



Clinical trial results:

The Effect of Tecfidera® (Dimethyl Fumarate, BG00012) on the Gut Microbiota as a Causal Factor for Gastro Intestinal Associated Adverse Events (TECONGUT)

Summary

EudraCT number	2015-001197-18
Trial protocol	NO
Global end of trial date	12 June 2017

Results information

Result version number	v1 (current)
This version publication date	05 January 2019
First version publication date	05 January 2019

Trial information

Trial identification

Sponsor protocol code	NOR-BGT-14-10665
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Additional study identifiers

ISRCTN number	-
ClinicalTrials.gov id (NCT number)	NCT02471560
WHO universal trial number (UTN)	-

Notes:

Sponsors

Sponsor organisation name	Biogen
Sponsor organisation address	250 Binney Street, Cambridge, Massachusetts, United States, 02142
Public contact	Study Medical Director, Biogen, clinicaltrials@biogen.com
Scientific contact	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	12 June 2017
Is this the analysis of the primary completion data?	No
Global end of trial reached?	Yes
Global end of trial date	12 June 2017
Was the trial ended prematurely?	Yes

Notes:

General information about the trial

Main objective of the trial:

The primary objective of the study was to determine if dimethyl fumarate (DMF) causes changes in the abundance and diversity of commensal microbiota.

Protection of trial subjects:

Subjects were treated according to clinical practice; protection of subjects was ensured by health care professional (HCP) as per clinical practice.

Background therapy: -

Evidence for comparator: -

Actual start date of recruitment	03 November 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	Norway: 36
Worldwide total number of subjects	36
EEA total number of subjects	36

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)	35
From 65 to 84 years	1
85 years and over	0

Subject disposition

Recruitment

Recruitment details:

A total of 38 subjects were screened from 7 sites in Norway.

Pre-assignment

Screening details:

A total of 38 subjects were screened, 1 subject withdrew due to screening failure and 1 subject withdrew informed consent before study start.

Period 1

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

Arms

Are arms mutually exclusive?	Yes
Arm title	Dimethyl Fumarate (DMF)

Arm description:

Subjects followed the dosing schedule recommended by summary of product characteristics (SPC) for DMF i.e., 120 milligram (mg) two time daily (BID) orally for 7 days, followed by recommended dose of 240 mg BID.

Arm type	Experimental
Investigational medicinal product name	Dimethyl Fumarate
Investigational medicinal product code	
Other name	BG00012
Pharmaceutical forms	Capsule, hard
Routes of administration	Oral use

Dosage and administration details:

DMF 120 mg capsules BID orally for 7 days, followed by recommended dose of 240 mg BID.

Arm title	Injectable (Multiple Sclerosis Disease Modifying Therapies)
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Arm description:

Subjects followed administration instructions and dosing schedule recommended in SPC.

Arm type	Experimental
Investigational medicinal product name	Multiple Sclerosis Disease Modifying Therapies (MS DMT)
Investigational medicinal product code	
Other name	IFN β -1a, IFN β -1b, Glatiramer Acetate
Pharmaceutical forms	Injection
Routes of administration	Intravenous use

Dosage and administration details:

Administered as recommended by SPC.

Number of subjects in period 1	Dimethyl Fumarate (DMF)	Injectable (Multiple Sclerosis Disease Modifying Therapies)
Started	27	9
Completed	22	9
Not completed	5	0
Adverse Event	3	-
Protocol Deviation	1	-
Lost to follow-up	1	-

Baseline characteristics

Reporting groups

Reporting group title	Dimethyl Fumarate (DMF)
Reporting group description: Subjects followed the dosing schedule recommended by summary of product characteristics (SPC) for DMF i.e., 120 milligram (mg) two time daily (BID) orally for 7 days, followed by recommended dose of 240 mg BID.	
Reporting group title	Injectable (Multiple Sclerosis Disease Modifying Therapies)
Reporting group description: Subjects followed administration instructions and dosing schedule recommended in SPC.	

Reporting group values	Dimethyl Fumarate (DMF)	Injectable (Multiple Sclerosis Disease Modifying Therapies)	Total
Number of subjects	27	9	36
Age Categorical Units: Subjects			
Age Continuous Units: years median inter-quartile range (Q1-Q3)	45 39 to 52	44 33 to 59	-
Gender Categorical Units: Subjects			
Female	19	7	26
Male	8	2	10

End points

End points reporting groups

Reporting group title	Dimethyl Fumarate (DMF)
Reporting group description: Subjects followed the dosing schedule recommended by summary of product characteristics (SPC) for DMF i.e., 120 milligram (mg) two time daily (BID) orally for 7 days, followed by recommended dose of 240 mg BID.	
Reporting group title	Injectable (Multiple Sclerosis Disease Modifying Therapies)
Reporting group description: Subjects followed administration instructions and dosing schedule recommended in SPC.	
Subject analysis set title	DMF Subjects Without GIAE
Subject analysis set type	Safety analysis
Subject analysis set description: Subjects who had received DMF and do not develop gastro-intestinal adverse event (GIAE).	
Subject analysis set title	DMF Subjects With GIAE
Subject analysis set type	Safety analysis
Subject analysis set description: Subjects who had received DMF and do develop GIAE.	

Primary: Change From Baseline in Gut Microbiota Composition in Subjects pre vs Post Initiation of DMF Treatment at Week 2

End point title	Change From Baseline in Gut Microbiota Composition in Subjects pre vs Post Initiation of DMF Treatment at Week 2 ^[1]
End point description:	
End point type	Primary
End point timeframe: Baseline, Week 2	

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: Only descriptive data was planned to be reported.

End point values	Dimethyl Fumarate (DMF)	Injectable (Multiple Sclerosis Disease Modifying Therapies)		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	27	9		
Units: relative abundance of bacterial phyla				
median (inter-quartile range (Q1-Q3))				
Actinobacteria	0.011 (0.005 to 0.02)	0.024 (0.02 to 0.04)		
Bifidobacterium	0.007 (0.001 to 0.01)	0.015 (0.004 to 0.03)		
Firmicutes	0.63 (0.52 to 0.77)	0.589 (0.53 to 0.73)		
Bacteroidetes	0.195 (0.15 to 0.44)	0.359 (0.21 to 0.45)		
Firmicutes:Bacteroidetes-ratio	2.26 (1.2 to 5.4)	1.651 (1.18 to 3.72)		

Ruminococcacea	0.32 (0.23 to 0.38)	0.28 (0.17 to 0.35)		
Faecalibacterium	0.055 (0.03 to 0.09)	0.06 (0.04 to 0.10)		
Bacteroides	0.14 (0.09 to 0.30)	0.117 (0.09 to 0.24)		

Statistical analyses

No statistical analyses for this end point

Primary: Change From Baseline in Gut Microbiota Composition in Subjects pre vs Post Initiation of DMF Treatment at Week 12

End point title	Change From Baseline in Gut Microbiota Composition in Subjects pre vs Post Initiation of DMF Treatment at Week 12 ^[2]
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End point description:

End point type	Primary
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End point timeframe:

Baseline, Week 12

Notes:

[2] - 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: Only descriptive data was planned to be reported.

End point values	Dimethyl Fumarate (DMF)	Injectable (Multiple Sclerosis Disease Modifying Therapies)		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	27	9		
Units: relative abundance of bacterial phyla				
median (inter-quartile range (Q1-Q3))				
Actinobacteria	0.016 (0.01 to 0.04)	0.02 (0.008 to 0.03)		
Bifidobacterium	0.012 (0.002 to 0.02)	0.011 (0.004 to 0.03)		
Firmicutes	0.679 (0.56 to 0.78)	0.659 (0.46 to 0.72)		
Bacteroidetes	0.246 (0.13 to 0.35)	0.292 (0.23 to 0.49)		
Firmicutes:Bacteroidetes-ratio	2.685 (1.51 to 6.35)	2.253 (1.10 to 3.17)		
Ruminococcacea	0.32 (0.27 to 0.41)	0.25 (0.18 to 0.38)		
Faecalibacterium	0.067 (0.04 to 0.11)	0.06 (0.05 to 0.08)		
Bacteroides	0.14 (0.07 to 0.23)	0.165 (0.09 to 0.28)		

Statistical analyses

No statistical analyses for this end point

Primary: Change From Baseline in Shannon Index in Subjects pre vs Post Initiation of DMF Treatment at Week 2

End point title	Change From Baseline in Shannon Index in Subjects pre vs Post Initiation of DMF Treatment at Week 2 ^[3]
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End point description:

Shannon diversity index is a quantitative measure that reflects how many different types (such as species) are in a dataset (a community), and simultaneously takes into account how evenly the basic entities (such as individuals) are distributed among those types. A community with only one species would have Shannon's index of 0. The higher the index, the more diverse a community.

End point type	Primary
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End point timeframe:

Baseline, Week 2

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: Only descriptive data was planned to be reported.

End point values	Dimethyl Fumarate (DMF)	Injectable (Multiple Sclerosis Disease Modifying Therapies)		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	27	9		
Units: shannon's diversity index				
median (inter-quartile range (Q1-Q3))	6.54 (6.03 to 6.76)	6.53 (5.80 to 7.09)		

Statistical analyses

No statistical analyses for this end point

Primary: Change From Baseline in Shannon Index in Subjects pre vs Post Initiation of DMF Treatment at Week 12

End point title	Change From Baseline in Shannon Index in Subjects pre vs Post Initiation of DMF Treatment at Week 12 ^[4]
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End point description:

Shannon diversity index is a quantitative measure that reflects how many different types (such as species) are in a dataset (a community), and simultaneously takes into account how evenly the basic entities (such as individuals) are distributed among those types. A community with only one species would have Shannon's index of 0. The higher the index, the more diverse a community.

End point type	Primary
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End point timeframe:

Baseline, Week 12

Notes:

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

Justification: Only descriptive data was planned to be reported.

End point values	Dimethyl Fumarate (DMF)	Injectable (Multiple Sclerosis Disease Modifying Therapies)		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	27	9		
Units: shannon's diversity index				
median (inter-quartile range (Q1-Q3))	6.49 (6.08 to 6.73)	6.74 (5.89 to 7.08)		

Statistical analyses

No statistical analyses for this end point

Secondary: Change From Baseline in Gut Microbiota composition Between DMF Treated Subjects That do or do not Develop Gastro-intestinal (GI) Adverse Evenrs (AEs) as Measured by an Increase in the Gastrointestinal Symptom Rating Scale (GSRS) Score at Week 2 and 12

End point title	Change From Baseline in Gut Microbiota composition Between DMF Treated Subjects That do or do not Develop Gastro-intestinal (GI) Adverse Evenrs (AEs) as Measured by an Increase in the Gastrointestinal Symptom Rating Scale (GSRS) Score at Week 2 and 12
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End point description:

GSRS is a self-reported questionnaire regarding GI symptoms comprising 15 items scored on a 7-point Likert scale. The 15 items can be grouped in 5 dimensions 1) abdominal pain (abdominal pain, gastric hunger pain, and nausea) 2) reflux (heartburn and acid regurgitation) 3) indigestion (borborygmus, bloating, eructation, and increased flatus) 4) diarrhea (diarrhea, loose stools, and urgency) and 5) constipation (constipation, hard stools, incomplete evacuation). A GI AE will be defined as an at least 2 point (≥ 2) increase from baseline in total score of any of the 5 dimensions in the GSRS. (maximum score per dimension is 3 items x 7 points = 21). Here, 'n' signifies that number of subjects evaluated for the specified bacterial composition.

End point type	Secondary
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End point timeframe:

Baseline, Week 2, Week 12

End point values	DMF Subjects Without GIAE	DMF Subjects With GIAE		
Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed	11 ^[5]	10 ^[6]		
Units: relative abundance of bacterial phyla				
median (inter-quartile range (Q1-Q3))				
Actinobacteria: Baseline for Week 2 (n =11, 10)	0.016 (0.012 to 0.032)	0.022 (0.008 to 0.045)		
Actinobacteria: Change at Week 2 (n =11, 10)	0.011 (0.005 to 0.022)	0.011 (0.003 to 0.024)		
Actinobacteria: Baseline for Week 12 (n =10, 10)	0.03 (0.013 to 0.046)	0.01 (0.004 to 0.024)		
Actinobacteria: Change at Week 12 (n =10, 10)	0.024 (0.009 to 0.048)	0.011 (0.004 to 0.03)		

Bifidobacterium: Baseline for Week 2 (n =11, 10)	0.011 (0.006 to 0.022)	0.012 (0.005 to 0.038)		
Bifidobacterium: Change at Week 2 (n =11, 10)	0.008 (0.003 to 0.014)	0.005 (0 to 0.015)		
Bifidobacterium: Baseline for Week 12 (n =10, 10)	0.016 (0.007 to 0.04)	0.007 (0.002 to 0.018)		
Bifidobacterium: Change at Week 12 (n =10, 10)	0.015 (0.004 to 0.028)	0.008 (0.001 to 0.027)		
Firmicutes: Baseline for Week 2 (n =11, 10)	0.546 (0.509 to 0.734)	0.728 (0.536 to 0.787)		
Firmicutes: Change at Week 2 (n =11, 10)	0.622 (0.533 to 0.799)	0.686 (0.515 to 0.782)		
Firmicutes: Baseline for Week 12 (n =10, 10)	0.632 (0.539 to 0.724)	0.702 (0.521 to 0.843)		
Firmicutes: Change at Week 12 (n =10, 10)	0.685 (0.597 to 0.784)	0.715 (0.563 to 0.866)		
Bacteroidetes: Baseline for Week 2 (n =11, 10)	0.388 (0.184 to 0.424)	0.188 (0.151 to 0.294)		
Bacteroidetes: Change at Week 2 (n =11, 10)	0.311 (0.138 to 0.437)	0.192 (0.145 to 0.368)		
Bacteroidetes: Baseline for Week 12 (n =10, 10)	0.319 (0.187 to 0.396)	0.22 (0.089 to 0.426)		
Bacteroidetes: Change at Week 12 (n =10, 10)	0.245 (0.151 to 0.29)	0.221 (0.078 to 0.405)		
Faecalibacterium: Baseline for Week 2 (n =11, 10)	0.036 (0.025 to 0.057)	0.057 (0.033 to 0.094)		
Faecalibacterium: Change at Week 2 (n =11, 10)	0.055 (0.037 to 0.072)	0.058 (0.024 to 0.139)		
Faecalibacterium: Baseline for Week 12 (n =10, 10)	0.044 (0.025 to 0.071)	0.052 (0.027 to 0.094)		
Faecalibacterium: Change at Week 12 (n =10, 10)	0.063 (0.035 to 0.117)	0.071 (0.051 to 0.119)		
Bacteroides: Baseline for Week 2 (n =11, 10)	0.304 (0.125 to 0.352)	0.115 (0.065 to 0.162)		
Bacteroides: Change at Week 2 (n =11, 10)	0.244 (0.088 to 0.379)	0.14 (0.052 to 0.26)		
Bacteroides: Baseline for Week 12 (n =10, 10)	0.25 (0.124 to 0.321)	0.104 (0.028 to 0.311)		
Bacteroides: Change at Week 12 (n =10, 10)	0.152 (0.074 to 0.224)	0.107 (0.019 to 0.261)		

Notes:

[5] - Number of subjects analysed is the number of subjects evaluated for this endpoint.

[6] - Number of subjects analysed is the number of subjects evaluated for this endpoint.

Statistical analyses

No statistical analyses for this end point

Secondary: Change From Baseline in Gut Microbiota Composition in Subjects Treated With DMF Compared to Subjects Treated With an Alternative MS DMT at Week 2 and 12

End point title	Change From Baseline in Gut Microbiota Composition in Subjects Treated With DMF Compared to Subjects Treated With an Alternative MS DMT at Week 2 and 12
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End point description:

Here, 'n' signifies the number of subjects evaluated for specified bacterial composition.

End point type	Secondary
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End point timeframe:

Baseline, Week 2, Week 12

End point values	Dimethyl Fumarate (DMF)	Injectable (Multiple Sclerosis Disease Modifying Therapies)		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	21 ^[7]	9 ^[8]		
Units: delta values of relative abundance				
median (inter-quartile range (Q1-Q3))				
Change in Actinobacteria at Week 2 (n =21, 9)	-0.006 (-0.026 to 0.002)	-0.001 (-0.008 to 0.016)		
Change in Actinobacteria at Week 12 (n =20, 9)	0 (-0.02 to 0.022)	-0.002 (-0.02 to 0.002)		
Change in Bifidobacterium at Week 2 (n =21, 9)	-0.002 (-0.013 to 0.001)	-0.002 (-0.012 to 0.011)		
Change in Bifidobacterium at Week 12 (n =20, 9)	0.001 (-0.015 to 0.013)	-0.003 (-0.023 to 0.001)		
Change in Firmicutes at Week 2 (n =21, 9)	0.011 (-0.06 to 0.078)	0.001 (-0.069 to 0.032)		
Change in Firmicutes at Week 12 (n =20, 9)	0.048 (0.002 to 0.088)	-0.012 (-0.032 to 0.066)		
Change in Bacteroidetes at Week 2 (n =21, 9)	-0.014 (-0.062 to 0.053)	0.025 (-0.031 to 0.066)		
Change in Bacteroidetes at Week 12 (n =20, 9)	-0.045 (-0.096 to -0.005)	0.011 (-0.061 to 0.061)		
Change in Faecalibacterium at Week 2 (n =21, 9)	0.004 (-0.009 to 0.033)	-0.018 (-0.039 to 0.003)		
Change in Faecalibacterium at Week 12 (n =20, 9)	0.021 (-0.001 to 0.046)	-0.007 (-0.035 to 0.011)		
Change in Bacteroides at Week 2 (n =21, 9)	-0.004 (-0.05 to 0.045)	0.008 (-0.049 to 0.051)		
Change in Bacteroides at Week 12 (n =20, 9)	-0.046 (-0.066 to -0.004)	-0.005 (-0.017 to 0.054)		

Notes:

[7] - Number of subjects analysed is the number of subjects evaluated for this endpoint.

[8] - Number of subjects analysed is the number of subjects evaluated for this endpoint.

Statistical analyses

No statistical analyses for this end point

Secondary: Baseline Differences in the Gut Microbiota composition Between DMF Treated Subjects That do or do not Develop GI AEs at Week 2 and 12

End point title	Baseline Differences in the Gut Microbiota composition Between DMF Treated Subjects That do or do not Develop GI AEs at Week 2 and 12
End point description:	Here, 'n' signifies the number of subjects evaluated for specified bacterial composition.
End point type	Secondary
End point timeframe:	Baseline, Week 2, Week 12

End point values	DMF Subjects Without GIAE	DMF Subjects With GIAE		
Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed	12	12		
Units: relative abundance of bacterial phyla				
median (inter-quartile range (Q1-Q3))				
Change in Actinobacteria at Week 2 (n =12, 12)	0.015 (0.012 to 0.031)	0.021 (0.008 to 0.035)		
Change in Actinobacteria at Week 12 (n =10, 11)	0.03 (0.013 to 0.046)	0.011 (0.004 to 0.023)		
Change in Bifidobacterium at Week 2 (n =12, 12)	0.011 (0.005 to 0.02)	0.012 (0.003 to 0.031)		
Change in Bifidobacterium at Week 12 (n =10, 11)	0.016 (0.007 to 0.04)	0.008 (0.002 to 0.017)		
Change in Firmicutes at Week 2 (n =12, 12)	0.545 (0.51 to 0.724)	0.708 (0.528 to 0.767)		
Change in Firmicutes at Week 12 (n =10, 11)	0.632 (0.539 to 0.724)	0.734 (0.524 to 0.835)		
Change in Bacteroidetes at Week 2 (n =12, 12)	0.39 (0.186 to 0.466)	0.206 (0.171 to 0.372)		
Change in Bacteroidetes at Week 12 (n =10, 11)	0.319 (0.187 to 0.396)	0.184 (0.092 to 0.424)		
Change in Faecalibacterium at Week 2 (n =12, 12)	0.037 (0.025 to 0.063)	0.056 (0.031 to 0.088)		
Change in Faecalibacterium at Week 12 (n =10, 11)	0.044 (0.025 to 0.071)	0.039 (0.029 to 0.093)		
Change in Bacteroides at Week 2 (n =12, 12)	0.308 (0.125 to 0.408)	0.124 (0.078 to 0.21)		
Change in Bacteroides at Week 12 (n =10, 11)	0.25 (0.124 to 0.321)	0.108 (0.031 to 0.306)		

Statistical analyses

No statistical analyses for this end point

Secondary: Change From Baseline in the Gut Microbiota Composition of DMF Treated Subjects After Resolution of GI AEs vs. During GI AE Occurrences at Week 2 and 12

End point title	Change From Baseline in the Gut Microbiota Composition of DMF Treated Subjects After Resolution of GI AEs vs. During GI AE Occurrences at Week 2 and 12
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End point description:

End point type	Secondary
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End point timeframe:

Baseline, Week 2, Week 12

End point values	Dimethyl Fumarate (DMF)	Injectable (Multiple Sclerosis Disease Modifying Therapies)		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	0 ^[9]	0 ^[10]		
Units: relative abundance of bacterial phyla				
median (standard deviation)	()	()		

Notes:

[9] - Data was not collected for the endpoint due to low number of subjects analysed.

[10] - Data was not collected for the endpoint due to low number of subjects analysed.

Statistical analyses

No statistical analyses for this end point

Adverse events

Adverse events information

Timeframe for reporting adverse events:

From start to last visit (Up to Week 12)

Assessment type	Systematic
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Dictionary used

Dictionary name	MedDRA
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Dictionary version	19.0
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Reporting groups

Reporting group title	Multiple Sclerosis Disease Modifying Therapies (MS DMT)
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Reporting group description:

Subjects followed administration instructions and dosing schedule recommended in SPC.

Reporting group title	Dimethyl Fumarate (DMF)
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Reporting group description:

Subjects followed the dosing schedule recommended by summary of product characteristics (SPC) for DMF i.e., 120 milligram (mg) two time daily (BID) orally for 7 days, followed by recommended dose of 240 mg BID.

Serious adverse events	Multiple Sclerosis Disease Modifying Therapies (MS DMT)	Dimethyl Fumarate (DMF)	
Total subjects affected by serious adverse events			
subjects affected / exposed	1 / 9 (11.11%)	1 / 27 (3.70%)	
number of deaths (all causes)	0	0	
number of deaths resulting from adverse events	0	0	
Nervous system disorders			
Relapsing-remitting multiple sclerosis			
subjects affected / exposed	0 / 9 (0.00%)	1 / 27 (3.70%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Multiple sclerosis relapse			
subjects affected / exposed	0 / 9 (0.00%)	1 / 27 (3.70%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Optic neuritis			
subjects affected / exposed	1 / 9 (11.11%)	0 / 27 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	

