



Clinical trial results:

A Multicenter, Treatment-Blind Phase 3b Study to Evaluate Whether 6-Week Up-Titration in Tecfidera® Dose is Effective in Reducing the Incidence of Gastrointestinal Adverse Events in Patients With Multiple Sclerosis

Summary

| | |
|--------------------------|-----------------|
| EudraCT number | 2014-004562-22 |
| Trial protocol | BE CZ HU IT DE |
| Global end of trial date | 08 January 2016 |

Results information

| | |
|--------------------------------|------------------|
| Result version number | v1 (current) |
| This version publication date | 29 December 2016 |
| First version publication date | 29 December 2016 |

Trial information

Trial identification

| | |
|-----------------------|----------|
| Sponsor protocol code | 109MS416 |
|-----------------------|----------|

Additional study identifiers

| | |
|------------------------------------|-------------|
| ISRCTN number | - |
| ClinicalTrials.gov id (NCT number) | NCT02428231 |
| 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 | 08 January 2016 |
| Is this the analysis of the primary completion data? | No |
| Global end of trial reached? | Yes |
| Global end of trial date | 08 January 2016 |
| Was the trial ended prematurely? | Yes |

Notes:

General information about the trial

Main objective of the trial:

The primary objective of the study is to assess whether a 6-week titration (compared with a 1-week titration) is effective in reducing the incidence of dimethyl fumarate (DMF)-related gastrointestinal (GI) adverse events (AEs) in subjects with multiple sclerosis (MS). The secondary objective of this study is to assess whether a 6-week titration (compared with a 1-week titration) is effective in reducing the average severity and duration of GI symptoms over 12 weeks of DMF treatment in this study population.

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 | 30 April 2015 |
| 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 | United States: 34 |
| Country: Number of subjects enrolled | Belgium: 23 |
| Country: Number of subjects enrolled | Italy: 3 |
| Country: Number of subjects enrolled | Czech Republic: 2 |
| Worldwide total number of subjects | 62 |
| EEA total number of subjects | 28 |

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) | 62 |
| From 65 to 84 years | 0 |
| 85 years and over | 0 |

Subject disposition

Recruitment

Recruitment details: -

Pre-assignment

Screening details:

This study included a 28-day screening period.

Period 1

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

Blinding implementation details:

All subjects remained blinded to the treatment assignment for the entire duration of the study. The study staff knew that all subjects were to receive placebo for the first 2 weeks; however, this information was not shared with the subjects in order to allow unbiased reporting of baseline GI symptoms. From Week 3 onwards, all study staff were blinded to the subject treatment assignments.

Arms

| | |
|------------------------------|---|
| Are arms mutually exclusive? | Yes |
| Arm title | Standard Treatment (One-Week Titration) |

Arm description:

Following a 2-week placebo run-in baseline period, 120 mg DMF twice daily for 1 week, then 240 mg (as 2 120-mg capsules) DMF twice daily for 11 weeks.

| | |
|--|--------------------------------|
| Arm type | Experimental |
| Investigational medicinal product name | dimethyl fumarate |
| Investigational medicinal product code | BG00012 |
| Other name | DMF, BG00012, Tecfidera |
| Pharmaceutical forms | Gastro-resistant capsule, hard |
| Routes of administration | Oral use |

Dosage and administration details:

Following the 2-week placebo baseline period, DMF was administered orally twice daily for 12 weeks as described in the arm description.

| | |
|--|---------------|
| Investigational medicinal product name | placebo |
| Investigational medicinal product code | |
| Other name | |
| Pharmaceutical forms | Capsule, hard |
| Routes of administration | Oral use |

Dosage and administration details:

Matching placebo was administered twice daily during the 2-week baseline period. In addition, placebo capsules were administered with the 120-mg doses such that 2 capsules were administered at each dose.

| | |
|------------------|--|
| Arm title | Slow Up-Titration (Six-Week Titration) |
|------------------|--|

Arm description:

Following a 2-week placebo run-in baseline period, 120 mg DMF once daily (morning dose) and placebo once daily (evening dose) for 2 weeks, then 120 mg DMF twice daily for 2 weeks, then 240 mg (as 2 120-mg capsules) DMF in the morning and 120 mg in the evening for 2 weeks, then 240 mg (as two 120-mg capsules) DMF twice daily for 6 weeks.

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

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

Dosage and administration details:

Following the 2-week placebo baseline period, DMF was given once daily for 2 weeks, then twice daily for remaining 10 weeks.

| | |
|--|---------------|
| Investigational medicinal product name | placebo |
| Investigational medicinal product code | |
| Other name | |
| Pharmaceutical forms | Capsule, hard |
| Routes of administration | Oral use |

Dosage and administration details:

Matching placebo was administered twice daily during the 2-week baseline period and as the evening dose during Weeks 3 and 4. In addition, placebo capsules were administered with the 120-mg doses such that 2 capsules were administered at each dose.

| Number of subjects in period 1 | Standard Treatment (One-Week Titration) | Slow Up-Titration (Six-Week Titration) |
|--------------------------------|--|---|
| | | |
| Started | 30 | 32 |
| Completed | 17 | 15 |
| Not completed | 13 | 17 |
| Adverse event, non-fatal | 3 | - |
| Not specified | 10 | 16 |
| Required symptomatic therapy | - | 1 |

Baseline characteristics

Reporting groups

| | |
|-----------------------|---|
| Reporting group title | Standard Treatment (One-Week Titration) |
|-----------------------|---|

Reporting group description:

Following a 2-week placebo run-in baseline period, 120 mg DMF twice daily for 1 week, then 240 mg (as 2 120-mg capsules) DMF twice daily for 11 weeks.

| | |
|-----------------------|--|
| Reporting group title | Slow Up-Titration (Six-Week Titration) |
|-----------------------|--|

Reporting group description:

Following a 2-week placebo run-in baseline period, 120 mg DMF once daily (morning dose) and placebo once daily (evening dose) for 2 weeks, then 120 mg DMF twice daily for 2 weeks, then 240 mg (as 2 120-mg capsules) DMF in the morning and 120 mg in the evening for 2 weeks, then 240 mg (as two 120-mg capsules) DMF twice daily for 6 weeks.

| Reporting group values | Standard Treatment (One-Week Titration) | Slow Up-Titration (Six-Week Titration) | Total |
|--|---|---|-------|
| Number of subjects | 30 | 32 | 62 |
| Age categorical Units: Subjects | | | |
| Adults (18-64 years) | 30 | 32 | 62 |
| Age Continuous Units: years | | | |
| arithmetic mean | 45.5 | 42.5 | |
| standard deviation | ± 11.77 | ± 11.12 | - |
| Gender, Male/Female Units: Subjects | | | |
| Female | 22 | 21 | 43 |
| Male | 8 | 11 | 19 |

End points

End points reporting groups

| | |
|--|---|
| Reporting group title | Standard Treatment (One-Week Titration) |
| Reporting group description: Following a 2-week placebo run-in baseline period, 120 mg DMF twice daily for 1 week, then 240 mg (as 2 120-mg capsules) DMF twice daily for 11 weeks. | |
| Reporting group title | Slow Up-Titration (Six-Week Titration) |
| Reporting group description: Following a 2-week placebo run-in baseline period, 120 mg DMF once daily (morning dose) and placebo once daily (evening dose) for 2 weeks, then 120 mg DMF twice daily for 2 weeks, then 240 mg (as 2 120-mg capsules) DMF in the morning and 120 mg in the evening for 2 weeks, then 240 mg (as two 120-mg capsules) DMF twice daily for 6 weeks. | |

