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

	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[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

No statistical analyses for this end point

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: