Clinical trial results:
A Multicenter, Open-Label, Single-Arm Study to Evaluate Gastrointestinal Tolerability in Subjects with Relapsing-Remitting Multiple Sclerosis Receiving Dimethyl Fumarate (TOLERATE)

Summary

EudraCT number	2013-001486-17
Trial protocol	DE
Global end of trial date	11 March 2016

Results information

Result version number	v1 (current)
This version publication date	23 March 2017
First version publication date	23 March 2017

Trial information

Trial identification

Sponsor protocol code	109MS407

Additional study identifiers

ISRCTN number	-
ClinicalTrials.gov id (NCT number)	NCT02125604
WHO universal trial number (UTN)	-

Notes:

Sponsors

Sponsor organisation name	Biogen
Sponsor organisation address	225 Binney Street, United States, 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	11 March 2016
Is this the analysis of the primary completion data?	No

Global end of trial reached?	Yes
Global end of trial date	11 March 2016
Was the trial ended prematurely?	No

Notes:

General information about the trial

Main objective of the trial:

This study was designed to assess the incidence, severity, and duration of GI-related events requiring symptomatic therapies in a clinical practice setting in Germany. The primary objective of this study is to evaluate the effect of symptomatic therapies on gastrointestinal-related events reported by participants with relapsing-remitting multiple sclerosis initiating therapy with BG00012 (dimethyl fumarate, DMF) in the clinical practice setting.

The secondary objectives of this study in this study population are as follows: to evaluate gastrointestinal-related events requiring symptomatic therapy and the role of those therapies over time; to evaluate gastrointestinal-related events that led to a physician’s decision to manage the events with BG00012 dose modification; and to evaluate gastrointestinal-related events that led to BG00012 discontinuation after the use of symptomatic therapy.

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	26 June 2014
Long term follow-up planned	No
Independent data monitoring committee (IDMC) involvement?	No

Notes:

Population of trial subjects

Subjects enrolled per country

Country: Number of subjects enrolled	Germany: 211
Worldwide total number of subjects	211
EEA total number of subjects	211

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)	211
From 65 to 84 years	0
85 years and over	0

Subject disposition

Recruitment

Recruitment details: -

Pre-assignment

Screening details:

A total of 214 subjects were screened and enrolled; 3 subjects did not receive study drug (1 withdrew consent and 2 did not meet all inclusion/exclusion criteria). A total of 211 subjects were included in the safety population.

Period 1

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

Arms

Arm title	Dimethyl Fumarate

Arm description:

Dimethyl fumarate administered orally at 120 mg BID for the first 7 days and 240 mg BID thereafter for a total of 12 weeks.

Arm type	Experimental
Investigational medicinal product name	Dimethyl fumarate administered orally at 120 mg twice daily (BID) for the first 7 days and 240 mg BID thereafter for a total of 12 weeks.
Investigational medicinal product code	BG00012
Other name	Tecfidera; DMF
Pharmaceutical forms	Gastro-resistant capsule, hard
Routes of administration	Oral use

Dosage and administration details:

Subjects received information relating to the timing of dosing,missed doses, and accountability of DMF capsules.

Number of subjects in period 1	Dimethyl Fumarate
Started	211
Completed	180
Not completed	31
Adverse event, non-fatal	20
Not Specified	4
Investigator Decision	1
Lost to follow-up	2
Consent Withdrawn	4

Baseline characteristics

Reporting groups	
Reporting group title	Dimethyl Fumarate
Reporting group description:	
Dimethyl fumarate administered orally at 120 mg BID for the first 7 days and 240 mg BID thereafter for a total of 12 weeks.	

Reporting group values	Dimethyl Fumarate	Total	
Number of subjects	211	211	
Age categorical Units: Subjects			
Adults (18-64 years)	211	211	
Age Continuous Units: years			
arithmetic mean	40.09		
standard deviation	± 10.97	-	
Gender, Male/Female Units: Subjects			
Female	149	149	
Male	62	62	

End points

End points reporting groups

Reporting group title	Dimethyl Fumarate

Reporting group description:

Dimethyl fumarate administered orally at 120 mg BID for the first 7 days and 240 mg BID thereafter for a total of 12 weeks.

Primary: Number of Subjects Who Utilized Symptomatic Therapy With Gastrointestinal-Related Events During the 12-Week Treatment Period: Modified Overall Gastrointestinal Symptom Scale (MOGISS)

End point title	Number of Subjects Who Utilized Symptomatic Therapy With Gastrointestinal-Related Events During the 12-Week Treatment Period: Modified Overall Gastrointestinal Symptom Scale (MOGISS)[1]

End point description:

The MOGISS is a questionnaire about the severity of overall gastrointestinal-related events, including specifically symptoms of nausea, diarrhea, upper abdominal pain, lower abdominal pain, vomiting, indigestion, constipation, bloating, and flatulence for 24 hours before the AM dose. Participants who rated the intensity of symptoms reported on the MOGISS and included each symptomatic therapy used in the eDiary are presented.

End point type	Primary

End point timeframe:

Up to Week 12

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: Descriptive statistics are presented for this endpoint, per protocol.

End point values	Dimethyl Fumarate			
Subject group type	Reporting group			
Number of subjects analysed	211[2]			
Units: Subjects				
Overall Treatment Period; n=211	82			
Weeks 1-4; n=211	71			
Weeks 5-8; n=186	33			
Weeks 9-12; n=178	22			

Notes:

[2] - n=subjects with an assessment in given time period

Statistical analyses

No statistical analyses for this end point

Primary: Number of Subjects Who Utilized Symptomatic Therapy With Gastrointestinal-Related Events During the 12-Week Treatment Period: Modified Acute Gastrointestinal Symptom Scale (MAGISS)

End point title	Number of Subjects Who Utilized Symptomatic Therapy With Gastrointestinal-Related Events During the 12-Week Treatment Period: Modified Acute Gastrointestinal Symptom Scale (MAGISS)[3]

End point description:

The MAGISS is a questionnaire in which participants reported overall acute gastrointestinal-related events (especially symptoms of nausea, diarrhea, upper abdominal pain, lower abdominal pain, vomiting, indigestion, constipation, bloating, and flatulence) for each 10 hours after the AM and PM doses of study drug. Participants who rated the intensity of gastrointestinal-related events reported on MAGISS, included the duration of the gastrointestinal-related events and each symptomatic therapy used in the eDiary are presented.

End point type	Primary

End point timeframe:

Up to Week 12

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: Descriptive statistics are presented for this endpoint, per protocol.

End point values	Dimethyl Fumarate			
Subject group type	Reporting group			
Number of subjects analysed	211[4]			
Units: Subjects				
Overall Treatment Period; n=211	83			
Weeks 1-4; n=211	72			
Weeks 5-8; n=189	34			
Weeks 9-12; n=180	26			

Notes:

[4] - n=subjects with an assessment in given time period

Statistical analyses

No statistical analyses for this end point

Primary: Worst Severity Of Gastrointestinal-Related Events In Subjects Who Utilized Symptomatic Therapy During the 12-Week Treatment Period, MOGISS

End point title	Worst Severity Of Gastrointestinal-Related Events In Subjects Who Utilized Symptomatic Therapy During the 12-Week Treatment Period, MOGISS[5]

End point description:

The MOGISS is a questionnaire about overall events related to the gastrointestinal system (including nausea, diarrhea, upper abdominal pain, lower abdominal pain, vomiting, indigestion, constipation, bloating, and flatulence) during the 24 hours prior to each AM dose. MOGISS is based on a 0- to 10-point scale, with 0 representing absence of symptoms and 10 representing the most severe symptoms. The worst overall severity score for gastrointestinal-related events was calculated for each participant for the overall treatment period of 12 weeks, and for each 4-week period therein.

End point type	Primary

End point timeframe:

Up to Week 12

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: Descriptive statistics are presented for this endpoint, per protocol.

