



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 | 04 September 2018 |

Results information

| | |
|--------------------------------|-------------------|
| Result version number | v2 (current) |
| This version publication date | 21 September 2019 |
| First version publication date | 19 June 2016 |
| Version creation reason | |

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 | Final |
| Date of interim/final analysis | 04 September 2018 |
| Is this the analysis of the primary completion data? | Yes |
| Primary completion date | 15 June 2015 |
| Global end of trial reached? | Yes |
| Global end of trial date | 04 September 2018 |
| Was the trial ended prematurely? | 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 | Yes |
| Long term follow-up rationale | Safety |
| Long term follow-up duration | 54 Months |
| 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 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) | 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 twice a day (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) |
| Is this the baseline period? | Yes |
| Allocation method | Randomised - controlled |
| Blinding used | Double blind |
| Roles blinded | Subject, Investigator |

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 |
| Adverse event, non-fatal | 2 | 1 |
| Not specified | - | 4 |

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 in the BG00012 240 mg BID arm was not dosed and is not included.

[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: The number of subjects who completed study drug is included for reference. 1 subject did not complete study drug but did complete the study.

Period 2

| | |
|------------------------------|---------------------------------------|
| Period 2 title | Part II (Open-label Treatment Period) |
| Is this the baseline period? | No |
| Allocation method | Not applicable |
| Blinding used | Not blinded |

Arms

| | |
|------------------------------|--|
| Are arms mutually exclusive? | Yes |
| Arm title | Part II: Placebo/BG00012 240 mg BID (Switchers): |

Arm description:

"PBO/BG12" – Subjects who received placebo in Part I before receiving BG00012 240 milligram (mg) BID in Part II for up to 4.5 years.

| | |
|----------|--------------|
| 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.

| | |
|------------------|---|
| Arm title | Part II: BG00012 240 mg BID/BG00012 240 mg BID (Continuers) |
|------------------|---|

Arm description:

"BG12/BG12" - Subjects who received BG00012 240 mg BID in Part I, continued receiving BG00012 in Part II for up to 4.5 years.

| | |
|--|-----------------------------------|
| 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 2 | Part II: Placebo/BG00012 240 mg BID (Switchers): | Part II: BG00012 240 mg BID/BG00012 240 mg BID (Continuers) |
|---------------------------------------|---|--|
| Started | 108 | 105 |
| Completed | 0 | 2 |
| Not completed | 108 | 103 |
| Adverse event, non-fatal | 9 | 4 |
| Investigator decision | 2 | 3 |
| Lost to follow-up | 1 | - |
| Reason not specified | 83 | 82 |
| Consent withdrawn | 13 | 14 |

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). | |
| Reporting group title | Part II: Placebo/BG00012 240 mg BID (Switchers): |
| Reporting group description: "PBO/BG12" – Subjects who received placebo in Part I before receiving BG00012 240 milligram (mg) BID in Part II for up to 4.5 years. | |
| Reporting group title | Part II: BG00012 240 mg BID/BG00012 240 mg BID (Continuers) |
| Reporting group description: "BG12/BG12" - Subjects who received BG00012 240 mg BID in Part I, continued receiving BG00012 in Part II for up to 4.5 years. | |
| 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. The Intent-to-Treat (ITT) population was defined as all randomized subjects who received at least 1 dose of study treatment (BG00012 or placebo). | |
| 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.

Primary: Number of Subjects with Treatment-Emergent Adverse Events (TEAEs): Part II

| | |
|-----------------|---|
| End point title | Number of Subjects with Treatment-Emergent Adverse Events (TEAEs): Part II ^[3] |
|-----------------|---|

End point description:

A treatment-emergent AE was defined as an AE that started or worsened on or after the date of the first dose of study treatment. The Safety population: analyses of the total BG00012 240 mg BID experience combined all data (Parts I and II) from subjects who received BG00012 in both Parts I and II with Part II only data from subjects who received BG00012 in Part II of the study after switching from placebo (in Part I).

| | |
|----------------------|---------|
| End point type | Primary |
| End point timeframe: | |
| Up to 4.5 Years | |

Notes:

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

Justification: No statistical analyses are reported for this endpoint.

| End point values | Part II: Placebo/BG00012 240 mg BID (Switchers): | Part II: BG00012 240 mg mg BID/BG00012 240 mg BID (Continuers) | | |
|-----------------------------|--|--|--|--|
| Subject group type | Reporting group | Reporting group | | |
| Number of subjects analysed | 108 | 105 | | |
| Units: subjects | | | | |
| number (not applicable) | 99 | 98 | | |

Statistical analyses

No statistical analyses for this end point

Primary: Number of Subjects with Treatment-Emergent Serious Adverse Events (SAEs): Part II

| | |
|-----------------|--|
| End point title | Number of Subjects with Treatment-Emergent Serious Adverse Events (SAEs): Part II ^[4] |
|-----------------|--|

