EU Clinical Trials Register

Clinical trial results:
An Open-Label Clinical Study to Evaluate the Long-Term Efficacy and Tolerability of Treatment With Dimethyl Fumarate (DMF) In Adults With Chronic Plaque Psoriasis (Study DIMESKIN 2)

Summary

EudraCT number	2017-003818-11
Trial protocol	IT
Global end of trial date	05 November 2020

Results information

Result version number	v1 (current)
This version publication date	16 October 2022
First version publication date	16 October 2022

Trial information

Trial identification

Sponsor protocol code	M-41008-42

Additional study identifiers

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

Notes:

Sponsors

Sponsor organisation name	Almirall, S.A
Sponsor organisation address	General Mitre, 151, Barcelona, Spain, 08022
Public contact	Almirall, S.A, Mercè De Frias, +34 933128993,
Scientific contact	Mercè De Frias, Almirall, S.A, +34 933128993,

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	05 November 2020
Is this the analysis of the primary completion data?	No

Global end of trial reached?	Yes
Global end of trial date	05 November 2020
Was the trial ended prematurely?	No

Notes:

General information about the trial

Main objective of the trial:

The main objective of this study was to evaluate the efficacy of dimethyl fumarate (DMF) in adults with moderate-to-severe chronic plaque psoriasis. Efficacy was expressed as the percentage of subjects with a greater than or equal to (>=) 75% reduction from baseline of the psoriasis area and severity index (PASI) after 1 year of treatment and to test the new drug on the Italian population.

Protection of trial subjects:

The study was carried out in compliance with the ethical principles established by the Declaration of Helsinki, including any amendments and conducted in accordance with the principles of Good Clinical Practice (GCP) as required by the Regulation (EU) No. 536/2014 and the Corrigendum to Regulation (EU) 536/2014, and local regulations.

Background therapy: -	
Evidence for comparator: -	
Actual start date of recruitment	31 May 2018
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	Italy: 165
Worldwide total number of subjects	165
EEA total number of subjects	165

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)	142
From 65 to 84 years	23

85 years and over	0

Subject disposition

Recruitment

Recruitment details:

This study was conducted at 36 sites in Italy from 31 May 2018 to 05 November 2020.

Pre-assignment

Screening details:

A total of 191 subjects were screened, of which 165 subjects were enrolled in this study and 26 subjects were excluded due to screening failure.

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 (DMF)

Arm description:

All subjects received DMF tablets at a dose of 30 mg for first three weeks and 120 mg for subsequent weeks. The total duration of treatment was 52 weeks.

Arm type	Experimental
Investigational medicinal product name	Dimethyl fumarate
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Tablet
Routes of administration	Oral use

Dosage and administration details:

Subjects received dimethyl fumarate tablets at a dose of 30 mg for first 3 three weeks and 120 mg for subsequent weeks.

Number of subjects in period 1	Dimethyl fumarate (DMF)
Started	165
Completed	66
Not completed	99
Adverse event, serious fatal	1
Consent withdrawn by subject	7
Adverse event, non-fatal	54
Incompliance with treatment	1
Unspecified	12
Lost to follow-up	7
Decision of the Investigator	17

Baseline characteristics

Reporting groups

Reporting group title	Dimethyl fumarate (DMF)

Reporting group description:

All subjects received DMF tablets at a dose of 30 mg for first three weeks and 120 mg for subsequent weeks. The total duration of treatment was 52 weeks.

Reporting group values	Dimethyl fumarate (DMF)	Total	
Number of subjects	165	165	
Age categorical			
Units: Subjects			
In utero	0	0	
Preterm newborn infants (gestational age < 37 wks)	0	0	
Newborns (0-27 days)	0	0	
Infants and toddlers (28 days-23 months)	0	0	
Children (2-11 years)	0	0	
Adolescents (12-17 years)	0	0	
Adults (18-64 years)	142	142	
From 65-84 years	23	23	
85 years and over	0	0	
Age continuous			
Units: years			
arithmetic mean	48.75		
standard deviation	± 14.92	-	
Gender categorical			
Units: Subjects			
Female	55	55	
Male	110	110	
Race			
Units: Subjects			
Arab	1	1	
Asian	1	1	
Black or Afroamerican	1	1	
Caucasian	162	162	

End points

End points reporting groups

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

All subjects received DMF tablets at a dose of 30 mg for first three weeks and 120 mg for subsequent weeks. The total duration of treatment was 52 weeks.

Primary: Percentage of Subjects Achieving 75% or Greater Reduction in Psoriasis Area and Severity Index (PASI 75) at Week 52

End point title	Percentage of Subjects Achieving 75% or Greater Reduction in Psoriasis Area and Severity Index (PASI 75) at Week 52[1]
End point description:	

The PASI was a quantitative rating score for measuring the severity of psoriatic lesions based on area coverage and plaque appearance. For each lesion, the PASI assigns a score ranging from 0 (no lesion) to 4 (extremely severe lesion) on the basis of three parameters (erythema, induration and desquamation) and a weighted assessment of the affected area classified by body part (head, trunk, upper limbs and lower limbs). The PASI score ranges from 0 (no psoriatic lesions) to 72 (severe psoriasis). PASI 75 is defined as at least a 75% reduction in PASI score compared with the Baseline PASI score. Intent to treat population (ITT) included all enrolled subjects who took the study product, had no protocol violations that regard inclusion/exclusion criteria and had at least one post-baseline assessment of the PASI. Multiple imputation (MI) method applied. Here, "number of subjects analysed" signifies number of subjects who were evaluable for this end point.

End point type	Primary
End point timeframe:	

Week 52

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 analysis was planned for this endpoint.

End point values	Dimethyl fumarate (DMF)			
Subject group type	Reporting group			
Number of subjects analysed	141			
Units: Percentage of Subjects				
number (confidence interval 95%)	86.67 (78.73 to 94.60)			

Statistical analyses

No statistical analyses for this end point

Secondary: Percentage of Subjects Achieving PASI 75 at Week 4, 8, 12, 24, 36 and 48

End point title	Percentage of Subjects Achieving PASI 75 at Week 4, 8, 12, 24, 36 and 48
End point description:	

The PASI was a quantitative rating score for measuring the severity of psoriatic lesions based on area

coverage and plaque appearance. For each lesion, the PASI assigns a score ranging from 0 (no lesion) to 4 (extremely severe lesion) on the basis of three parameters (erythema, induration and desquamation) and a weighted assessment of the affected area classified by body part (head, trunk, upper limbs and lower limbs). The PASI score ranges from 0 (no psoriatic lesions) to 72 (severe psoriasis). PASI 75 is defined as at least a 75% reduction in PASI score compared with the Baseline PASI score. ITT included all enrolled subjects who took the study product, had no protocol violations that regard inclusion/exclusion criteria and had at least one post-baseline assessment of the PASI. MI method applied. -99999, 99999= 95% confidence interval (CI) not estimable. Here, "number of subjects analysed" signifies number of subjects who were evaluable for this end point.

End point type	Secondary

End point timeframe:	
Week 4, 8, 12, 24, 36 and 48	

End point values	Dimethyl fumarate (DMF)			
Subject group type	Reporting group			
Number of subjects analysed	141			
Units: Percentage of Subjects				
number (confidence interval 95%)				
Week 4	8.51 (-99999 to 99999)			
Week 8	17.38 (10.80 to 23.96)			
Week 12	40.74 (31.79 to 49.70)			
Week 24	70.64 (60.85 to 80.43)			
Week 36	78.76 (69.30 to 88.22)			
Week 48	86.24 (78.63 to 93.85)			

Statistical analyses

No statistical analyses for this end point

Secondary: Percentage of Subjects Achieving 50% or Greater Reduction in Psoriasis Area and Severity Index (PASI 50) at Week 4, 8, 12, 24, 36, 48 and 52

End point title	Percentage of Subjects Achieving 50% or Greater Reduction in Psoriasis Area and Severity Index (PASI 50) at Week 4, 8, 12, 24, 36, 48 and 52

End point description:

The PASI was a quantitative rating score for measuring the severity of psoriatic lesions based on area coverage and plaque appearance. For each lesion, the PASI assigns a score ranging from 0 (no lesion) to 4 (extremely severe lesion) on the basis of three parameters (erythema, induration and desquamation) and a weighted assessment of the affected area classified by body part (head, trunk, upper limbs and lower limbs). The PASI score ranges from 0 (no psoriatic lesions) to 72 (severe psoriasis). PASI 50 is defined as at least a 50% reduction in PASI score compared with the Baseline PASI score. ITT included all enrolled subjects who took the study product, had no protocol violations that regard inclusion/exclusion criteria and had at least one post-baseline assessment of the PASI. MI method applied. -99999, 99999= 95% CI not estimable. Here, "number of subjects analysed" signifies number of subjects who were evaluable for this end point.

End point type	Secondary

End point timeframe:

Week 4, 8, 12, 24, 36, 48 and 52

End point values	Dimethyl fumarate (DMF)			
Subject group type	Reporting group			
Number of subjects analysed	141			
Units: Percentage of Subjects				
number (confidence interval 95%)				
Week 4	15.60 (-99999 to 99999)			
Week 8	41.06 (32.76 to 49.36)			
Week 12	68.12 (59.27 to 76.97)			
Week 24	86.52 (79.38 to 93.67)			
Week 36	93.97 (89.22 to 98.73)			
Week 48	95.60 (91.61 to 99.60)			
Week 52	95.96 (91.51 to 100.00)			

Statistical analyses

No statistical analyses for this end point

Secondary: Percentage of Subjects Achieving 90% or Greater Reduction in Psoriasis Area and Severity Index (PASI 90) at Week 4, 8, 12, 24, 36, 48 and 52

End point title	Percentage of Subjects Achieving 90% or Greater Reduction in Psoriasis Area and Severity Index (PASI 90) at Week 4, 8, 12, 24, 36, 48 and 52

End point description:

The PASI was a quantitative rating score for measuring the severity of psoriatic lesions based on area coverage and plaque appearance. For each lesion, the PASI assigns a score ranging from 0 (no lesion) to 4 (extremely severe lesion) on the basis of three parameters (erythema, induration and desquamation) and a weighted assessment of the affected area classified by body part (head, trunk, upper limbs and lower limbs). The PASI score ranges from 0 (no psoriatic lesions) to 72 (severe psoriasis). PASI 90 is defined as at least a 90% reduction in PASI score compared with the Baseline PASI score. ITT included all enrolled subjects who took the study product, had no protocol violations that regard inclusion/exclusion criteria and had at least one post-baseline assessment of the PASI. MI method applied. -99999, 99999 = 95% CI not estimable. Here, "number of subjects analysed" signifies number of subjects who were evaluable for this end point.

End point type	Secondary

End point timeframe:

Week 4, 8, 12, 24, 36, 48 and 52

End point values	Dimethyl fumarate (DMF)			
Subject group type	Reporting group			
Number of subjects analysed	141			
Units: Percentage of Subjects				
number (confidence interval 95%)				
Week 4	1.42 (-99999 to 99999)			
Week 8	6.88 (2.65 to 11.11)			
Week 12	14.93 (8.48 to 21.38)			
Week 24	40.60 (31.05 to 50.15)			
Week 36	45.92 (34.36 to 57.49)			
Week 48	57.02 (46.75 to 67.29)			
Week 52	56.17 (46.68 to 65.66)			

Statistical analyses

No statistical analyses for this end point

Secondary: Percentage of Subjects Achieving 100% or Greater Reduction in Psoriasis Area and Severity Index (PASI 100) at Week 4, 8, 12, 24, 36, 48 and 52

End point title	Percentage of Subjects Achieving 100% or Greater Reduction in Psoriasis Area and Severity Index (PASI 100) at Week 4, 8, 12, 24, 36, 48 and 52

End point description:

The PASI was a quantitative rating score for measuring the severity of psoriatic lesions based on area coverage and plaque appearance. For each lesion, the PASI assigns a score ranging from 0 (no lesion) to 4 (extremely severe lesion) on the basis of three parameters (erythema, induration and desquamation) and a weighted assessment of the affected area classified by body part (head, trunk, upper limbs and lower limbs). The PASI score ranges from 0 (no psoriatic lesions) to 72 (severe psoriasis). PASI 100 is defined as at least a 100% reduction in PASI score compared with the Baseline PASI score. ITT included all enrolled subjects who took the study product, had no protocol violations that regard inclusion/exclusion criteria and had at least one post-baseline assessment of the PASI. MI method applied. -99999, 99999 = 95% CI not estimable. Here, "number of subjects analysed" signifies number of subjects who were evaluable f

End point type	Secondary

End point timeframe:

Week 4, 8, 12, 24, 36, 48 and 52

End point values	Dimethyl fumarate (DMF)			
Subject group type	Reporting group			
Number of subjects analysed	141			
Units: Percentage of Subjects				
number (confidence interval 95%)				

Week 4	0.71 (-99999 to 99999)				
Week 8	0.74 (0.00 to 2.20)				
Week 12	6.81 (2.20 to 11.42)				
Week 24	15.50 (8.68 to 22.31)				
Week 36	18.90 (11.31 to 26.49)				
Week 48	20.92 (11.64 to 30.20)				
Week 52	22.13 (13.92 to 30.33)				

Statistical analyses

No statistical analyses for this end point

Secondary: Change From Baseline in PASI Index at Week 52

End point title	Change From Baseline in PASI Index at Week 52

End point description:

The PASI was a quantitative rating score for measuring the severity of psoriatic lesions based on area coverage and plaque appearance. For each lesion, the PASI assigns a score ranging from 0 (no lesion) to 4 (extremely severe lesion) on the basis of three parameters (erythema, induration and desquamation) and a weighted assessment of the affected area classified by body part (head, trunk, upper limbs and lower limbs). The PASI score ranges from 0 (no psoriatic lesions) to 72 (severe psoriasis). ITT included all enrolled subjects who took the study product, had no protocol violations that regard inclusion/exclusion criteria and had at least one post-baseline assessment of the PASI. Here, "number of subjects analysed" signifies number of subjects who were evaluable for this end point.

End point type	Secondary

End point timeframe:

Baseline, Week 52

End point values	Dimethyl fumarate (DMF)			
Subject group type	Reporting group			
Number of subjects analysed	65			
Units: Units on a scale				
arithmetic mean (standard deviation)	-13.10 (± 5.18)			

Statistical analyses

No statistical analyses for this end point

Secondary: Change From Baseline in Physician's Global Assessment (PGA) Score at Week 52

End point title	Change From Baseline in Physician's Global Assessment (PGA) Score at Week 52

End point description:

The PGA index provides a descriptive evaluation of disease severity. The evaluation, based on clinical judgment, is global and does not distinguish the different body areas affected by the disease. The PGA provides an evaluation of treatment efficacy by means of a score ranging from 0 (no sign of psoriasis) to 5 (severe psoriasis). ITT included all enrolled subjects who took the study product, had no protocol violations that regard inclusion/exclusion criteria and had at least one post-baseline assessment of the PASI. Here, "number of subjects analysed" signifies number of subjects who were evaluable for this end point.

End point type	Secondary

End point timeframe:

Baseline, Week 52

End point values	Dimethyl fumarate (DMF)			
Subject group type	Reporting group			
Number of subjects analysed	65			
Units: Units on a scale				
arithmetic mean (standard deviation)	-2.32 (± 0.87)			

Statistical analyses

No statistical analyses for this end point

Secondary: Change From Baseline in Body Surface Area (BSA) Score at Week 52

End point title	Change From Baseline in Body Surface Area (BSA) Score at Week 52

End point description:

The BSA index provides an evaluation of the extension of the body area affected by psoriasis. ITT included all enrolled subjects who took the study product, had no protocol violations that regard inclusion/exclusion criteria and had at least one post-baseline assessment of the PASI. Here, "number of subjects analysed" signifies number of subjects who were evaluable for this end point.