Primary: Proportion of Participants With a Worsening in Severity of Gastrointestinal (GI) Adverse Events (AEs) on the Gastrointestinal Symptom Rating Scale (GSRS)

| | |
|--|--|
| End point title | Proportion of Participants With a Worsening in Severity of Gastrointestinal (GI) Adverse Events (AEs) on the Gastrointestinal Symptom Rating Scale (GSRS) ^[1] |
| End point description: The GSRS is a weekly recall scale to rate the severity of GI symptoms in participants. It has been modified for daily recall in this study. The severity of each of the 15 questions of the GSRS have a number assigned from 0 (no discomfort at all) to 6 (very severe discomfort). | |
| End point type | Primary |
| End point timeframe: from Week 2 (Baseline) to Week 14 | |
| Notes: [1] - No statistical analyses have been specified for this primary end point. It is expected there is at least one statistical analysis for each primary end point. Justification: The planned efficacy analyses were not performed due to early study termination. | |

| End point values | Standard Treatment (One-Week Titration) | Slow Up-Titration (Six-Week Titration) | | |
|-----------------------------|---|--|--|--|
| Subject group type | Reporting group | Reporting group | | |
| Number of subjects analysed | 0 ^[2] | 0 ^[3] | | |
| Units: participants | | | | |

Notes:
[2] - The planned efficacy analyses were not performed due to early study termination.
[3] - The planned efficacy analyses were not performed due to early study termination.

Statistical analyses

No statistical analyses for this end point

Secondary: Average Change From Baseline in GSRS Scores During DMF Treatment

| | |
|--|--|
| End point title | Average Change From Baseline in GSRS Scores During DMF Treatment |
| End point description: Average change from baseline in GSRS scores over the 12 weeks of DMF treatment as measured by the total change in GSRS scores from baseline divided by the total number of days with GSRS scores recorded. The GSRS is a weekly recall scale to rate the severity of GI symptoms in participants. It has | |

been modified for daily recall in this study. The severity of each of the 15 questions of the GSRS have a number assigned from 0 (no discomfort at all) to 6 (very severe discomfort).

| | |
|----------------------------|-----------|
| End point type | Secondary |
| End point timeframe: | |
| Week 2 (Baseline), Week 14 | |

| End point values | Standard Treatment (One-Week Titration) | Slow Up-Titration (Six-Week Titration) | | |
|--------------------------------------|---|--|--|--|
| Subject group type | Reporting group | Reporting group | | |
| Number of subjects analysed | 0 ^[4] | 0 ^[5] | | |
| Units: units on a scale | | | | |
| arithmetic mean (standard deviation) | () | () | | |

Notes:

[4] - The planned efficacy analyses were not performed due to early study termination.

[5] - The planned efficacy analyses were not performed due to early study termination.

Statistical analyses

No statistical analyses for this end point

Secondary: Time to First Worsening From Baseline in GSRS Score

| | |
|--|---|
| End point title | Time to First Worsening From Baseline in GSRS Score |
| End point description: | |
| The GSRS is a weekly recall scale to rate the severity of GI symptoms in participants. It has been modified for daily recall in this study. The severity of each of the 15 questions of the GSRS have a number assigned from 0 (no discomfort at all) to 6 (very severe discomfort). | |
| End point type | Secondary |
| End point timeframe: | |
| Week 2 (Baseline), Week 14 | |

| End point values | Standard Treatment (One-Week Titration) | Slow Up-Titration (Six-Week Titration) | | |
|-----------------------------|---|--|--|--|
| Subject group type | Reporting group | Reporting group | | |
| Number of subjects analysed | 0 ^[6] | 0 ^[7] | | |
| Units: days | | | | |

Notes:

[6] - The planned efficacy analyses were not performed due to early study termination.

[7] - The planned efficacy analyses were not performed due to early study termination.