End point description:

A SAE is any untoward medical occurrence that at any dose: results in death, in the view of the Investigator, places the subject at immediate risk of death, requires inpatient hospitalization or prolongation of existing hospitalization, results in persistent or significant disability/incapacity, or results in a congenital anomaly/birth defect. The Safety population: analyses of the total BG00012 240 mg BID experience combined all data (Parts I and II) from subjects who received BG00012 in both Parts I and II with Part II only data from subjects who received BG00012 in Part II of the study after switching from placebo (in Part I).

| | |
|----------------|---------|
| End point type | Primary |
|----------------|---------|

End point timeframe:

Up to 4.5 Years

Notes:

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

Justification: No statistical analyses are reported for this endpoint.

| End point values | Part II: Placebo/BG00012 240 mg BID (Switchers): | Part II: BG00012 240 mg mg BID/BG00012 240 mg BID (Continuers) | | |
|-----------------------------|--|--|--|--|
| Subject group type | Reporting group | Reporting group | | |
| Number of subjects analysed | 108 | 105 | | |
| Units: subjects | | | | |
| number (not applicable) | 28 | 28 | | |

Statistical analyses

Primary: Number of Subjects with Clinically Significant Laboratory Values Reported as Adverse Events: Part II

| | |
|---|---|
| End point title | Number of Subjects with Clinically Significant Laboratory Values Reported as Adverse Events: Part II ^[5] |
| End point description: | |
| Clinical laboratory evaluations included haematology, blood chemistry, lipid profile, and urinalysis. The Safety population: analyses of the total BG00012 240 mg BID experience combined all data (Parts I and II) from subjects who received BG00012 in both Parts I and II with Part II only data from subjects who received BG00012 in Part II of the study after switching from placebo (in Part I). | |
| End point type | Primary |
| End point timeframe: | |
| Up to 4.5 Years | |

Notes:

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

Justification: No statistical analyses are reported for this endpoint.

| End point values | Part II: Placebo/BG00012 240 mg BID (Switchers): | Part II: BG00012 240 mg BID/BG00012 240 mg BID (Continuers) | | |
|--------------------------------------|---|--|--|--|
| Subject group type | Reporting group | Reporting group | | |
| Number of subjects analysed | 108 | 105 | | |
| Units: subjects | | | | |
| number (not applicable) | | | | |
| LYMPHOCYTE COUNT DECREASED | 6 | 9 | | |
| ALANINE AMINOTRANSFERASE INCREASED | 5 | 8 | | |
| ASPARTATE AMINOTRANSFERASE INCREASED | 4 | 5 | | |
| BLOOD GLUCOSE INCREASED | 0 | 3 | | |
| GAMMA-GLUTAMYLTRANSFERASE INCREASED | 2 | 3 | | |
| WHITE BLOOD CELL COUNT DECREASED | 4 | 3 | | |
| BLOOD URIC ACID INCREASED | 0 | 2 | | |
| BLOOD BILIRUBIN INCREASED | 0 | 1 | | |
| BLOOD CHOLESTEROL INCREASED | 0 | 1 | | |
| BLOOD TRIGLYCERIDES INCREASED | 0 | 1 | | |
| HAEMATOCRIT DECREASED | 0 | 1 | | |
| HAEMOGLOBIN DECREASED | 0 | 1 | | |
| LIVER FUNCTION TEST ABNORMAL | 1 | 1 | | |
| NEUTROPHIL COUNT DECREASED | 1 | 1 | | |
| PROTEIN URINE | 1 | 1 | | |
| WHITE BLOOD CELLS URINE POSITIVE | 0 | 1 | | |
| BETA 2 MICROGLOBULIN INCREASED | 1 | 0 | | |
| BLOOD ALKALINE PHOSPHATASE INCREASED | 1 | 0 | | |
| BLOOD URINE PRESENT | 1 | 0 | | |
| EOSINOPHIL COUNT INCREASED | 1 | 0 | | |
| HEPATIC ENZYME INCREASED | 1 | 0 | | |

| | | | | |
|-----------------------------------|---|---|--|--|
| LOW DENSITY LIPOPROTEIN INCREASED | 1 | 0 | | |
| MEAN CELL VOLUME INCREASED | 1 | 0 | | |
| OCCULT BLOOD | 1 | 0 | | |
| OCCULT BLOOD POSITIVE | 1 | 0 | | |
| TRANSAMINASES INCREASED | 1 | 0 | | |
| URINARY CASTS | 1 | 0 | | |

Statistical analyses

No statistical analyses for this end point

Primary: Number of Subjects with Clinically Significant Changes in Vital Signs: Part II

| | |
|-----------------|---|
| End point title | Number of Subjects with Clinically Significant Changes in Vital Signs: Part II ^[6] |
|-----------------|---|

End point description:

Vital signs were examined to determine the incidence of clinically relevant abnormalities and include diastolic and systolic blood pressure, heart rate, and temperature. The Safety population: analyses of the total BG00012 240 mg BID experience combined all data (Parts I and II) from subjects who received BG00012 in both Parts I and II with Part II only data from subjects who received BG00012 in Part II of the study after switching from placebo (in Part I).

| | |
|----------------|---------|
| End point type | Primary |
|----------------|---------|

End point timeframe:

Up to 4.5 Years

Notes:

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

Justification: No statistical analyses are reported for this endpoint.

| End point values | Part II: Placebo/BG00012 240 mg BID (Switchers): | Part II: BG00012 240 mg mg BID/BG00012 240 mg BID (Continuers) | | |
|-----------------------------|---|---|--|--|
| Subject group type | Reporting group | Reporting group | | |
| Number of subjects analysed | 108 | 105 | | |
| Units: subjects | | | | |
| number (not applicable) | 0 | 0 | | |

Statistical analyses

No statistical analyses for this end point

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. The ITT population was defined as all randomized subjects who received at least 1 dose of study treatment (BG00012 or placebo).

| | |
|----------------------|-----------|
| 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 (\pm 10.7) | 2.6 (\pm 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. The ITT population was defined as all randomized subjects who received at least 1 dose of study treatment (BG00012 or placebo). |
| 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:

First dose of study treatment to the End of Study (Up to 4.5 Years)

| | |
|-----------------|------------|
| Assessment type | Systematic |
|-----------------|------------|

Dictionary used

| | |
|-----------------|--------|
| Dictionary name | MedDRA |
|-----------------|--------|

| | |
|--------------------|------|
| Dictionary version | 13.1 |
|--------------------|------|

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 title | Part II: Placebo/BG00012 240 mg BID (Switchers) |
|-----------------------|---|

Reporting group description:

"PBO/BG12" – Subjects who received placebo in Part I before receiving BG00012 240 milligram (mg) BID in Part II for up to 4.5 years.

| | |
|-----------------------|---|
| Reporting group title | Part II: BG00012 240 mg BID/BG00012 240 mg BID (Continuers) |
|-----------------------|---|

Reporting group description:

"BG12/BG12" – Subjects who received BG00012 240 mg BID in Part I, continued receiving BG00012 in Part II for up to 4.5 years.

| Serious adverse events | Part I Placebo | Part I BG00012 240 mg BID | Part II: Placebo/BG00012 240 mg BID (Switchers) |
|---|-------------------|---------------------------|---|
| Total subjects affected by serious adverse events | | | |
| subjects affected / exposed | 16 / 113 (14.16%) | 13 / 111 (11.71%) | 28 / 108 (25.93%) |
| number of deaths (all causes) | 0 | 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%) | 0 / 108 (0.00%) |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Pregnancy, puerperium and perinatal conditions | | | |
| Pregnancy | | | |

| | | | |
|---|-----------------|-----------------|-----------------|
| subjects affected / exposed | 0 / 113 (0.00%) | 0 / 111 (0.00%) | 1 / 108 (0.93%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 1 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Reproductive system and breast disorders | | | |
| Cervical dysplasia | | | |
| subjects affected / exposed | 0 / 113 (0.00%) | 0 / 111 (0.00%) | 1 / 108 (0.93%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 1 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Respiratory, thoracic and mediastinal disorders | | | |
| Pneumothorax | | | |
| subjects affected / exposed | 0 / 113 (0.00%) | 0 / 111 (0.00%) | 0 / 108 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Psychiatric disorders | | | |
| Anxiety | | | |
| subjects affected / exposed | 0 / 113 (0.00%) | 1 / 111 (0.90%) | 0 / 108 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Somatoform disorder | | | |
| subjects affected / exposed | 0 / 113 (0.00%) | 0 / 111 (0.00%) | 1 / 108 (0.93%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 1 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Suicide attempt | | | |
| subjects affected / exposed | 0 / 113 (0.00%) | 0 / 111 (0.00%) | 0 / 108 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Investigations | | | |
| Protein urine | | | |
| subjects affected / exposed | 0 / 113 (0.00%) | 0 / 111 (0.00%) | 0 / 108 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Injury, poisoning and procedural complications | | | |
| Alcohol poisoning | | | |

| | | | |
|---|-----------------|-----------------|-----------------|
| subjects affected / exposed | 0 / 113 (0.00%) | 0 / 111 (0.00%) | 0 / 108 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Clavicle fracture | | | |
| subjects affected / exposed | 0 / 113 (0.00%) | 0 / 111 (0.00%) | 0 / 108 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Drug toxicity | | | |
| subjects affected / exposed | 0 / 113 (0.00%) | 0 / 111 (0.00%) | 0 / 108 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Fall | | | |
| subjects affected / exposed | 0 / 113 (0.00%) | 0 / 111 (0.00%) | 0 / 108 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Hip fracture | | | |
| subjects affected / exposed | 0 / 113 (0.00%) | 0 / 111 (0.00%) | 0 / 108 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Humerus fracture | | | |
| subjects affected / exposed | 0 / 113 (0.00%) | 1 / 111 (0.90%) | 0 / 108 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Rib fracture | | | |
| subjects affected / exposed | 0 / 113 (0.00%) | 0 / 111 (0.00%) | 0 / 108 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Road traffic accident | | | |
| subjects affected / exposed | 0 / 113 (0.00%) | 1 / 111 (0.90%) | 0 / 108 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Tibia fracture | | | |

| | | | |
|---|-------------------|------------------|-------------------|
| subjects affected / exposed | 0 / 113 (0.00%) | 1 / 111 (0.90%) | 0 / 108 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Wrist fracture | | | |
| subjects affected / exposed | 0 / 113 (0.00%) | 0 / 111 (0.00%) | 0 / 108 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Cardiac disorders | | | |
| Acute myocardial infarction | | | |
| subjects affected / exposed | 0 / 113 (0.00%) | 0 / 111 (0.00%) | 0 / 108 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Atrial fibrillation | | | |
| subjects affected / exposed | 0 / 113 (0.00%) | 0 / 111 (0.00%) | 1 / 108 (0.93%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 1 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Myocardial infarction | | | |
| subjects affected / exposed | 0 / 113 (0.00%) | 0 / 111 (0.00%) | 0 / 108 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Nervous system disorders | | | |
| Epilepsy | | | |
| subjects affected / exposed | 0 / 113 (0.00%) | 0 / 111 (0.00%) | 0 / 108 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Multiple sclerosis relapse | | | |
| subjects affected / exposed | 16 / 113 (14.16%) | 10 / 111 (9.01%) | 18 / 108 (16.67%) |
| occurrences causally related to treatment / all | 2 / 22 | 1 / 15 | 0 / 29 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Optic neuritis | | | |
| subjects affected / exposed | 0 / 113 (0.00%) | 0 / 111 (0.00%) | 0 / 108 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Gastrointestinal disorders | | | |

| | | | |
|---|-----------------|-----------------|-----------------|
| Diarrhoea | | | |
| subjects affected / exposed | 0 / 113 (0.00%) | 0 / 111 (0.00%) | 1 / 108 (0.93%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 1 / 1 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Gastrointestinal disorder | | | |
| subjects affected / exposed | 0 / 113 (0.00%) | 0 / 111 (0.00%) | 1 / 108 (0.93%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 1 / 1 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Hepatobiliary disorders | | | |
| Cholelithiasis | | | |
| subjects affected / exposed | 0 / 113 (0.00%) | 0 / 111 (0.00%) | 0 / 108 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Renal and urinary disorders | | | |
| Hypertonic bladder | | | |
| subjects affected / exposed | 0 / 113 (0.00%) | 0 / 111 (0.00%) | 1 / 108 (0.93%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 1 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Microalbuminuria | | | |
| subjects affected / exposed | 0 / 113 (0.00%) | 0 / 111 (0.00%) | 1 / 108 (0.93%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 1 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Musculoskeletal and connective tissue disorders | | | |
| Arthralgia | | | |
| subjects affected / exposed | 0 / 113 (0.00%) | 0 / 111 (0.00%) | 0 / 108 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Arthritis | | | |
| subjects affected / exposed | 0 / 113 (0.00%) | 0 / 111 (0.00%) | 0 / 108 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Intervertebral disc disorder | | | |

| | | | |
|---|-----------------|-----------------|-----------------|
| subjects affected / exposed | 0 / 113 (0.00%) | 0 / 111 (0.00%) | 0 / 108 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Infections and infestations | | | |
| Appendicitis | | | |
| subjects affected / exposed | 0 / 113 (0.00%) | 0 / 111 (0.00%) | 1 / 108 (0.93%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 1 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Chronic tonsillitis | | | |
| subjects affected / exposed | 0 / 113 (0.00%) | 0 / 111 (0.00%) | 1 / 108 (0.93%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 1 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Cystitis | | | |
| subjects affected / exposed | 0 / 113 (0.00%) | 0 / 111 (0.00%) | 0 / 108 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Pelvic inflammatory disease | | | |
| subjects affected / exposed | 0 / 113 (0.00%) | 0 / 111 (0.00%) | 1 / 108 (0.93%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 1 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Pyelonephritis | | | |
| subjects affected / exposed | 0 / 113 (0.00%) | 1 / 111 (0.90%) | 0 / 108 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 2 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Urinary tract infection | | | |
| subjects affected / exposed | 0 / 113 (0.00%) | 0 / 111 (0.00%) | 1 / 108 (0.93%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 1 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Metabolism and nutrition disorders | | | |
| Type 2 diabetes mellitus | | | |
| subjects affected / exposed | 0 / 113 (0.00%) | 0 / 111 (0.00%) | 0 / 108 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |

| | | | |
|---|--|--|--|
| Serious adverse events | Part II: BG00012 240 mg BID/BG00012 240 mg BID (Continuers) | | |
| Total subjects affected by serious adverse events | | | |
| subjects affected / exposed | 28 / 105 (26.67%) | | |
| number of deaths (all causes) | 0 | | |
| number of deaths resulting from adverse events | | | |
| Neoplasms benign, malignant and unspecified (incl cysts and polyps) | | | |
| Fallopian tube cancer | | | |
| subjects affected / exposed | 0 / 105 (0.00%) | | |
| occurrences causally related to treatment / all | 0 / 0 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Pregnancy, puerperium and perinatal conditions | | | |
| Pregnancy | | | |
| subjects affected / exposed | 0 / 105 (0.00%) | | |
| occurrences causally related to treatment / all | 0 / 0 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Reproductive system and breast disorders | | | |
| Cervical dysplasia | | | |
| subjects affected / exposed | 0 / 105 (0.00%) | | |
| occurrences causally related to treatment / all | 0 / 0 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Respiratory, thoracic and mediastinal disorders | | | |
| Pneumothorax | | | |
| subjects affected / exposed | 1 / 105 (0.95%) | | |
| occurrences causally related to treatment / all | 0 / 1 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Psychiatric disorders | | | |
| Anxiety | | | |
| subjects affected / exposed | 0 / 105 (0.00%) | | |
| occurrences causally related to treatment / all | 0 / 0 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Somatoform disorder | | | |

| | | | |
|---|-----------------|--|--|
| subjects affected / exposed | 0 / 105 (0.00%) | | |
| occurrences causally related to treatment / all | 0 / 0 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Suicide attempt | | | |
| subjects affected / exposed | 1 / 105 (0.95%) | | |
| occurrences causally related to treatment / all | 0 / 1 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Investigations | | | |
| Protein urine | | | |
| subjects affected / exposed | 1 / 105 (0.95%) | | |
| occurrences causally related to treatment / all | 1 / 1 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Injury, poisoning and procedural complications | | | |
| Alcohol poisoning | | | |
| subjects affected / exposed | 1 / 105 (0.95%) | | |
| occurrences causally related to treatment / all | 0 / 1 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Clavicle fracture | | | |
| subjects affected / exposed | 1 / 105 (0.95%) | | |
| occurrences causally related to treatment / all | 0 / 1 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Drug toxicity | | | |
| subjects affected / exposed | 1 / 105 (0.95%) | | |
| occurrences causally related to treatment / all | 0 / 1 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Fall | | | |
| subjects affected / exposed | 3 / 105 (2.86%) | | |
| occurrences causally related to treatment / all | 0 / 3 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Hip fracture | | | |
| subjects affected / exposed | 1 / 105 (0.95%) | | |
| occurrences causally related to treatment / all | 0 / 1 | | |
| deaths causally related to treatment / all | 0 / 0 | | |

| | | | |
|---|-----------------|--|--|
| Humerus fracture | | | |
| subjects affected / exposed | 1 / 105 (0.95%) | | |
| occurrences causally related to treatment / all | 0 / 1 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Rib fracture | | | |
| subjects affected / exposed | 1 / 105 (0.95%) | | |
| occurrences causally related to treatment / all | 0 / 1 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Road traffic accident | | | |
| subjects affected / exposed | 0 / 105 (0.00%) | | |
| occurrences causally related to treatment / all | 0 / 0 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Tibia fracture | | | |
| subjects affected / exposed | 0 / 105 (0.00%) | | |
| occurrences causally related to treatment / all | 0 / 0 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Wrist fracture | | | |
| subjects affected / exposed | 1 / 105 (0.95%) | | |
| occurrences causally related to treatment / all | 0 / 1 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Cardiac disorders | | | |
| Acute myocardial infarction | | | |
| subjects affected / exposed | 1 / 105 (0.95%) | | |
| occurrences causally related to treatment / all | 0 / 1 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Atrial fibrillation | | | |
| subjects affected / exposed | 0 / 105 (0.00%) | | |
| occurrences causally related to treatment / all | 0 / 0 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Myocardial infarction | | | |
| subjects affected / exposed | 1 / 105 (0.95%) | | |
| occurrences causally related to treatment / all | 0 / 1 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Nervous system disorders | | | |

| | | | |
|---|-------------------|--|--|
| Epilepsy | | | |
| subjects affected / exposed | 1 / 105 (0.95%) | | |
| occurrences causally related to treatment / all | 0 / 1 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Multiple sclerosis relapse | | | |
| subjects affected / exposed | 16 / 105 (15.24%) | | |
| occurrences causally related to treatment / all | 1 / 31 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Optic neuritis | | | |
| subjects affected / exposed | 1 / 105 (0.95%) | | |
| occurrences causally related to treatment / all | 0 / 1 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Gastrointestinal disorders | | | |
| Diarrhoea | | | |
| subjects affected / exposed | 0 / 105 (0.00%) | | |
| occurrences causally related to treatment / all | 0 / 0 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Gastrointestinal disorder | | | |
| subjects affected / exposed | 0 / 105 (0.00%) | | |
| occurrences causally related to treatment / all | 0 / 0 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Hepatobiliary disorders | | | |
| Cholelithiasis | | | |
| subjects affected / exposed | 1 / 105 (0.95%) | | |
| occurrences causally related to treatment / all | 0 / 1 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Renal and urinary disorders | | | |
| Hypertonic bladder | | | |
| subjects affected / exposed | 0 / 105 (0.00%) | | |
| occurrences causally related to treatment / all | 0 / 0 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Microalbuminuria | | | |

| | | | |
|--|-----------------|--|--|
| subjects affected / exposed | 0 / 105 (0.00%) | | |
| occurrences causally related to treatment / all | 0 / 0 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Musculoskeletal and connective tissue disorders | | | |
| Arthralgia | | | |
| subjects affected / exposed | 1 / 105 (0.95%) | | |
| occurrences causally related to treatment / all | 0 / 1 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Arthritis | | | |
| subjects affected / exposed | 1 / 105 (0.95%) | | |
| occurrences causally related to treatment / all | 0 / 1 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Intervertebral disc disorder | | | |
| subjects affected / exposed | 1 / 105 (0.95%) | | |
| occurrences causally related to treatment / all | 0 / 1 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Infections and infestations | | | |
| Appendicitis | | | |
| subjects affected / exposed | 0 / 105 (0.00%) | | |
| occurrences causally related to treatment / all | 0 / 0 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Chronic tonsillitis | | | |
| subjects affected / exposed | 0 / 105 (0.00%) | | |
| occurrences causally related to treatment / all | 0 / 0 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Cystitis | | | |
| subjects affected / exposed | 1 / 105 (0.95%) | | |
| occurrences causally related to treatment / all | 1 / 1 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Pelvic inflammatory disease | | | |
| subjects affected / exposed | 0 / 105 (0.00%) | | |
| occurrences causally related to treatment / all | 0 / 0 | | |
| deaths causally related to treatment / all | 0 / 0 | | |

| | | | |
|---|-----------------|--|--|
| Pyelonephritis | | | |
| subjects affected / exposed | 1 / 105 (0.95%) | | |
| occurrences causally related to treatment / all | 1 / 1 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Urinary tract infection | | | |
| subjects affected / exposed | 0 / 105 (0.00%) | | |
| occurrences causally related to treatment / all | 0 / 0 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Metabolism and nutrition disorders | | | |
| Type 2 diabetes mellitus | | | |
| subjects affected / exposed | 1 / 105 (0.95%) | | |
| 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 | Part I Placebo | Part I BG00012 240 mg BID | Part II: Placebo/BG00012 240 mg BID (Switchers) |
|---|-------------------|---------------------------|---|
| Total subjects affected by non-serious adverse events | | | |
| subjects affected / exposed | 71 / 113 (62.83%) | 85 / 111 (76.58%) | 95 / 108 (87.96%) |
| Investigations | | | |
| Alanine aminotransferase increased | | | |
| subjects affected / exposed | 1 / 113 (0.88%) | 7 / 111 (6.31%) | 5 / 108 (4.63%) |
| occurrences (all) | 1 | 8 | 8 |
| Lymphocyte count decreased | | | |
| subjects affected / exposed | 0 / 113 (0.00%) | 2 / 111 (1.80%) | 6 / 108 (5.56%) |
| occurrences (all) | 0 | 3 | 7 |
| Vascular disorders | | | |
| Flushing | | | |
| subjects affected / exposed | 10 / 113 (8.85%) | 26 / 111 (23.42%) | 38 / 108 (35.19%) |
| occurrences (all) | 12 | 28 | 85 |
| Hot flush | | | |
| subjects affected / exposed | 1 / 113 (0.88%) | 7 / 111 (6.31%) | 4 / 108 (3.70%) |
| occurrences (all) | 1 | 7 | 4 |
| Nervous system disorders | | | |

| | | | |
|--|-------------------------|-------------------------|-------------------------|
| Dizziness subjects affected / exposed occurrences (all) | 1 / 113 (0.88%) 1 | 3 / 111 (2.70%) 3 | 3 / 108 (2.78%) 5 |
| Headache subjects affected / exposed occurrences (all) | 2 / 113 (1.77%) 4 | 4 / 111 (3.60%) 5 | 12 / 108 (11.11%) 13 |
| Hypoaesthesia subjects affected / exposed occurrences (all) | 0 / 113 (0.00%) 0 | 3 / 111 (2.70%) 3 | 4 / 108 (3.70%) 6 |
| Multiple sclerosis relapse subjects affected / exposed occurrences (all) | 31 / 113 (27.43%) 41 | 23 / 111 (20.72%) 31 | 39 / 108 (36.11%) 77 |
| Paraesthesia subjects affected / exposed occurrences (all) | 0 / 113 (0.00%) 0 | 2 / 111 (1.80%) 2 | 8 / 108 (7.41%) 10 |
| Blood and lymphatic system disorders Lymphopenia subjects affected / exposed occurrences (all) | 0 / 113 (0.00%) 0 | 2 / 111 (1.80%) 2 | 7 / 108 (6.48%) 10 |
| General disorders and administration site conditions Fatigue subjects affected / exposed occurrences (all) | 2 / 113 (1.77%) 2 | 1 / 111 (0.90%) 1 | 5 / 108 (4.63%) 5 |
| Gastrointestinal disorders Abdominal pain subjects affected / exposed occurrences (all) | 0 / 113 (0.00%) 0 | 8 / 111 (7.21%) 11 | 8 / 108 (7.41%) 8 |
| Abdominal pain upper subjects affected / exposed occurrences (all) | 6 / 113 (5.31%) 8 | 5 / 111 (4.50%) 5 | 16 / 108 (14.81%) 22 |
| Diarrhoea subjects affected / exposed occurrences (all) | 6 / 113 (5.31%) 6 | 11 / 111 (9.91%) 12 | 15 / 108 (13.89%) 20 |
| Dyspepsia subjects affected / exposed occurrences (all) | 3 / 113 (2.65%) 3 | 2 / 111 (1.80%) 2 | 7 / 108 (6.48%) 8 |

| | | | |
|---|--|--|---|
| Nausea subjects affected / exposed occurrences (all) | 6 / 113 (5.31%) 7 | 10 / 111 (9.01%) 10 | 13 / 108 (12.04%) 19 |
| Vomiting subjects affected / exposed occurrences (all) | 0 / 113 (0.00%) 0 | 5 / 111 (4.50%) 6 | 9 / 108 (8.33%) 13 |
| Respiratory, thoracic and mediastinal disorders Oropharyngeal pain subjects affected / exposed occurrences (all) | 2 / 113 (1.77%) 2 | 0 / 111 (0.00%) 0 | 6 / 108 (5.56%) 6 |
| Skin and subcutaneous tissue disorders Pruritus subjects affected / exposed occurrences (all) Rash subjects affected / exposed occurrences (all) | 2 / 113 (1.77%) 7 0 / 113 (0.00%) 0 | 8 / 111 (7.21%) 9 3 / 111 (2.70%) 4 | 10 / 108 (9.26%) 12 3 / 108 (2.78%) 4 |
| Psychiatric disorders Insomnia subjects affected / exposed occurrences (all) | 4 / 113 (3.54%) 4 | 3 / 111 (2.70%) 4 | 6 / 108 (5.56%) 6 |
| Musculoskeletal and connective tissue disorders Arthralgia subjects affected / exposed occurrences (all) Back pain subjects affected / exposed occurrences (all) Pain in extremity subjects affected / exposed occurrences (all) | 4 / 113 (3.54%) 6 3 / 113 (2.65%) 3 1 / 113 (0.88%) 1 | 1 / 111 (0.90%) 1 3 / 111 (2.70%) 3 2 / 111 (1.80%) 2 | 9 / 108 (8.33%) 10 4 / 108 (3.70%) 5 6 / 108 (5.56%) 8 |
| Infections and infestations Cystitis subjects affected / exposed occurrences (all) Gastroenteritis | 0 / 113 (0.00%) 0 | 1 / 111 (0.90%) 1 | 7 / 108 (6.48%) 9 |

| | | | |
|-----------------------------------|-------------------|-------------------|-------------------|
| subjects affected / exposed | 0 / 113 (0.00%) | 4 / 111 (3.60%) | 3 / 108 (2.78%) |
| occurrences (all) | 0 | 4 | 5 |
| Herpes zoster | | | |
| subjects affected / exposed | 1 / 113 (0.88%) | 0 / 111 (0.00%) | 6 / 108 (5.56%) |
| occurrences (all) | 1 | 0 | 6 |
| Influenza | | | |
| subjects affected / exposed | 1 / 113 (0.88%) | 2 / 111 (1.80%) | 6 / 108 (5.56%) |
| occurrences (all) | 1 | 2 | 8 |
| Nasopharyngitis | | | |
| subjects affected / exposed | 28 / 113 (24.78%) | 25 / 111 (22.52%) | 41 / 108 (37.96%) |
| occurrences (all) | 45 | 28 | 123 |
| Upper respiratory tract infection | | | |
| subjects affected / exposed | 11 / 113 (9.73%) | 5 / 111 (4.50%) | 21 / 108 (19.44%) |
| occurrences (all) | 17 | 7 | 43 |

| | | | |
|---|--|--|--|
| Non-serious adverse events | Part II: BG00012 240 mg BID/BG00012 240 mg BID (Continuers) | | |
| Total subjects affected by non-serious adverse events | | | |
| subjects affected / exposed | 91 / 105 (86.67%) | | |
| Investigations | | | |
| Alanine aminotransferase increased | | | |
| subjects affected / exposed | 8 / 105 (7.62%) | | |
| occurrences (all) | 16 | | |
| Lymphocyte count decreased | | | |
| subjects affected / exposed | 9 / 105 (8.57%) | | |
| occurrences (all) | 15 | | |
| Vascular disorders | | | |
| Flushing | | | |
| subjects affected / exposed | 3 / 105 (2.86%) | | |
| occurrences (all) | 6 | | |
| Hot flush | | | |
| subjects affected / exposed | 4 / 105 (3.81%) | | |
| occurrences (all) | 5 | | |
| Nervous system disorders | | | |
| Dizziness | | | |
| subjects affected / exposed | 6 / 105 (5.71%) | | |
| occurrences (all) | 6 | | |

| | | | |
|--|-------------------|--|--|
| Headache | | | |
| subjects affected / exposed | 12 / 105 (11.43%) | | |
| occurrences (all) | 26 | | |
| Hypoaesthesia | | | |
| subjects affected / exposed | 6 / 105 (5.71%) | | |
| occurrences (all) | 7 | | |
| Multiple sclerosis relapse | | | |
| subjects affected / exposed | 39 / 105 (37.14%) | | |
| occurrences (all) | 79 | | |
| Paraesthesia | | | |
| subjects affected / exposed | 2 / 105 (1.90%) | | |
| occurrences (all) | 2 | | |
| Blood and lymphatic system disorders | | | |
| Lymphopenia | | | |
| subjects affected / exposed | 6 / 105 (5.71%) | | |
| occurrences (all) | 9 | | |
| General disorders and administration site conditions | | | |
| Fatigue | | | |
| subjects affected / exposed | 6 / 105 (5.71%) | | |
| occurrences (all) | 6 | | |
| Gastrointestinal disorders | | | |
| Abdominal pain | | | |
| subjects affected / exposed | 0 / 105 (0.00%) | | |
| occurrences (all) | 0 | | |
| Abdominal pain upper | | | |
| subjects affected / exposed | 2 / 105 (1.90%) | | |
| occurrences (all) | 2 | | |
| Diarrhoea | | | |
| subjects affected / exposed | 6 / 105 (5.71%) | | |
| occurrences (all) | 7 | | |
| Dyspepsia | | | |
| subjects affected / exposed | 4 / 105 (3.81%) | | |
| occurrences (all) | 4 | | |
| Nausea | | | |
| subjects affected / exposed | 5 / 105 (4.76%) | | |
| occurrences (all) | 7 | | |

| | | | |
|---|--|--|--|
| Vomiting subjects affected / exposed occurrences (all) | 4 / 105 (3.81%) 4 | | |
| Respiratory, thoracic and mediastinal disorders Oropharyngeal pain subjects affected / exposed occurrences (all) | 6 / 105 (5.71%) 7 | | |
| Skin and subcutaneous tissue disorders Pruritus subjects affected / exposed occurrences (all) Rash subjects affected / exposed occurrences (all) | 6 / 105 (5.71%) 7 10 / 105 (9.52%) 14 | | |
| Psychiatric disorders Insomnia subjects affected / exposed occurrences (all) | 6 / 105 (5.71%) 7 | | |
| Musculoskeletal and connective tissue disorders Arthralgia subjects affected / exposed occurrences (all) Back pain subjects affected / exposed occurrences (all) Pain in extremity subjects affected / exposed occurrences (all) | 15 / 105 (14.29%) 20 8 / 105 (7.62%) 10 4 / 105 (3.81%) 4 | | |
| Infections and infestations Cystitis subjects affected / exposed occurrences (all) Gastroenteritis subjects affected / exposed occurrences (all) Herpes zoster | 8 / 105 (7.62%) 9 9 / 105 (8.57%) 9 | | |

| | | | |
|-----------------------------------|-------------------|--|--|
| subjects affected / exposed | 5 / 105 (4.76%) | | |
| occurrences (all) | 7 | | |
| Influenza | | | |
| subjects affected / exposed | 18 / 105 (17.14%) | | |
| occurrences (all) | 20 | | |
| Nasopharyngitis | | | |
| subjects affected / exposed | 47 / 105 (44.76%) | | |
| occurrences (all) | 131 | | |
| Upper respiratory tract infection | | | |
| subjects affected / exposed | 8 / 105 (7.62%) | | |
| occurrences (all) | 17 | | |

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/mm ³ 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