Frequency threshold for reporting non-serious adverse events: 0 %

Non-serious adverse events	Multiple Sclerosis Disease Modifying Therapies (MS DMT)	Dimethyl Fumarate (DMF)	
Total subjects affected by non-serious adverse events			
subjects affected / exposed	8 / 9 (88.89%)	15 / 27 (55.56%)	
Injury, poisoning and procedural complications			
Fall			
subjects affected / exposed	1 / 9 (11.11%)	0 / 27 (0.00%)	
occurrences (all)	1	0	
Vascular disorders			
Flushing			
subjects affected / exposed	0 / 9 (0.00%)	4 / 27 (14.81%)	
occurrences (all)	0	4	
Hot Flush			
subjects affected / exposed	0 / 9 (0.00%)	1 / 27 (3.70%)	
occurrences (all)	0	1	
Hypertension			
subjects affected / exposed	0 / 9 (0.00%)	1 / 27 (3.70%)	
occurrences (all)	0	1	
Nervous system disorders			
Monoparesis			
subjects affected / exposed	0 / 9 (0.00%)	1 / 27 (3.70%)	
occurrences (all)	0	1	
General disorders and administration site conditions			
Injection site rash			
subjects affected / exposed	1 / 9 (11.11%)	0 / 27 (0.00%)	
occurrences (all)	1	0	
Pain			
subjects affected / exposed	1 / 9 (11.11%)	0 / 27 (0.00%)	
occurrences (all)	1	0	
Pyrexia			
subjects affected / exposed	1 / 9 (11.11%)	0 / 27 (0.00%)	
occurrences (all)	1	0	
Hunger			

subjects affected / exposed occurrences (all)	0 / 9 (0.00%) 0	1 / 27 (3.70%) 1	
Gastrointestinal disorders			
Nausea			
subjects affected / exposed	0 / 9 (0.00%)	4 / 27 (14.81%)	
occurrences (all)	0	3	
Abdominal pain			
subjects affected / exposed	0 / 9 (0.00%)	2 / 27 (7.41%)	
occurrences (all)	0	2	
Diarrhoea			
subjects affected / exposed	0 / 9 (0.00%)	1 / 27 (3.70%)	
occurrences (all)	0	1	
Lip oedema			
subjects affected / exposed	0 / 9 (0.00%)	1 / 27 (3.70%)	
occurrences (all)	0	1	
Vomiting			
subjects affected / exposed	0 / 9 (0.00%)	2 / 27 (7.41%)	
occurrences (all)	0	2	
Abdominal discomfort			
subjects affected / exposed	0 / 9 (0.00%)	1 / 27 (3.70%)	
occurrences (all)	0	1	
Constipation			
subjects affected / exposed	0 / 9 (0.00%)	1 / 27 (3.70%)	
occurrences (all)	0	1	
Skin and subcutaneous tissue disorders			
Acne			
subjects affected / exposed	0 / 9 (0.00%)	1 / 27 (3.70%)	
occurrences (all)	0	1	
Dermatitis contact			
subjects affected / exposed	0 / 9 (0.00%)	1 / 27 (3.70%)	
occurrences (all)	0	1	
Psychiatric disorders			
Depression			
subjects affected / exposed	0 / 9 (0.00%)	1 / 27 (3.70%)	
occurrences (all)	0	1	
Musculoskeletal and connective tissue disorders			

Myalgia subjects affected / exposed occurrences (all)	1 / 9 (11.11%) 1	0 / 27 (0.00%) 0	
Infections and infestations			
Influenza subjects affected / exposed occurrences (all)	1 / 9 (11.11%) 1	0 / 27 (0.00%) 0	
Gastroenteritis subjects affected / exposed occurrences (all)	0 / 9 (0.00%) 0	1 / 27 (3.70%) 1	
Urinary tract infection subjects affected / exposed occurrences (all)	0 / 9 (0.00%) 0	1 / 27 (3.70%) 1	
Sinusitis subjects affected / exposed occurrences (all)	0 / 9 (0.00%) 0	2 / 27 (7.41%) 2	
Metabolism and nutrition disorders			
Decreased appetite subjects affected / exposed occurrences (all)	1 / 9 (11.11%) 1	0 / 27 (0.00%) 0	

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? No

Interruptions (globally)

Were there any global interruptions to the trial? Yes

Date	Interruption	Restart date
12 June 2017	Due to poor recruitment level in the study, it was decided to stop recruitment before the target number of subjects was reached.	-

Notes:

Limitations and caveats

None reported