Statistical analyses

No statistical analyses for this end point

Secondary: Time to Recovery to Baseline From Last Occurrence of Worst GSRS Score

| | |
|-----------------|--|
| End point title | Time to Recovery to Baseline From Last Occurrence of Worst |
|-----------------|--|

End point description:

The GSRS is a weekly recall scale to rate the severity of GI symptoms in participants. It has been modified for daily recall in this study. The severity of each of the 15 questions of the GSRS have a number assigned from 0 (no discomfort at all) to 6 (very severe discomfort).

End point type

Secondary

End point timeframe:

Week 2 (Baseline), Week 14

| End point values | Standard Treatment (One-Week Titration) | Slow Up-Titration (Six-Week Titration) | | |
|-----------------------------|---|--|--|--|
| Subject group type | Reporting group | Reporting group | | |
| Number of subjects analysed | 0 ^[8] | 0 ^[9] | | |
| Units: days | | | | |

Notes:

[8] - The planned efficacy analyses were not performed due to early study termination.

[9] - The planned efficacy analyses were not performed due to early study termination.

Statistical analyses

No statistical analyses for this end point

Secondary: Average Change From Baseline in GSRS Scores to the End of Weeks 4, 6, 8, 10, 12, and 14

| | |
|-----------------|---|
| End point title | Average Change From Baseline in GSRS Scores to the End of Weeks 4, 6, 8, 10, 12, and 14 |
|-----------------|---|

End point description:

Average change from baseline to end of DMF treatment in the GSRS. The GSRS is a weekly recall scale to rate the severity of GI symptoms in participants. It has been modified for daily recall in this study. The severity of each of the 15 questions of the GSRS have a number assigned from 0 (no discomfort at all) to 6 (very severe discomfort).

End point type

Secondary

End point timeframe:

Week 2 (Baseline), Weeks 4, 6, 8, 10, 12, 14

| End point values | Standard Treatment (One-Week Titration) | Slow Up-Titration (Six-Week Titration) | | |
|--------------------------------------|---|--|--|--|
| Subject group type | Reporting group | Reporting group | | |
| Number of subjects analysed | 0 ^[10] | 0 ^[11] | | |
| Units: units on a scale | | | | |
| arithmetic mean (standard deviation) | () | () | | |

Notes:

[10] - The planned efficacy analyses were not performed due to early study termination.

[11] - The planned efficacy analyses were not performed due to early study termination.

Statistical analyses

Adverse events

Adverse events information

Timeframe for reporting adverse events:

From start of study through Week 14 plus 2 weeks (± 5 days) follow-up. Serious events were collected from time of informed consent and non-serious events were collected from the first dose and throughout the study.

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

Dictionary used

| | |
|--------------------|--------|
| Dictionary name | MedDRA |
| Dictionary version | 18.1 |

Reporting groups

| | |
|-----------------------|----------------------|
| Reporting group title | 6-Week Titration Arm |
|-----------------------|----------------------|

Reporting group description:

Following a 2-week placebo run-in baseline period, 120 mg DMF once daily (morning dose) and placebo once daily (evening dose) for 2 weeks, then 120 mg DMF twice daily for 2 weeks, then 240 mg (as 2 120-mg capsules) DMF in the morning and 120 mg in the evening for 2 weeks, then 240 mg (as two 120-mg capsules) DMF twice daily for 6 weeks.

| | |
|-----------------------|-------------------------------|
| Reporting group title | Standard 1-Week Titration Arm |
|-----------------------|-------------------------------|

Reporting group description:

Following a 2-week placebo run-in baseline period, 120 mg DMF twice daily for 1 week, then 240 mg (as 2 120-mg capsules) DMF twice daily for 11 weeks.

| Serious adverse events | 6-Week Titration Arm | Standard 1-Week Titration Arm | |
|---|----------------------|-------------------------------|--|
| Total subjects affected by serious adverse events | | | |
| subjects affected / exposed | 1 / 32 (3.13%) | 2 / 30 (6.67%) | |
| number of deaths (all causes) | 0 | 0 | |
| number of deaths resulting from adverse events | | | |
| Injury, poisoning and procedural complications | | | |
| Hip fracture | | | |
| subjects affected / exposed | 0 / 32 (0.00%) | 1 / 30 (3.33%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Musculoskeletal and connective tissue disorders | | | |
| Arthralgia | | | |
| subjects affected / exposed | 1 / 32 (3.13%) | 0 / 30 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Osteoarthritis | | | |

| | | | |
|---|----------------|----------------|--|
| subjects affected / exposed | 1 / 32 (3.13%) | 0 / 30 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Infections and infestations | | | |
| Gastrointestinal infection | | | |
| subjects affected / exposed | 0 / 32 (0.00%) | 1 / 30 (3.33%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |

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

| Non-serious adverse events | 6-Week Titration Arm | Standard 1-Week Titration Arm | |
|---|----------------------|-------------------------------|--|
| Total subjects affected by non-serious adverse events | | | |
| subjects affected / exposed | 14 / 32 (43.75%) | 18 / 30 (60.00%) | |
| Vascular disorders | | | |
| Flushing | | | |
| subjects affected / exposed | 6 / 32 (18.75%) | 7 / 30 (23.33%) | |
| occurrences (all) | 9 | 11 | |
| Nervous system disorders | | | |
| Headache | | | |
| subjects affected / exposed | 4 / 32 (12.50%) | 2 / 30 (6.67%) | |
| occurrences (all) | 5 | 2 | |
| Multiple sclerosis relapse | | | |
| subjects affected / exposed | 1 / 32 (3.13%) | 3 / 30 (10.00%) | |
| occurrences (all) | 1 | 3 | |
| Gastrointestinal disorders | | | |
| Abdominal pain upper | | | |
| subjects affected / exposed | 0 / 32 (0.00%) | 2 / 30 (6.67%) | |
| occurrences (all) | 0 | 2 | |
| Skin and subcutaneous tissue disorders | | | |
| Pruritus | | | |
| subjects affected / exposed | 1 / 32 (3.13%) | 2 / 30 (6.67%) | |
| occurrences (all) | 2 | 2 | |
| Rash | | | |
| subjects affected / exposed | 1 / 32 (3.13%) | 3 / 30 (10.00%) | |
| occurrences (all) | 1 | 3 | |

| | | | |
|---|----------------|-----------------|--|
| Musculoskeletal and connective tissue disorders | | | |
| Back pain | | | |
| subjects affected / exposed | 2 / 32 (6.25%) | 1 / 30 (3.33%) | |
| occurrences (all) | 2 | 1 | |
| Infections and infestations | | | |
| Cystitis | | | |
| subjects affected / exposed | 2 / 32 (6.25%) | 2 / 30 (6.67%) | |
| occurrences (all) | 2 | 2 | |
| Gastroenteritis viral | | | |
| subjects affected / exposed | 3 / 32 (9.38%) | 1 / 30 (3.33%) | |
| occurrences (all) | 3 | 1 | |
| Nasopharyngitis | | | |
| subjects affected / exposed | 3 / 32 (9.38%) | 3 / 30 (10.00%) | |
| occurrences (all) | 4 | 3 | |

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

| Date | Amendment |
|---------------|---|
| 16 March 2015 | A global amendment was issued on 16 March 2015 to clarify only 1 strength of capsule was to be administered (120 mg), clarify clinical laboratory test results from screening had to be reviewed before the baseline visit, and extend the period of time men had to use contraceptives to 90 days after the last dose of study treatment. In addition, administrative and other minor changes were included. |

Notes:

Interruptions (globally)

Were there any global interruptions to the trial? No

Limitations and caveats

Limitations of the trial such as small numbers of subjects analysed or technical problems leading to unreliable data.

| |
|--|
| The Sponsor decided to terminate the study as a result of an evaluation of ongoing development programs. |
|--|

Notes: