in Quality of Life (QoL) Over Two Years as Measured by the EQ-5D Health Survey

End point description:

The EQ-5D is a widely-used survey instrument for measuring economic preferences for health states and quality of life. It is a self-administered questionnaire consisting of questions pertaining to 5 specific health states (mobility, self-care, pain, usual activities, anxiety). The subject is asked to indicate his/her health state at one of three levels: no problems, some problems, or extreme problems. Health state values are used to generate an index score, with a minimum score of 0 (death) and a maximum score of 1 (full health). A positive change from Baseline indicates an increase in QoL. Here, 'n' signifies those subjects who were evaluable at the specified time point.

End point type	Secondary

End point timeframe:

Baseline, Visit 2 (6 months), Visit 4 (12 months), Visit 6 (18 months), End of Study (24 months or ET)

End point values	BG00012 Intent to Treat (ITT)			
Subject group type	Subject analysis set			
Number of subjects analysed	217			
Units: score on a scale				
least squares mean (confidence interval 95%)				
Baseline	0.7550 (0.7207 to 0.7892)			
Change from Baseline at Visit 2	0.04517 (0.02264 to 0.06770)			
Change from Baseline at Visit 4	0.04903 (0.02621 to 0.07185)			
Change from Baseline at Visit 6	0.05276 (0.02903 to 0.07649)			
Change from Baseline at End of Study/ET	0.04516 (0.02206 to 0.06827)			

Statistical analyses

No statistical analyses for this end point

Adverse events

Adverse events information	
Timeframe for reporting adverse events: 24 months ± 5 days	
Assessment type	Systematic

Dictionary used	
Dictionary name	MedDRA
Dictionary version	20.0

Reporting groups	
Reporting group title	BG00012
Reporting group description: Subjects with RRMS received 240 milligrams (mg) BG00012 twice daily for 24 months.	

Serious adverse events	BG00012		
Total subjects affected by serious adverse events			
subjects affected / exposed	11 / 217 (5.07%)		
number of deaths (all causes)	0		
number of deaths resulting from adverse events	0		
Neoplasms benign, malignant and unspecified (incl cysts and polyps)			
Hepatic Adenoma			
subjects affected / exposed	1 / 217 (0.46%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Intraductal Papilloma Of Breast			
subjects affected / exposed	1 / 217 (0.46%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Injury, poisoning and procedural complications			
Accident			
subjects affected / exposed	1 / 217 (0.46%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Ankle Fracture			

subjects affected / exposed	1 / 217 (0.46%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Immune system disorders			
Hypersensitivity			
subjects affected / exposed	1 / 217 (0.46%)		
occurrences causally related to treatment / all	1 / 1		
deaths causally related to treatment / all	0 / 0		
Gastrointestinal disorders			
Small Intestinal Perforation			
subjects affected / exposed	1 / 217 (0.46%)		
occurrences causally related to treatment / all	1 / 1		
deaths causally related to treatment / all	0 / 0		
Hepatobiliary disorders			
Cholelithiasis			
subjects affected / exposed	1 / 217 (0.46%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Skin and subcutaneous tissue disorders			
Angioedema			
subjects affected / exposed	1 / 217 (0.46%)		
occurrences causally related to treatment / all	1 / 1		
deaths causally related to treatment / all	0 / 0		
Renal and urinary disorders			
Renal Colic			
subjects affected / exposed	1 / 217 (0.46%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Infections and infestations			
Bronchopulmonary Aspergillosis			
subjects affected / exposed	1 / 217 (0.46%)		
occurrences causally related to treatment / all	1 / 1		
deaths causally related to treatment / all	0 / 0		
Diverticulitis			

subjects affected / exposed	1 / 217 (0.46%)		
occurrences causally related to treatment / all	1 / 1		
deaths causally related to treatment / all	0 / 0		
Herpes Zoster			
subjects affected / exposed	1 / 217 (0.46%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Pneumonia			
subjects affected / exposed	1 / 217 (0.46%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Pyelonephritis			
subjects affected / exposed	1 / 217 (0.46%)		
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	126 / 217 (58.06%)		
Vascular disorders			
Flushing			
subjects affected / exposed	91 / 217 (41.94%)		
occurrences (all)	119		
Nervous system disorders			
Headache			
subjects affected / exposed	11 / 217 (5.07%)		
occurrences (all)	11		
Blood and lymphatic system disorders			
Lymphopenia			
subjects affected / exposed	12 / 217 (5.53%)		
occurrences (all)	12		
General disorders and administration site conditions			

Asthenia subjects affected / exposed occurrences (all)	15 / 217 (6.91%) 15		
Gastrointestinal disorders Diarrhoea subjects affected / exposed occurrences (all) Gastrointestinal Disorder subjects affected / exposed occurrences (all) Abdominal Pain subjects affected / exposed occurrences (all)	 17 / 217 (7.83%) 17 11 / 217 (5.07%) 12 18 / 217 (8.29%) 21		
Skin and subcutaneous tissue disorders Rash subjects affected / exposed occurrences (all)	 19 / 217 (8.76%) 22		
Infections and infestations Influenza subjects affected / exposed occurrences (all) Urinary Tract Infection subjects affected / exposed occurrences (all)	 20 / 217 (9.22%) 22 12 / 217 (5.53%) 14		

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

Date	Amendment
10 May 2016	The primary reasons for this amendment to Protocol ITA-BGT-12-10389 are: * The schedule of hematology parameters has been aligned with the monitoring (i.e. every three months) recommended in the SmPC of the investigational product. * The number of subjects to be enrolled in the study has been better specified (changed from 220 to 221). * A new section with subparagraphs has been added to define the procedures for modification of dose and of treatment schedule for abnormal laboratory values and for abnormal lymphocyte count. * The section on Withdrawal of Subjects from Study Treatment and/or the Study has been updated to better reflect the procedures for modification of dose and of treatment schedule for abnormal laboratory values and for abnormal lymphocyte count.

Notes:

Interruptions (globally)

Were there any global interruptions to the trial? No

Limitations and caveats

None reported