End point values	Dimethyl Fumarate			
Subject group type	Reporting group			
Number of subjects analysed	84[6]			
Units: units on a scale				
arithmetic mean (standard deviation)				
Overall treatment period; n=84	5.94 (± 2.427)			
Week 1-4; n=73	5.75 (± 2.554)			
Week 5-8; n=38	3.53 (± 2.533)			
Week 9-12; n=29	3.1 (± 2.568)			

Notes:

[6] - n=subjects with an assessment in given time period

Statistical analyses

No statistical analyses for this end point

Primary: Worst Severity Of Gastrointestinal-Related Events In Subjects Who Utilized Symptomatic Therapy During the 12-Week Treatment Period, MAGISS

End point title	Worst Severity Of Gastrointestinal-Related Events In Subjects Who Utilized Symptomatic Therapy During the 12-Week Treatment Period, MAGISS[7]

End point description:

The MAGISS is a questionnaire about the overall events related to the gastrointestinal system (including nausea, diarrhea, upper abdominal pain, lower abdominal pain, vomiting, indigestion, constipation, bloating, and flatulence) following drug administration (acute symptoms). MAGISS is based on a 0- to 10-point scale, with 0 representing absence of symptoms and 10 representing the most severe symptoms. The worst overall severity score for gastrointestinal-related events was calculated for each participant for the overall treatment period of 12 weeks, and for each 4-week period therein.

End point type	Primary

End point timeframe:

Up to Week 12

Notes:

[7] - 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: Descriptive statistics are presented for this endpoint, per protocol.

End point values	Dimethyl Fumarate			
Subject group type	Reporting group			
Number of subjects analysed	84[8]			
Units: units on a scale				
arithmetic mean (standard deviation)				
Overall treatment period; n=84	5.93 (± 2.516)			
Week 1-4; n=73	5.88 (± 2.614)			
Week 5-8; n=39	3.31 (± 2.307)			
Week 9-12; n=29	3.55 (± 2.772)			

Notes:

[8] - n=subjects with an assessment in given time period

Statistical analyses

No statistical analyses for this end point

Primary: Duration of Gastrointestinal-Related Events in Subjects Who Utilized Symptomatic Therapy During the 12-Week Treatment Period, MOGISS

End point title	Duration of Gastrointestinal-Related Events in Subjects Who Utilized Symptomatic Therapy During the 12-Week Treatment Period, MOGISS[9]

End point description:

The percentage of days with GI events as reported on MOGISS was calculated for each subject and each analysis period using the following formula: 100 x (# of days with [GI] events / # of days tolerability scale completed). The symptomatic therapy (ST) categories were provided by Biogen Medical team as follows: ST1=anti-acid production; ST2=anti-bloating/anti-constipation agent; ST3=multitarget/ herbal agents; ST4=anti-diarrheal (anti-peristaltic); ST5=analgesic (NSAID); ST6=anti-emetic (central); ST7=anti-emetic (pro-kinetic); ST8=antacid; ST9=other; ST10=laxative (pro-kinetic). Overall GI events were reported in the second day after the dose. Relative day for Overall GI events = assessment date-first dose date.

End point type	Primary

End point timeframe:

Up to Week 12

Notes:

[9] - 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: Descriptive statistics are presented for this endpoint, per protocol.

End point values	Dimethyl Fumarate			
Subject group type	Reporting group			
Number of subjects analysed	84[10]			
Units: percentage of days				
arithmetic mean (standard deviation)				
Overall treatment period; All STs(n=84)	38.13 (± 29.263)			
Overall treatment period; ST1 (n=50)	42.08 (± 27.495)			
Overall treatment period; ST2 (n=26)	36.98 (± 29.754)			
Overall treatment period; ST3 (n=20)	39.61 (± 29.197)			
Overall treatment period; ST4 (n=16)	48.15 (± 30.14)			
Overall treatment period; ST5 (n=10)	45.94 (± 27.147)			
Overall treatment period; ST6 (n=8)	44.33 (± 29.095)			
Overall treatment period; ST7 (n=6)	57.52 (± 21.998)			
Overall treatment period; ST8 (n=5)	52.71 (± 31.829)			
Overall treatment period; ST9 (n=3)	32.78 (± 26.995)			
Overall treatment period; ST10 (n=2)	9.2 (± 2.137)			
Week 1-4; All ST (n=73)	49.58 (± 29.547)			
Week 1-4; ST1 (n=44)	53.92 (± 27.197)			
Week 1-4; ST2 (n=23)	49.53 (± 32.012)			
Week 1-4; ST3 (n=18)	55.31 (± 29.869)			
Week 1-4; ST4 (n=13)	56.63 (± 25.764)			