End point type	Secondary

End point timeframe:

Baseline, Week 52

End point values	Dimethyl fumarate (DMF)			
Subject group type	Reporting group			
Number of subjects analysed	65			
Units: Units on a scale				
arithmetic mean (standard deviation)	-20.74 (± 11.69)			

Statistical analyses

No statistical analyses for this end point

Secondary: Change From Baseline in Dermatology Life Quality Index (DLQI) Score at Week 52

End point title	Change From Baseline in Dermatology Life Quality Index (DLQI) Score at Week 52

End point description:

The DLQI is a questionnaire used to quantifying the impact of dermatological disease on the subject's quality of life. In psoriasis subjects, DLQI score is used to assess the impact of psoriasis in daily life, asking simple questions related to work, school, personal relationships, and therapy. The DLQI questionnaire is based on 10 questions and provides an evaluation of a subject's quality of life by means of a score ranging from 0 to 30. 0-1: no effect, 2-5: small effect, 6-10: moderate effect, 11-20: very large effect and 21-30: extremely large effect on subject's life. The higher the score, the more quality of life is impaired. ITT included all enrolled subjects who took the study product, had no protocol violations that regard inclusion/exclusion criteria and had at least one post-baseline assessment of the PASI. Here, "number of subjects analysed" signifies number of subjects who were evaluable for this end point.

End point type	Secondary

End point timeframe:

Baseline, Week 52

End point values	Dimethyl fumarate (DMF)			
Subject group type	Reporting group			
Number of subjects analysed	63			
Units: Units on a scale				
arithmetic mean (standard deviation)	-6.63 (± 5.06)			

Statistical analyses

No statistical analyses for this end point

Secondary: Percentage Change From Baseline in Pruritus Visual Analogic Scale (VAS) at Week 52

End point title	Percentage Change From Baseline in Pruritus Visual Analogic Scale (VAS) at Week 52

End point description:

Pruritus VAS is a visual method to assess the intensity of itching. The subject is asked to place a single mark along a 100 millimetre(mm) line, the left extremity represents the absence of itching (i.e., pruritus VAS equal to 0) and the right one unbearable itching (i.e., pruritus VAS equal to 100). ITT included all enrolled subjects who took the study product, had no protocol violations that regard inclusion/exclusion criteria and had at least one post-baseline assessment of the PASI. Here, "number of subjects analysed" signifies number of subjects who were evaluable for this end point.

End point type	Secondary

End point timeframe:

Baseline, Week 52

End point values	Dimethyl fumarate (DMF)			
Subject group type	Reporting group			
Number of subjects analysed	62			
Units: Percent Change				
arithmetic mean (standard deviation)	-34.93 (± 138.74)			

Statistical analyses

No statistical analyses for this end point

Secondary: Subject Satisfaction VAS Score Assessment at Week 24 and 52

End point title	Subject Satisfaction VAS Score Assessment at Week 24 and 52

End point description:

Satisfaction VAS is a visual method to assess satisfaction grade of treatment. The subject is asked to place a single mark along a 100 mm line, the left extremity represents complete unsatisfaction (i.e., satisfaction VAS equal to 0) and the right one complete satisfaction (i.e., satisfaction VAS equal to 100).). ITT included all enrolled subjects who took the study product, had no protocol violations that regard inclusion/exclusion criteria and had at least one post-baseline assessment of the PASI. Here, "number of subjects analysed (N)" signifies number of subjects who were evaluable for this end point. Number analysed (n) signifies number of subjects evaluable for specified rows.

End point type	Secondary

End point timeframe:

Week 24 and 52

End point values	Dimethyl fumarate (DMF)			
Subject group type	Reporting group			
Number of subjects analysed	75			
Units: Units on a scale				
arithmetic mean (standard deviation)				
Week 24 (n=75)	79.89 (± 23.00)			
Week 52 (n=63)	79.37 (± 29.39)			

Statistical analyses

No statistical analyses for this end point

Secondary: Duration of Treatment Exposure

End point title	Duration of Treatment Exposure

End point description:

Safety population included all enrolled subjects who took at least one dose of the study treatment. Here, "number of subjects analysed" signifies number of subjects who were evaluable for this end point.

End point type	Secondary

End point timeframe:

Week 52

End point values	Dimethyl fumarate (DMF)			
Subject group type	Reporting group			
Number of subjects analysed	158			
Units: Months				
median (full range (min-max))	5.78 (0.30 to 17.22)			

Statistical analyses

No statistical analyses for this end point

Secondary: Percentage of Subjects With Adverse Events (AEs) and Serious Adverse Events (SAEs)

End point title	Percentage of Subjects With Adverse Events (AEs) and Serious Adverse Events (SAEs)

End point description:

An AE was any untoward medical occurrence in a clinical trial subject administered a medicinal product and which does not necessarily have a causal relationship with this treatment. SAE was any untoward medical occurrence that at any dose resulted in death; was life-threatening; required in-patient hospitalisation or prolongation of existing hospitalization; resulted in a persistent or significant disability or incapacity; congenital anomaly or birth defect; was considered as "clinically relevant event". Safety population included all enrolled subjects who took at least one dose of the study treatment. Here, "number of subjects analysed" signifies number of subjects who were evaluable for this end point.

End point type	Secondary

End point timeframe:

From Baseline up to end of study or premature discontinuation (up to Week 52)

End point values	Dimethyl fumarate (DMF)			
Subject group type	Reporting group			
Number of subjects analysed	158			
Units: Percentage of Subjects				
number (not applicable)				

AEs	89.24				
SAEs	4.43				

Statistical analyses

No statistical analyses for this end point

Secondary: Percentage of Subjects With AEs Leading to Permanent Interruption of Treatment With DMF

End point title	Percentage of Subjects With AEs Leading to Permanent Interruption of Treatment With DMF

End point description:

An AE was any untoward medical occurrence in a clinical trial subject administered a medicinal product and which does not necessarily have a causal relationship with this treatment. Percentage of subjects with AEs led to permanent interruption of treatment with DMF were reported. Safety population included all enrolled subjects who took at least one dose of the study treatment. Here, "number of subjects analysed" signifies number of subjects who were evaluable for this end point.

End point type	Secondary

End point timeframe:

From Baseline up to end of study or premature discontinuation (up to Week 52)

End point values	Dimethyl fumarate (DMF)				
Subject group type	Reporting group				
Number of subjects analysed	158				
Units: Percentage of Subjects					
number (not applicable)	34.18				

Statistical analyses

No statistical analyses for this end point

Secondary: Percentage of Subjects with Laboratory Abnormalities: Hematology Parameters

End point title	Percentage of Subjects with Laboratory Abnormalities: Hematology Parameters

End point description:

Hematology parameters included white blood cells, red blood cells, hemoglobin, hematocrit, platelets, absolute neutrophils, absolute lymphocytes, absolute monocytes, absolute eosinophils, absolute basophils. Low indicates lower than normal range and high indicates higher than normal range. Safety population included all enrolled subjects who took at least one dose of the study treatment. Here, "99999" signifies low and high values were not observed in subjects for specific categories. Here, "number of subjects analysed" signifies number of subjects who were evaluable for this end point.

End point type	Secondary

End point timeframe:

Week 52

End point values	Dimethyl fumarate (DMF)			
Subject group type	Reporting group			
Number of subjects analysed	52			
Units: Percentage of Subjects				
number (not applicable)				
White blood cells - Low	9.62			
White blood cells - High	99999			
Red blood cells - Low	7.69			
Red blood cells - High	3.85			
Hemoglobin - Low	13.46			
Hemoglobin - High	1.92			
Hematocrit - Low	5.77			
Hematocrit - High	99999			
Platelets - Low	1.92			
Platelets - High	99999			
Absolute Neutrophils - Low	99999			
Absolute Neutrophils - High	13.46			
Absolute Lymphocytes - Low	53.85			
Absolute Lymphocytes - High	99999			
Absolute Monocytes - Low	99999			
Absolute Monocytes - High	1.92			
Absolute Eosinophils - Low	99999			
Absolute Eosinophils - High	99999			
Absolute Basophils - Low	1.92			
Absolute Basophils - High	99999			

Statistical analyses

No statistical analyses for this end point

Secondary: Percentage of Subjects with Laboratory Abnormalities: Biochemistry Parameters

End point title	Percentage of Subjects with Laboratory Abnormalities: Biochemistry Parameters

End point description:

Biochemistry parameters included creatinine, total bilirubin, aspartate aminotransferase (AST)/ serum glutamic oxaloacetic transaminase (SGOT), alanine aminotransferase (ALT)/ serum glutamate pyruvate transaminase (SGPT), gamma glutamyl transferase (Gamma-GT), alkaline phosphatase. Low indicates lower than normal range and high indicates higher than normal range. Safety population included all enrolled subjects who took at least one dose of the study treatment. Here, "99999" signifies low and high values were not observed in subjects for specific categories. . Here, "number of subjects analysed (N)" signifies number of subjects who were evaluable for this end point. Number analysed (n) signifies number of subjects evaluable for specified rows.

End point type	Secondary

End point timeframe:

Week 52

End point values	Dimethyl fumarate (DMF)			
Subject group type	Reporting group			
Number of subjects analysed	52			
Units: Percentage of Subjects				
number (not applicable)				
Creatinine - Low (n=52)	9.62			
Creatinine - High (n=52)	1.92			
Total bilirubin - Low (n=51)	99999			
Total bilirubin - High (n=51)	7.84			
AST/SGOT - Low (n=52)	1.92			
AST/SGOT - High (n=52)	3.85			
ALT/SGPT - Low (n=52)	99999			
ALT/SGPT - High (n=52)	5.77			
Gamma-GT - Low (n=52)	99999			
Gamma-GT - High (n=52)	7.69			
Alkaline phosphatase - Low (n=52)	99999			
Alkaline phosphatase - High (n=52)	1.92			

Statistical analyses

No statistical analyses for this end point

Adverse events

Adverse events information

Timeframe for reporting adverse events:

From Baseline up to end of study or premature discontinuation (up to week 52)

Adverse event reporting additional description:

The number of occurrences were updated same as the number of subjects affected for non-serious adverse events. Safety population included all enrolled subjects who took at least one dose of the study treatment.

Assessment type	Systematic

Dictionary used

Dictionary name	MedDRA
Dictionary version	23.1

Reporting groups

Reporting group title	Dimethyl fumarate (DMF)

Reporting group description:

All subjects received DMF tablets at a dose of 30 mg for first three weeks and 120 mg for subsequent weeks. The total duration of treatment was 52 weeks.

Serious adverse events	Dimethyl fumarate (DMF)		
Total subjects affected by serious adverse events			
subjects affected / exposed	7 / 158 (4.43%)		
number of deaths (all causes)	1		
number of deaths resulting from adverse events			
Cardiac disorders			
Myocardial infarction			
subjects affected / exposed	1 / 158 (0.63%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 1		
Nervous system disorders			
Multiple sclerosis			
subjects affected / exposed	1 / 158 (0.63%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Blood and lymphatic system disorders			
Leukopenia			
subjects affected / exposed	1 / 158 (0.63%)		
occurrences causally related to treatment / all	1 / 1		
deaths causally related to treatment / all	0 / 0		
Lymphopenia			

subjects affected / exposed	3 / 158 (1.90%)		
occurrences causally related to treatment / all	3 / 3		
deaths causally related to treatment / all	0 / 0		
Skin and subcutaneous tissue disorders			
Dermatitis exfoliative generalised			
subjects affected / exposed	1 / 158 (0.63%)		
occurrences causally related to treatment / all	1 / 1		
deaths causally related to treatment / all	0 / 0		
Infections and infestations			
Infection			
subjects affected / exposed	1 / 158 (0.63%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		

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

Non-serious adverse events	Dimethyl fumarate (DMF)		
Total subjects affected by non-serious adverse events			
subjects affected / exposed	134 / 158 (84.81%)		
Vascular disorders			
Circulatory collapse			
subjects affected / exposed	1 / 158 (0.63%)		
occurrences (all)	1		
Flushing			
subjects affected / exposed	3 / 158 (1.90%)		
occurrences (all)	3		
Hot flush			
subjects affected / exposed	3 / 158 (1.90%)		
occurrences (all)	3		
Hypertension			
subjects affected / exposed	3 / 158 (1.90%)		
occurrences (all)	3		
Pallor			
subjects affected / exposed	1 / 158 (0.63%)		
occurrences (all)	1		

Surgical and medical procedures			
Cataract operation			
subjects affected / exposed	1 / 158 (0.63%)		
occurrences (all)	1		
Haemorrhoid operation			
subjects affected / exposed	1 / 158 (0.63%)		
occurrences (all)	1		
Knee operation			
subjects affected / exposed	1 / 158 (0.63%)		
occurrences (all)	1		
Tooth extraction			
subjects affected / exposed	1 / 158 (0.63%)		
occurrences (all)	1		
General disorders and administration site conditions			
Asthenia			
subjects affected / exposed	3 / 158 (1.90%)		
occurrences (all)	3		
Chills			
subjects affected / exposed	1 / 158 (0.63%)		
occurrences (all)	1		
Feeling hot			
subjects affected / exposed	2 / 158 (1.27%)		
occurrences (all)	2		
Influenza like illness			
subjects affected / exposed	1 / 158 (0.63%)		
occurrences (all)	1		
Malaise			
subjects affected / exposed	1 / 158 (0.63%)		
occurrences (all)	1		
Oedema peripheral			
subjects affected / exposed	1 / 158 (0.63%)		
occurrences (all)	1		
Pain			
subjects affected / exposed	2 / 158 (1.27%)		
occurrences (all)	2		
Pyrexia			

