



Clinical trial results:

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

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

Results information

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

Trial information

Trial identification

| | |
|-----------------------|----------|
| Sponsor protocol code | 109MS305 |
|-----------------------|----------|

Additional study identifiers

| | |
|------------------------------------|-------------|
| ISRCTN number | - |
| ClinicalTrials.gov id (NCT number) | NCT01838668 |
| WHO universal trial number (UTN) | - |

Notes:

Sponsors

| | |
|------------------------------|--|
| Sponsor organisation name | Biogen |
| Sponsor organisation address | 225 Binney Street, Cambridge, Massachusetts, United States, 02142 |
| Public contact | Biogen Study Medical Director, Biogen , clinicaltrials@biogen.com |
| Scientific contact | Biogen Study Medical Director, Biogen , clinicaltrials@biogen.com |

Notes:

Paediatric regulatory details

| | |
|--|----|
| Is trial part of an agreed paediatric investigation plan (PIP) | No |
| Does article 45 of REGULATION (EC) No 1901/2006 apply to this trial? | No |
| Does article 46 of REGULATION (EC) No 1901/2006 apply to this trial? | No |

Notes:

Results analysis stage

| | |
|--|--------------|
| Analysis stage | Interim |
| Date of interim/final analysis | 16 June 2015 |
| Is this the analysis of the primary completion data? | Yes |
| Primary completion date | 16 June 2015 |
| Global end of trial reached? | No |

Notes:

General information about the trial

Main objective of the trial:

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

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

Protection of trial subjects:

Written informed consent was obtained from each subject prior to evaluations being performed for eligibility. Subjects were given adequate time to review the information in the informed consent and were allowed to ask, and have answered, questions concerning all portions of the conduct of the study. Through the informed consent process each subject was made aware of the purpose of the study, the procedures, the benefits and risks of the study, the discomforts and the precautions taken. Any side effects or other health issues occurring during the study were followed up by the study doctor. Subjects were able to stop taking part in the study at any time without giving any reason.

Background therapy: -

Evidence for comparator: -

| | |
|---|---------------|
| Actual start date of recruitment | 28 March 2013 |
| Long term follow-up planned | No |
| Independent data monitoring committee (IDMC) involvement? | No |

Notes:

Population of trial subjects

Subjects enrolled per country

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

Notes:

Subjects enrolled per age group

| | |
|--|---|
| In utero | 0 |
| Preterm newborn - gestational age < 37 | 0 |

| | |
|--|-----|
| wk | |
| Newborns (0-27 days) | 0 |
| Infants and toddlers (28 days-23 months) | 0 |
| Children (2-11 years) | 0 |
| Adolescents (12-17 years) | 0 |
| Adults (18-64 years) | 225 |
| From 65 to 84 years | 0 |
| 85 years and over | 0 |

Subject disposition

Recruitment

Recruitment details: -

Pre-assignment

Screening details:

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

Pre-assignment period milestones

| | |
|------------------------------|-----|
| Number of subjects started | 225 |
| Number of subjects completed | 224 |

Pre-assignment subject non-completion reasons

| | |
|----------------------------|-----------------------------|
| Reason: Number of subjects | Randomized but not dosed: 1 |
|----------------------------|-----------------------------|

Period 1

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

Blinding implementation details:

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

Arms

| | |
|------------------------------|----------------|
| Are arms mutually exclusive? | Yes |
| Arm title | Part I Placebo |

Arm description:

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

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

Dosage and administration details:

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

| | |
|-----------|---------------------------|
| Arm title | Part I BG00012 240 mg BID |
|-----------|---------------------------|

Arm description:

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

| | |
|----------|--------------|
| Arm type | Experimental |
|----------|--------------|

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

Dosage and administration details:

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

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

Notes:

[1] - The number of subjects reported to be in the baseline period are not the same as the worldwide number enrolled in the trial. It is expected that these numbers will be the same.

Justification: 1 subject was enrolled and randomized but was not treated.

[2] - The number of subjects at this milestone seems inconsistent with the number of subjects in the arm. It is expected that the number of subjects will be greater than, or equal to the number that completed, minus those who left.

Justification: 1 subject who did not complete treatment with study drug did not withdraw prematurely from Part I of the study .

Baseline characteristics

Reporting groups

| | |
|-----------------------|----------------|
| Reporting group title | Part I Placebo |
|-----------------------|----------------|

Reporting group description:

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

| | |
|-----------------------|---------------------------|
| Reporting group title | Part I BG00012 240 mg BID |
|-----------------------|---------------------------|

Reporting group description:

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

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

End points

End points reporting groups

| | |
|-----------------------|----------------|
| Reporting group title | Part I Placebo |
|-----------------------|----------------|

Reporting group description:

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

| | |
|-----------------------|---------------------------|
| Reporting group title | Part I BG00012 240 mg BID |
|-----------------------|---------------------------|

Reporting group description:

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

| | |
|----------------------------|-------------------------|
| Subject analysis set title | ITT Population: Placebo |
|----------------------------|-------------------------|

| | |
|---------------------------|--------------------|
| Subject analysis set type | Intention-to-treat |
|---------------------------|--------------------|

Subject analysis set description:

ITT Population: subjects who were randomized to placebo and received at least 1 dose of study treatment.

| | |
|----------------------------|------------------------------------|
| Subject analysis set title | ITT Population: BG00012 240 mg BID |
|----------------------------|------------------------------------|

| | |
|---------------------------|--------------------|
| Subject analysis set type | Intention-to-treat |
|---------------------------|--------------------|

Subject analysis set description:

ITT Population: subjects who were randomized to BG00012 and received at least 1 dose of study treatment.