Week 1-4; ST5 (n=9)	44.42 (± 32.47)			
Week 1-4; ST6 (n=6)	48.48 (± 35.539)			
Week 1-4; ST7 (n=6)	69.78 (± 24.808)			
Week 1-4; ST8 (n=5)	66.43 (± 31.4)			
Week 1-4; ST9 (n=3)	41.41 (± 34.085)			
Week 5-8; All ST (n=38)	41.55 (± 38.612)			
Week 5-8; ST1 (n=23)	44.04 (± 41.414)			
Week 5-8; ST2 (n=3)	41.67 (± 52.042)			
Week 5-8; ST3 (n=8)	37.45 (± 37.388)			
Week 5-8; ST4 (n=3)	69.14 (± 44.186)			
Week 5-8; ST5 (n=3)	63.75 (± 31.332)			
Week 5-8; ST6 (n=3)	70.42 (± 25.699)			
Week 5-8; ST7 (n=1)	35.71 (± 9999)			
Week 5-8; ST8 (n=2)	56.88 (± 40.032)			
Week 5-8; ST10 (n=2)	1.79 (± 2.525)			
Week 9-12; All ST (n=29)	43.27 (± 42.322)			
Week 9-12; ST1 (n=15)	47.66 (± 43.191)			
Week 9-12; ST2 (n=3)	82.72 (± 29.937)			
Week 9-12; ST3 (n=6)	48.85 (± 50.931)			
Week 9-12; ST4 (n=4)	22.12 (± 20.834)			
Week 9-12; ST5 (n=2)	62.5 (± 53.033)			
Week 9-12; ST8 (n=2)	9.26 (± 13.095)			

Notes:

[10] - n=subjects with an assessment in given time period; 9999=not applicable (1 subject in this group)

Statistical analyses

No statistical analyses for this end point

Primary: Duration of Gastrointestinal-Related Events in Subjects Who Utilize Symptomatic Therapy During the 12-Week Treatment Period, MAGISS

End point title	Duration of Gastrointestinal-Related Events in Subjects Who Utilize Symptomatic Therapy During the 12-Week Treatment Period, MAGISS[11]

End point description:

Percentage of days with GI events as reported on MAGISS was calculated for each subject and each analysis period using the following formula: 100 x (# of days with [GI] events / # of days tolerability scale completed). The ST categories were provided by Biogen Medical team as follows: ST1=anti-acid production; ST2=anti-bloating/anti-constipation agent; ST3=multitarget/ herbal agents; ST4=anti-diarrheal (anti-peristaltic); ST5=analgesic (NSAID); ST6=anti-emetic (central); ST7=anti-emetic (pro-kinetic); ST8=antacid; ST9=other; ST10=laxative (pro-kinetic). Overall GI events were reported in the

second day after the dose. Relative day for Overall GI events = assessment date-first dose date.

End point type	Primary

End point timeframe:

Up to Week 12

Notes:

[11] - 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: Descriptive statistics are presented for this endpoint, per protocol.