subjects affected / exposed	7 / 158 (4.43%)		
occurrences (all)	7		

Reproductive system and breast disorders

Benign prostatic hyperplasia

subjects affected / exposed	1 / 158 (0.63%)		
occurrences (all)	1		

Dysmenorrhoea

subjects affected / exposed	2 / 158 (1.27%)		
occurrences (all)	2		

Respiratory, thoracic and mediastinal disorders

Cough

subjects affected / exposed	3 / 158 (1.90%)		
occurrences (all)	3		

Epiglottic oedema

subjects affected / exposed	1 / 158 (0.63%)		
occurrences (all)	1		

Epistaxis

subjects affected / exposed	1 / 158 (0.63%)		
occurrences (all)	1		

Oropharyngeal pain

subjects affected / exposed	3 / 158 (1.90%)		
occurrences (all)	3		

Pneumonitis

subjects affected / exposed	1 / 158 (0.63%)		
occurrences (all)	1		

Rhinitis allergic

subjects affected / exposed	1 / 158 (0.63%)		
occurrences (all)	1		

Rhinorrhoea

subjects affected / exposed	1 / 158 (0.63%)		
occurrences (all)	1		

Psychiatric disorders

Anxiety

subjects affected / exposed	2 / 158 (1.27%)		
occurrences (all)	2		

Insomnia

subjects affected / exposed	3 / 158 (1.90%)		
occurrences (all)	3		
Mixed anxiety and depressive disorder			
subjects affected / exposed	1 / 158 (0.63%)		
occurrences (all)	1		
Panic attack			
subjects affected / exposed	1 / 158 (0.63%)		
occurrences (all)	1		
Investigations			
Blood pressure decreased			
subjects affected / exposed	1 / 158 (0.63%)		
occurrences (all)	1		
Gamma-glutamyltransferase increased			
subjects affected / exposed	1 / 158 (0.63%)		
occurrences (all)	1		
Platelet count decreased			
subjects affected / exposed	1 / 158 (0.63%)		
occurrences (all)	1		
Injury, poisoning and procedural complications			
Foreign body in eye			
subjects affected / exposed	1 / 158 (0.63%)		
occurrences (all)	1		
Cardiac disorders			
Tachycardia			
subjects affected / exposed	1 / 158 (0.63%)		
occurrences (all)	1		
Nervous system disorders			
Dysgeusia			
subjects affected / exposed	1 / 158 (0.63%)		
occurrences (all)	1		
Headache			
subjects affected / exposed	13 / 158 (8.23%)		
occurrences (all)	13		
Lumbar radiculopathy			

subjects affected / exposed	1 / 158 (0.63%)
occurrences (all)	1
Migraine	
subjects affected / exposed	10 / 158 (6.33%)
occurrences (all)	10
Neuralgia	
subjects affected / exposed	1 / 158 (0.63%)
occurrences (all)	1
Paraesthesia	
subjects affected / exposed	2 / 158 (1.27%)
occurrences (all)	2
Post herpetic neuralgia	
subjects affected / exposed	1 / 158 (0.63%)
occurrences (all)	1
Somnolence	
subjects affected / exposed	1 / 158 (0.63%)
occurrences (all)	1
Blood and lymphatic system disorders	
Eosinophilia	
subjects affected / exposed	3 / 158 (1.90%)
occurrences (all)	3
Leukocytosis	
subjects affected / exposed	2 / 158 (1.27%)
occurrences (all)	2
Leukopenia	
subjects affected / exposed	4 / 158 (2.53%)
occurrences (all)	4
Lymphopenia	
subjects affected / exposed	34 / 158 (21.52%)
occurrences (all)	34
Neutrophilia	
subjects affected / exposed	2 / 158 (1.27%)
occurrences (all)	2
Ear and labyrinth disorders	
Vertigo	

subjects affected / exposed	1 / 158 (0.63%)		
occurrences (all)	1		

Eye disorders

Diabetic retinopathy
subjects affected / exposed	1 / 158 (0.63%)		
occurrences (all)	1		

Retinal detachment
subjects affected / exposed	1 / 158 (0.63%)		
occurrences (all)	1		

Visual impairment
subjects affected / exposed	2 / 158 (1.27%)		
occurrences (all)	2		

Gastrointestinal disorders

Abdominal distension
subjects affected / exposed	1 / 158 (0.63%)		
occurrences (all)	1		

Abdominal pain
subjects affected / exposed	41 / 158 (25.95%)		
occurrences (all)	41		

Abdominal pain upper
subjects affected / exposed	22 / 158 (13.92%)		
occurrences (all)	22		

Abdominal tenderness
subjects affected / exposed	1 / 158 (0.63%)		
occurrences (all)	1		

Colitis
subjects affected / exposed	1 / 158 (0.63%)		
occurrences (all)	1		

Constipation
subjects affected / exposed	1 / 158 (0.63%)		
occurrences (all)	1		

Diarrhoea
subjects affected / exposed	51 / 158 (32.28%)		
occurrences (all)	51		

Dry mouth

subjects affected / exposed	1 / 158 (0.63%)
occurrences (all)	1
Dyspepsia	
subjects affected / exposed	4 / 158 (2.53%)
occurrences (all)	4
Faeces soft	
subjects affected / exposed	1 / 158 (0.63%)
occurrences (all)	1
Flatulence	
subjects affected / exposed	3 / 158 (1.90%)
occurrences (all)	3
Gastritis	
subjects affected / exposed	2 / 158 (1.27%)
occurrences (all)	2
Gastrointestinal disorder	
subjects affected / exposed	7 / 158 (4.43%)
occurrences (all)	7
Gastrointestinal pain	
subjects affected / exposed	4 / 158 (2.53%)
occurrences (all)	4
Gastrooesophageal reflux disease	
subjects affected / exposed	3 / 158 (1.90%)
occurrences (all)	3
Haemorrhoidal haemorrhage	
subjects affected / exposed	1 / 158 (0.63%)
occurrences (all)	1
Nausea	
subjects affected / exposed	24 / 158 (15.19%)
occurrences (all)	24
Stomatitis	
subjects affected / exposed	1 / 158 (0.63%)
occurrences (all)	1
Tooth disorder	
subjects affected / exposed	1 / 158 (0.63%)
occurrences (all)	1
Toothache	

subjects affected / exposed	2 / 158 (1.27%)
occurrences (all)	2
Vomiting	
subjects affected / exposed	9 / 158 (5.70%)
occurrences (all)	9
Gastroenteritis viral	
subjects affected / exposed	1 / 158 (0.63%)
occurrences (all)	1
Skin and subcutaneous tissue disorders	
Dermatitis	
subjects affected / exposed	3 / 158 (1.90%)
occurrences (all)	3
Dermatitis allergic	
subjects affected / exposed	1 / 158 (0.63%)
occurrences (all)	1
Erythema	
subjects affected / exposed	42 / 158 (26.58%)
occurrences (all)	42
Erythrodermic psoriasis	
subjects affected / exposed	1 / 158 (0.63%)
occurrences (all)	1
Pruritus	
subjects affected / exposed	17 / 158 (10.76%)
occurrences (all)	17
Rash	
subjects affected / exposed	1 / 158 (0.63%)
occurrences (all)	1
Rash pruritic	
subjects affected / exposed	1 / 158 (0.63%)
occurrences (all)	1
Trichorrhexis	
subjects affected / exposed	1 / 158 (0.63%)
occurrences (all)	1
Urticaria	
subjects affected / exposed	2 / 158 (1.27%)
occurrences (all)	2

Renal and urinary disorders			
Renal colic			
subjects affected / exposed	1 / 158 (0.63%)		
occurrences (all)	1		
Musculoskeletal and connective tissue disorders			
Arthralgia			
subjects affected / exposed	4 / 158 (2.53%)		
occurrences (all)	4		
Back pain			
subjects affected / exposed	9 / 158 (5.70%)		
occurrences (all)	9		
Bone pain			
subjects affected / exposed	1 / 158 (0.63%)		
occurrences (all)	1		
Intervertebral disc disorder			
subjects affected / exposed	1 / 158 (0.63%)		
occurrences (all)	1		
Myalgia			
subjects affected / exposed	2 / 158 (1.27%)		
occurrences (all)	2		
Neck pain			
subjects affected / exposed	5 / 158 (3.16%)		
occurrences (all)	5		
Pain in extremity			
subjects affected / exposed	4 / 158 (2.53%)		
occurrences (all)	4		
Spinal pain			
subjects affected / exposed	1 / 158 (0.63%)		
occurrences (all)	1		
Infections and infestations			
Acariasis			
subjects affected / exposed	1 / 158 (0.63%)		
occurrences (all)	1		
Asymptomatic COVID-19			
subjects affected / exposed	1 / 158 (0.63%)		
occurrences (all)	1		

Conjunctivitis				
subjects affected / exposed	1 / 158 (0.63%)			
occurrences (all)	1			
Cystitis				
subjects affected / exposed	3 / 158 (1.90%)			
occurrences (all)	3			
Diverticulitis				
subjects affected / exposed	1 / 158 (0.63%)			
occurrences (all)	1			
Dysentery				
subjects affected / exposed	1 / 158 (0.63%)			
occurrences (all)	1			
Gastroenteritis				
subjects affected / exposed	3 / 158 (1.90%)			
occurrences (all)	3			
Haemorrhoid infection				
subjects affected / exposed	1 / 158 (0.63%)			
occurrences (all)	1			
Herpes zoster				
subjects affected / exposed	1 / 158 (0.63%)			
occurrences (all)	1			
Infected cyst				
subjects affected / exposed	1 / 158 (0.63%)			
occurrences (all)	1			
Infection				
subjects affected / exposed	1 / 158 (0.63%)			
occurrences (all)	1			
Influenza				
subjects affected / exposed	15 / 158 (9.49%)			
occurrences (all)	15			
Oral herpes				
subjects affected / exposed	1 / 158 (0.63%)			
occurrences (all)	1			
Nasopharyngitis				
subjects affected / exposed	3 / 158 (1.90%)			
occurrences (all)	3			

Pharyngitis			
subjects affected / exposed	2 / 158 (1.27%)		
occurrences (all)	2		
Respiratory tract infection			
subjects affected / exposed	1 / 158 (0.63%)		
occurrences (all)	1		
Tinea versicolour			
subjects affected / exposed	1 / 158 (0.63%)		
occurrences (all)	1		
Tonsillitis			
subjects affected / exposed	1 / 158 (0.63%)		
occurrences (all)	1		
Tooth abscess			
subjects affected / exposed	1 / 158 (0.63%)		
occurrences (all)	1		
Tracheitis			
subjects affected / exposed	1 / 158 (0.63%)		
occurrences (all)	1		
Urinary tract infection			
subjects affected / exposed	1 / 158 (0.63%)		
occurrences (all)	1		
Vaginal infection			
subjects affected / exposed	1 / 158 (0.63%)		
occurrences (all)	1		
Metabolism and nutrition disorders			
Decreased appetite			
subjects affected / exposed	2 / 158 (1.27%)		
occurrences (all)	2		
Lactose intolerance			
subjects affected / exposed	1 / 158 (0.63%)		
occurrences (all)	1		

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

Date	Amendment
24 November 2017	Reviewed the study of safety measures in relation to progressive multifocal leukoencephalopathy. Moreover, methodological considerations were reported, following which the study was described as a Phase IIIb study. In addition, the possibility of using the MDRD equation for the estimated glomerular filtration rate (eGFR) was added, changes were made in patient recommendations on taking the experimental drug with milk or derivatives.
17 January 2018	Provided information on highly effective contraceptive measures adopted both by women of childbearing age and by sexually active males with heterosexual partners of childbearing age; HIV, HBV, HCV and/or tuberculosis tests to selection visit; treatment interruption criteria in case of adverse events or lack of efficacy.

Notes:

Interruptions (globally)

Were there any global interruptions to the trial? No

Limitations and caveats

 None reported