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

| | |
|-----------------|---|
| End point title | MRI: Total Number of New Gd-Enhancing Lesions From Scans at Week 12 to 24: Part I |
|-----------------|---|

End point description:

The total number of new Gd-enhancing lesions from qualified MRI scans at Weeks 12, 16, 20, and 24, calculated as the sum of new Gd-enhancing lesions from these four scans. Gd-enhancing lesions are detected when Gd leaks into the perivascular space due to local breakdown of the blood-brain barrier, indicating the presence of active inflammation in periventricular lesions.

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

End point timeframe:

Week 12 to Week 24

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

Statistical analyses

| | |
|----------------------------|------------------------|
| Statistical analysis title | Statistical Analysis 1 |
|----------------------------|------------------------|

Statistical analysis description:

Percentage change, 95% CI and p-value for comparison between the active and placebo groups, based

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

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

| | |
|--|--|
| Statistical analysis title | Statistical Analysis 2 |
| Statistical analysis description: Percentage change, 95% CI and p-value for comparison between the active and placebo groups, based on negative binomial regression, adjusted for region (Japan/Non-Japan) and baseline number of Gd lesions. | |
| Comparison groups | ITT Population: Placebo v ITT Population: BG00012 240 mg BID |
| Number of subjects included in analysis | 224 |
| Analysis specification | Pre-specified |
| Analysis type | superiority |
| P-value | < 0.0001 |
| Method | negative binomial regression |
| Parameter estimate | percentage reduction (vs. placebo) |
| Point estimate | 83.6 |
| Confidence interval | |
| level | 95 % |
| sides | 2-sided |
| lower limit | 73.4 |
| upper limit | 89.9 |

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

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

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

Notes:

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

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

Notes:

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

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

| | |
|--|---|
| End point title | MRI: Total Number of New Gd-Enhancing Lesions From Scans at Weeks 4 to 24: Part I |
| End point description: The cumulative number of new Gd-enhancing lesions over the six MRI scans in the placebo-controlled phase was calculated as the sum of the new Gd-enhancing lesions from the Week 4 to Week 24 scans. | |
| End point type | Secondary |
| End point timeframe: Week 4 to Week 24 | |

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

Statistical analyses

| | |
|--|--|
| Statistical analysis title | Statistical Analysis 1 |
| Statistical analysis description: Percentage change, 95% CI and p-value for comparison between the active and placebo groups, based on negative binomial regression, adjusted for region (Japan/Non-Japan) and baseline number of Gd lesions. | |
| Comparison groups | ITT Population: Placebo v ITT Population: BG00012 240 mg BID |

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

| | |
|-----------------------------------|------------------------|
| Statistical analysis title | Statistical Analysis 2 |
|-----------------------------------|------------------------|

Statistical analysis description:

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

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

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

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

End point description:

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

| | |
|----------------|-----------|
| End point type | Secondary |
|----------------|-----------|

End point timeframe:

Baseline, Week 24

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

Statistical analyses

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

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

Adverse events

Adverse events information

Timeframe for reporting adverse events:

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

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

Dictionary used

| | |
|--------------------|--------|
| Dictionary name | MedDRA |
| Dictionary version | 13.1 |

Reporting groups

| | |
|-----------------------|---------|
| Reporting group title | Placebo |
|-----------------------|---------|

Reporting group description:

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

| | |
|-----------------------|--------------------|
| Reporting group title | BG00012 240 mg BID |
|-----------------------|--------------------|

Reporting group description:

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

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

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

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

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

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

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

| Date | Amendment |
|------------------|--|
| 19 November 2012 | The primary reason for this amendment was to extend the contraception requirement from 30 days after the last dose of study treatment through the Final Safety Follow-Up Visit 12 weeks after the last dose of study treatment. |
| 22 November 2013 | <p>The primary reasons for this amendment were to:</p> <ul style="list-style-type: none">- 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 | <p>The primary reasons for this amendment were to:</p> <ul style="list-style-type: none">- Enable the early identification of subjects in Parts I or II who are at risk for developing severe, prolonged lymphopenia, and to provide additional guidance on the management of such subjects. In addition, lymphocyte and subset counts have been supplemented as an exploratory endpoint with the objective to study the impact of BG00012 treatment on lymphocytes and the recovery of lymphocyte count in patients with lymphopenia.- Extend the duration of study participation from 28 or 40 weeks to 28 to 52 weeks to reflect the additional safety follow-up for subjects with abnormally low lymphocyte counts. Subjects who completed Part I and did not enroll in Part II of the study or subjects who permanently discontinued study treatment for any reason and had a lymphocyte count <LLN were to be followed until the lymphocyte count was ≥LLN or until 24 weeks after the last dose (whichever was sooner).- Clarify that the use of alternative MS therapies was allowed only after the Investigators had contacted Biogen or its designee to determine their necessity in subjects who completed Part I and did not enroll in Part II of the study or subjects who permanently discontinued study treatment.- Country was added as a covariate for the statistical modelling of additional endpoints to be consistent with the analysis of the primary and secondary endpoints.- If lymphocyte count remains <500/mm³ for ≥24 weeks consecutively, study treatment will be permanently discontinued, and recovery of lymphocytes will be followed. |

Notes:

Interruptions (globally)

Were there any global interruptions to the trial? No

Limitations and caveats

None reported