End point values	Dimethyl Fumarate			
Subject group type	Reporting group			
Number of subjects analysed	84[12]			
Units: percentage of days				
arithmetic mean (standard deviation)				
Overall treatment period; All ST (n=84)	38.2 (± 30.516)			
Overall treatment period; ST1 (n=50)	41.29 (± 29.517)			
Overall treatment period; ST2 (n=26)	33.67 (± 27.31)			
Overall treatment period; ST3 (n=20)	39.28 (± 29.165)			
Overall treatment period; ST4 (n=16)	49.94 (± 33.291)			
Overall treatment period; ST5 (n=10)	45.65 (± 27.118)			
Overall treatment period; ST6 (n=8)	44.71 (± 30.374)			
Overall treatment period; ST7 (n=6)	55.32 (± 23.097)			
Overall treatment period; ST8 (n=5)	53.42 (± 31.443)			
Overall treatment period; ST9 (n=3)	36.92 (± 27.8)			
Overall treatment period; ST10 (n=2)	10.88 (± 1.924)			
Week 1-4; All ST (n=73)	51.03 (± 30.36)			
Week 1-4; ST1 (n=44)	54.41 (± 29.608)			
Week 1-4; ST2 (n=23)	47.84 (± 30.764)			
Week 1-4; ST3 (n=18)	56.67 (± 30.711)			
Week 1-4; ST4 (n=13)	58.9 (± 27.111)			
Week 1-4; ST5 (n=9)	53.74 (± 32.304)			
Week 1-4; ST6 (n=6)	46.43 (± 33.221)			
Week 1-4; ST7 (n=6)	67.54 (± 25.296)			
Week 1-4; ST8 (n=5)	69.86 (± 28.919)			
Week 1-4; ST9 (n=3)	47.61 (± 32.59)			
Week 5-8; All ST (n=38)	40.59 (± 37.836)			
Week 5-8; ST1 (n=23)	41.59 (± 41.442)			

Week 5-8; ST2 (n=3)	47.14 (± 45.781)			
Week 5-8; ST3 (n=8)	38.5 (± 35.493)			
Week 5-8; ST4 (n=3)	62.58 (± 45.775)			
Week 5-8; ST5 (n=3)	56.33 (± 33.011)			
Week 5-8; ST6 (n=3)	71.61 (± 24.587)			
Week 5-8; ST7 (n=1)	35.71 (± 9999)			
Week 5-8; ST8 (n=2)	62.24 (± 32.456)			
Week 5-8; ST10 (n=2)	10 (± 14.142)			
Week 9-12; All ST (n=29)	41.28 (± 42.466)			
Week 9-12; ST1 (n=15)	44.24 (± 44.754)			
Week 9-12; ST2 (n=3)	76.19 (± 41.239)			
Week 9-12; ST3 (n=6)	51.99 (± 50.113)			
Week 9-12; ST4 (n=4)	15.48 (± 10.178)			
Week 9-12; ST5 (n=2)	63.16 (± 52.103)			
Week 9-12; ST8 (n=2)	13.11 (± 7.655)			

Notes:

[12] - n=subjects with an assessment in given time period; 9999=not applicable (1 subject in this group)

Statistical analyses

No statistical analyses for this end point

Secondary: Percentage of Subjects Who First Took Symptomatic Therapy for Gastrointestinal-Related Events by Weeks 4, 8, and 12

End point title	Percentage of Subjects Who First Took Symptomatic Therapy for Gastrointestinal-Related Events by Weeks 4, 8, and 12

End point description:

The cumulative percentage of dimethyl fumarate-treated subjects with relapsing-remitting multiple sclerosis who required symptomatic therapy up to Week 4, Week 8, and Week 12 were estimated using the Kaplan-Meier method.

End point type	Secondary

End point timeframe:

Week 4, Week 8, Week 12

End point values	Dimethyl Fumarate			
Subject group type	Reporting group			
Number of subjects analysed	84[13]			
Units: percentage of subjects				
number (not applicable)				
Week 4	35.3			

Week 8	38.4			
Week 12	41.1			

Notes:

[13] - Subjects who reported taking symptomatic therapy.

Statistical analyses

No statistical analyses for this end point

Secondary: Number of Subjects Who Used Symptomatic Therapies for Gastrointestinal-Related Events During the 12-Week Treatment Period, by Category

End point title	Number of Subjects Who Used Symptomatic Therapies for Gastrointestinal-Related Events During the 12-Week Treatment Period, by Category

End point description:

Symptomatic therapies were classified into 10 main categories: anti-acid production (eg, pantoprazole, omeprazole, esomeprazole, ranitidine); anti-bloating/anti-constipation agents (eg, hyoscine butylbromide, sodium picosulfate, Agiolax, dimeticone, lactulose, Movicol, simethicone); multitarget/herbal agents (includes Iberogast, Gaviscon, amaratropfen, Wikalin, Gaviscon & Iberogast, Iberogast & Wikalin); anti-diarrheal (anti-peristaltic; loperamide, racecadotril); analgesic (non-steroidal anti-inflammatory drug [NSAID]; ibuprofen, paracetamol, metamizole); anti-emetic (central; dimenhydrinate, domperidone); anti-emetic (pro-kinetic; metoclopramide); anti-acid (calcium carbonate, magaldrat, sodium hydrogen carbonate, sodium hydroxide/aluminium oxide, Talcid); other (Saccharomyces boulardii, carbon tablet, Lactobacillus acidophilus); laxative (pro-kinetic; bisacodyl). Subjects may have taken > 1 symptomatic therapy but were counted only once for the 'All therapies' summary.

End point type	Secondary

End point timeframe:

Up to Week 12

End point values	Dimethyl Fumarate			
Subject group type	Reporting group			
Number of subjects analysed	211			
Units: subjects				
Overall treatment period (OTP): All therapies	84			
OTP: Anti-acid production	50			
OTP: Anti-bloating/anti-constipation agent	26			
OTP: Multi-target/herbal agents	20			
OTP: Anti-diarrheal (anti-peristaltic)	16			
OTP: Analgesic (NSAID)	10			
OTP: Anti-emetic (central)	8			
OTP: Anti-emetic (pro-kinetic)	6			
OTP: Antacid	5			
OTP: Other	3			
OTP: Laxative (pro-kinetic)	2			
Week 1-4: All therapies	73			
Week 1-4: Anti-acid production	44			
Week 1-4: Anti-bloating/anti-constipation agent	23			

Week 1-4: Multi-target/herbal agents	18			
Week 1-4: Anti-diarrheal (anti-peristaltic)	13			
Week 1-4: Analgesic (NSAID)	9			
Week 1-4: Anti-emetic (central)	6			
Week 1-4: Anti-emetic (pro-kinetic)	6			
Week 1-4: Antacid	5			
Week 1-4: Other	3			
Week 5-8: All therapies	38			
Week 5-8: Anti-acid production	23			
Week 5-8: Multi-target/herbal agents	8			
Week 5-8: Analgesic (NSAID)	3			
Week 5-8: Anti-bloating/anti-constipation agent	3			
Week 5-8: Anti-diarrheal (anti-peristaltic)	3			
Week 5-8: Anti-emetic (central)	3			
Week 5-8: Antacid	2			
Week 5-8: Laxative (pro-kinetic)	2			
Week 5-8: Anti-emetic (pro-kinetic)	1			
Week 9-12: All therapies	29			
Week 9-12: Anti-acid production	15			
Week 9-12: Multi-target/herbal agents	6			
Week 9-12: Anti-diarrheal (anti-peristaltic)	4			
Week 9-12: Anti-bloating/anti-constipation agent	3			
Week 9-12: Analgesic (NSAID)	2			
Week 9-12: Antacid	2			

Statistical analyses

No statistical analyses for this end point

Secondary: Duration of Use of Symptomatic Therapies for Gastrointestinal-Related Events During the 12-Week Treatment Period, by Category

End point title	Duration of Use of Symptomatic Therapies for Gastrointestinal-Related Events During the 12-Week Treatment Period, by Category

End point description:

Symptomatic therapies were classified into 10 categories: anti-acid production (eg, pantoprazole, omeprazole, esomeprazole, ranitidine); anti-bloating/anti-constipation agents (eg, hyoscine butylbromide, sodium picosulfate, Agiolax, dimeticone, lactulose, Movicol, simethicone); multitarget/herbal agents (eg, Iberogast, Gaviscon, amaratropfen, Wikalin, Gaviscon & Iberogast, Iberogast & Wikalin); anti-diarrheal (anti-peristaltic; loperamide, racecadotril); analgesic (NSAID; ibuprofen, paracetamol, metamizole); anti-emetic (central; dimenhydrinate, domperidone); anti-emetic (pro-kinetic; metoclopramide); anti-acid (calcium carbonate, magaldrat, sodium hydrogen carbonate, sodium hydroxide/aluminium oxide, Talcid); other (Saccharomyces boulardii, carbon tablet, Lactobacillus acidophilus); laxative (pro-kinetic; bisacodyl). If a subject had multiple different therapies on the same day, the days on symptomatic therapy was calculated as 1 day in 'All therapies'.

End point type	Secondary

End point timeframe:

Up to Week 12

End point values	Dimethyl Fumarate			
Subject group type	Reporting group			
Number of subjects analysed	84[14]			
Units: days				
arithmetic mean (standard deviation)				
OTP: All therapies; n=84	13.15 (± 19.21)			
OTP: Anti-acid production; n=50	16.62 (± 22.21)			
OTP: Anti-bloating/anti-constipation agent; n=26	2.42 (± 1.81)			
OTP: Multi-target/herbal agents; n=20	9.4 (± 13.95)			
OTP: Anti-diarrheal (anti-peristaltic); n=16	3.13 (± 2.53)			
OTP: Analgesic (NSAID); n=10	3.1 (± 1.73)			
OTP: Anti-emetic (central); n=8	3.25 (± 4.43)			
OTP: Anti-emetic (pro-kinetic); n=6	1.83 (± 0.98)			
OTP: Antacid; n=5	3.6 (± 4.22)			
OTP: Other; n=3	1.67 (± 0.58)			
OTP: Laxative (pro-kinetic); n=2	1 (± 0)			
Week 1-4: All therapies; n=73	6.03 (± 6.12)			
Week 1-4: Anti-acid production; n=44	7.07 (± 6.73)			
Week 1-4: Anti-bloating/anti-constipation; n=23	2.3 (± 1.89)			
Week 1-4: Multi-target/herbal agents; n=18	3.78 (± 3.06)			
Week 1-4: Anti-diarrheal (anti-peristaltic); n=13	2.62 (± 1.45)			
Week 1-4: Analgesic (NSAID); n=9	2.11 (± 0.93)			
Week 1-4: Anti-emetic (central); n=6	3.17 (± 3.92)			
Week 1-4: Anti-emetic (pro-kinetic); n=6	1.67 (± 0.82)			
Week 1-4: Antacid; n=5	1.8 (± 1.3)			
Week 1-4: Other; n=3	1.67 (± 0.58)			
Week 5-8: All therapies; n=38	10.08 (± 10.56)			
Week 5-8: Anti-acid production; n=23	13 (± 11.14)			
Week 5-8: Multi-target/herbal agents; n=8	8.5 (± 10.45)			
Week 5-8: Analgesic (NSAID); n=3	2 (± 1)			
Week 5-8: Anti-bloating/anti-constipation; n=3	1.33 (± 0.58)			
Week 5-8: Anti-diarrheal (anti-peristaltic); n=3	4 (± 3.61)			
Week 5-8: Anti-emetic (central); n=3	2.33 (± 1.15)			
Week 5-8: Antacid; n=2	2.5 (± 2.12)			
Week 5-8: Laxative (pro-kinetic); n=2	1 (± 0)			
Week 5-8: Anti-emetic (prokinetic); n=1	1 (± 9999)			
Week 9-12: All therapies; n=29	9.72 (± 10.31)			
Week 9-12: Anti-acid production; n=15	14.73 (± 10.91)			

Week 9-12: Multi-target/herbal agents; n=6	8.67 (± 8.57)			
Week 9-12: Anti-diarrheal (anti-peristaltic); n=4	1 (± 0)			
Week 9-12: Anti-bloating/anti-constipation; n=3	2 (± 1)			
Week 9-12: Analgesic (NSAID); n=2	3 (± 0)			
Week 9-12: Antacid; n=2	2 (± 1.41)			

Notes:

[14] - n=subjects with an assessment in given time period; 9999=not applicable (1 subject in group).

Statistical analyses

No statistical analyses for this end point

Secondary: Percentage of Subjects Who Required Dimethyl Fumarate Dose Reduction In Response To Gastrointestinal-Related Events

End point title	Percentage of Subjects Who Required Dimethyl Fumarate Dose Reduction In Response To Gastrointestinal-Related Events

End point description:

Dose reductions are defined as subjects who took any dimethyl fumarate 120 mg or 0 mg since initiation of dimethyl fumarate 240 mg.

End point type	Secondary

End point timeframe:

Up to Week 12

End point values	Dimethyl Fumarate			
Subject group type	Reporting group			
Number of subjects analysed	211			
Units: percentage of subjects				
number (not applicable)	34.6			

Statistical analyses

No statistical analyses for this end point

Secondary: Percentage of Subjects Who Discontinued Dimethyl Fumarate due to Gastrointestinal-Related Treatment-Emergent Adverse Events

End point title	Percentage of Subjects Who Discontinued Dimethyl Fumarate due to Gastrointestinal-Related Treatment-Emergent Adverse Events

End point description:

End point type	Secondary

End point timeframe:

Up to Week 12

End point values	Dimethyl Fumarate			
Subject group type	Reporting group			
Number of subjects analysed	211			
Units: percentage of subjects				
number (not applicable)	6.6			

Statistical analyses

No statistical analyses for this end point

Adverse events

Adverse events information

Timeframe for reporting adverse events:

Events presented are treatment emergent: reported from time of first dose of dimethyl fumarate through last dose (up to 12 weeks (±5 days) plus 2 weeks (±5 days) follow up.

Assessment type	Systematic

Dictionary used

Dictionary name	MedDRA
Dictionary version	19.0

Reporting groups

Reporting group title	Dimethyl Fumarate

Reporting group description:

Dimethyl fumarate administered orally at 120 mg BID for the first 7 days and 240 mg BID thereafter for a total of 12 weeks.

Serious adverse events	Dimethyl Fumarate		
Total subjects affected by serious adverse events			
subjects affected / exposed	5 / 211 (2.37%)		
number of deaths (all causes)	0		
number of deaths resulting from adverse events	0		
Investigations			
Alanine aminotransferase increased			
subjects affected / exposed	1 / 211 (0.47%)		
occurrences causally related to treatment / all	1 / 1		
deaths causally related to treatment / all	0 / 0		
Aspartate aminotransferase increased			
subjects affected / exposed	1 / 211 (0.47%)		
occurrences causally related to treatment / all	1 / 1		
deaths causally related to treatment / all	0 / 0		
Gamma-glutamyltransferase increased			
subjects affected / exposed	1 / 211 (0.47%)		
occurrences causally related to treatment / all	1 / 1		
deaths causally related to treatment / all	0 / 0		
Nervous system disorders			
Multiple sclerosis relapse			

subjects affected / exposed	2 / 211 (0.95%)		
occurrences causally related to treatment / all	0 / 2		
deaths causally related to treatment / all	0 / 0		
Immune system disorders			
Hypersensitivity			
subjects affected / exposed	1 / 211 (0.47%)		
occurrences causally related to treatment / all	1 / 1		
deaths causally related to treatment / all	0 / 0		
Psychiatric disorders			
Alcohol abuse			
subjects affected / exposed	1 / 211 (0.47%)		
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	Dimethyl Fumarate		
Total subjects affected by non-serious adverse events			
subjects affected / exposed	129 / 211 (61.14%)		
Vascular disorders			
Flushing			
subjects affected / exposed	105 / 211 (49.76%)		
occurrences (all)	118		
Nervous system disorders			
Headache			
subjects affected / exposed	14 / 211 (6.64%)		
occurrences (all)	22		
General disorders and administration site conditions			
Fatigue			
subjects affected / exposed	12 / 211 (5.69%)		
occurrences (all)	12		
Skin and subcutaneous tissue disorders			
Pruritis			
subjects affected / exposed	12 / 211 (5.69%)		
occurrences (all)	13		
Infections and infestations			

Nasopharyngitis subjects affected / exposed occurrences (all)	31 / 211 (14.69%) 33		

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

Date	Amendment
07 October 2013	- To update the protocol to reflect the use of electronic patient reported outcomes on hand-held devices instead of paper questionnaires. - To update DMF storage information for consistency with the drug label – DMF should be protected from light.
20 July 2015	- To update the contact details of the pharmacovigilance provider for this study.

Notes:

Interruptions (globally)

Were there any global interruptions to the trial? No

Limitations and caveats

None reported