Clinical trial results:
A 24-week, multicenter, exploratory, two arm study to assess the effect of Dimethyl fumarate on Immune-Modulatory Action on T cells in patients with relapsing remitting Multiple Sclerosis

Summary

EudraCT number	2014-003481-25
Trial protocol	DE
Global end of trial date	07 May 2018

Results information

Result version number	v1 (current)
This version publication date	04 January 2020
First version publication date	04 January 2020

Trial information

Trial identification

Sponsor protocol code	DIMAT-MS

Additional study identifiers

ISRCTN number	-
ClinicalTrials.gov id (NCT number)	-
WHO universal trial number (UTN)	U1111-1164-2476

Notes:

Sponsors

Sponsor organisation name	Universitätsklinikum Münster
Sponsor organisation address	Albert-Schweitzer-Campus 1, Gebäude D5, Münster, Germany, 48149
Public contact	Klinik für Allgemeine Neurologie, Universitätsklinikum Münster, Luisa.Klotz@ukmuenster.de
Scientific contact	Klinik für Allgemeine Neurologie, Universitätsklinikum Münster, Luisa.Klotz@ukmuenster.de

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	07 May 2018
Is this the analysis of the primary completion data?	Yes
Primary completion date	07 May 2018
Global end of trial reached?	Yes
Global end of trial date	07 May 2018
Was the trial ended prematurely?	No

Notes:

General information about the trial

Main objective of the trial:

This is an exploratory study design, which allows analysis of multiple immune parameters derived from peripheral blood mononuclear cells (PBMCs) from patients with relapsing remitting multiple sclerosis before and during immune-modulatory treatment with dimethyl fumarate (Tecfidera) in comparison to PBMCs from healthy subjects.

Protection of trial subjects:

The study was conducted in accordance with the Declaration of Helsinki and the ICH Guidelines in Good Clinical Practice. The study was not started before the competent ethics committee had given a favorable opinion. Written informed consent was obtained from all patients and the study was only conducted as approved by the Ethics committee and the competent authority. Amendments were only implemented after approval.

Background therapy:

A standard course of corticosteroids (methylprednisolone) on an inpatient or outpatient basis was allowed for treatment of relapses at any time during the study as clinically warranted. Steroid treatment should consist of 3-5 days and up to 1,000 mg methylprednisolone/day intravenously.

Evidence for comparator:

Healthy subjects were used as a reference group and were not treated.

Actual start date of recruitment	05 June 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	Germany: 67
Worldwide total number of subjects	67
EEA total number of subjects	67

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)	67
From 65 to 84 years	0
85 years and over	0

Subject disposition

Recruitment

Recruitment details:

The RRMS (relapsing remitting multiple sclerosis) patients were recruited from three university hospitals and one neurological specialist practice throughout Germany. Healthy subjects were only recruited at the Universitätsklinikum Münster. The recruitment period was from June 2015 to January 2018.

Pre-assignment

Screening details:

The study included untreated healthy subjects and patients with RRMS according to the 2010 revised McDonald`s criteria who were either treatment-naïve (i.e. no dimethyl fumarate treatment for at least 1 month) or willing to switch from conventional first-line immunomodulatory therapy (beta-interferons, glatiramer acetate) to dimethyl fumarate.

Pre-assignment period milestones

Number of subjects started	67
Number of subjects completed	58

Pre-assignment subject non-completion reasons

Reason: Number of subjects	Not meeting inclusion criteria: 8
Reason: Number of subjects	Consent withdrawn by subject: 1

Period 1

Period 1 title	Overall trial (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) (RRMS patients)

Arm description:

RRMS patients treated with dimethyl fumarate.

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

Dosage and administration details:

RRMS patients received dimethyl fumarate (Tecfidera) from week 0 to week 24. Dimethyl fumarate (Tecfidera®) treatment was initiated by daily administration of 120 mg Tecfidera® p.o. in the morning in week 0. At week 1, the dose was increased to 120 mg Tecfidera® p.o. twice daily, split into a morning and an evening dose. At week 2, the daily dose was further increased to 240 mg Tecfidera® p.o. in the morning and 120 mg Tecfidera® p.o. in the evening. Finally at week 3, the dose was increased to the final daily dose of 240 mg Tecfidera® p.o. in the morning and 240 mg Tecfidera® p.o. in the evening and maintained throughout the study. Study participants were able to perform an optional 24-week follow-up Phase. No study treatment was performed in the follow-up phase. However, RRMS patients were able to continue treatment with dimethyl fumarate (Tecfidera).

Arm title	No treatment (Healthy subjects)

Arm description:

Healthy subjects who have not been treated.

Arm type	No intervention

No investigational medicinal product assigned in this arm

Number of subjects in period 1[1]	Dimethyl fumarate (DMF) (RRMS patients)	No treatment (Healthy subjects)
Started	42	16
End of core study phase (Week 24)	37	14
Completed	33	14
Not completed	9	2
Consent withdrawn by subject	1	1
Relapse	1	-
End of study after core study phase	2	-
Adverse event, non-fatal	2	-
Pregnancy	2	1
Lost to follow-up	1	-

Notes:

[1] - The number of subjects reported to be in the baseline period are not the same as the worldwide number enrolled in the trial. It is expected that these numbers will be the same.
Justification: 51 RRMS patients were enrolled in the study and assessed for eligibility. Because 8 patients did not meet the inclusion criteria and one patient withdrew consent before start of treatment, only 42 RRMS patients entered the baseline period.

Baseline characteristics

Reporting groups	
Reporting group title	Dimethyl fumarate (DMF) (RRMS patients)
Reporting group description:	
RRMS patients treated with dimethyl fumarate.	
Reporting group title	No treatment (Healthy subjects)
Reporting group description:	
Healthy subjects who have not been treated.	

Reporting group values	Dimethyl fumarate (DMF) (RRMS patients)	No treatment (Healthy subjects)	Total
Number of subjects	42	16	58
Age categorical Units: Subjects			
In utero	0	0	0
Preterm newborn infants (gestational age < 37 wks)	0	0	0
Newborns (0-27 days)	0	0	0
Infants and toddlers (28 days-23 months)	0	0	0
Children (2-11 years)	0	0	0
Adolescents (12-17 years)	0	0	0
Adults (18-64 years)	42	16	58
From 65-84 years	0	0	0
85 years and over	0	0	0
Gender categorical Units: Subjects			
Female	28	11	39
Male	14	5	19

End points

End points reporting groups

Reporting group title	Dimethyl fumarate (DMF) (RRMS patients)
Reporting group description: RRMS patients treated with dimethyl fumarate.	
Reporting group title	No treatment (Healthy subjects)
Reporting group description: Healthy subjects who have not been treated.	

Primary: Number of lymphocytes in PBMCs

End point title	Number of lymphocytes in PBMCs[1][2]
End point description: The number of lymphocytes in the PBMC (peripheral blood mononuclear cell) population during DMF treatment.	
End point type	Primary
End point timeframe: Months 0, 2, 4, 6 and 11.	

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: Since this is an explorative study, the endpoints were only evaluated descriptively.

[2] - The end point is not reporting statistics for all the arms in the baseline period. It is expected all the baseline period arms will be reported on when providing values for an end point on the baseline period.
Justification: Because there were not enough samples from healthy subjects, this arm was not evaluated.

End point values	Dimethyl fumarate (DMF) (RRMS patients)			
Subject group type	Reporting group			
Number of subjects analysed	34			
Units: Lymphocytes (percent of PBMCs)				
median (inter-quartile range (Q1-Q3))				
Month 0 (n = 34)	79.13 (74.27 to 84.97)			
Month 2 (n = 19)	76.78 (73.23 to 85.05)			
Month 4 (n = 19)	77.14 (72.71 to 81.83)			
Month 6 (n = 34)	72.75 (68.18 to 81.91)			
Month 11 (n = 19)	73.76 (68.59 to 80.86)			

Statistical analyses

No statistical analyses for this end point

Primary: Absolute change of lymphocytes in PBMCs

End point title	Absolute change of lymphocytes in PBMCs[3][4]

End point description:

Absolute change of lymphocytes from baseline (month 0) within the PBMC population during DMF treatment.

End point type	Primary

End point timeframe:

Months 0, 2, 4, 6 and 11.

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: Since this is an explorative study, the endpoints were only evaluated descriptively.

[4] - The end point is not reporting statistics for all the arms in the baseline period. It is expected all the baseline period arms will be reported on when providing values for an end point on the baseline period.
Justification: Because there were not enough samples from healthy subjects, this arm was not evaluated.

End point values	Dimethyl fumarate (DMF) (RRMS patients)			
Subject group type	Reporting group			
Number of subjects analysed	34			
Units: Lymphocytes (percent of PBMCs)				
median (inter-quartile range (Q1-Q3))				
Month 2 (n = 19)	-2.13 (-4.62 to 2.74)			
Month 4 (n = 19)	-3.09 (-11.95 to 3.22)			
Month 6 (n = 34)	-7.16 (-16.40 to 2.98)			
Month 11 (n = 19)	-3.50 (-13.94 to 2.15)			

Statistical analyses

No statistical analyses for this end point

Primary: Number of monocytes in PBMCs

End point title	Number of monocytes in PBMCs[5][6]

End point description:

The number of monocytes in the PBMC population during DMF treatment.

End point type	Primary

End point timeframe:

Months 0, 2, 4, 6 and 11.

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: Since this is an explorative study, the endpoints were only evaluated descriptively.

[6] - The end point is not reporting statistics for all the arms in the baseline period. It is expected all the baseline period arms will be reported on when providing values for an end point on the baseline period.
Justification: Because there were not enough samples from healthy subjects, this arm was not evaluated.

End point values	Dimethyl fumarate (DMF) (RRMS patients)			
Subject group type	Reporting group			
Number of subjects analysed	34			
Units: Monocytes (percent of PBMCs)				
median (inter-quartile range (Q1-Q3))				
Month 0 (n = 34)	20.83 (14.96 to 25.66)			
Month 2 (n = 19)	23.20 (14.91 to 26.71)			
Month 4 (n = 19)	22.83 (18.09 to 27.11)			
Month 6 (n = 34)	27.20 (17.62 to 31.74)			
Month 11 (n = 19)	26.08 (19.10 to 31.33)			

Statistical analyses

No statistical analyses for this end point

Primary: Absolute change of monocytes in PBMCs

End point title	Absolute change of monocytes in PBMCs[7][8]

End point description:

Absolute change of monocytes from baseline (month 0) within the PBMC population during DMF treatment.

End point type	Primary

End point timeframe:

Months 0, 2, 4, 6 and 11.

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: Since this is an explorative study, the endpoints were only evaluated descriptively.

[8] - The end point is not reporting statistics for all the arms in the baseline period. It is expected all the baseline period arms will be reported on when providing values for an end point on the baseline period.
Justification: Because there were not enough samples from healthy subjects, this arm was not evaluated.

End point values	Dimethyl fumarate (DMF) (RRMS patients)			
Subject group type	Reporting group			
Number of subjects analysed	34			
Units: Monocytes (percent of PBMCs)				
median (inter-quartile range (Q1-Q3))				
Month 2 (n = 19)	2.15 (-2.72 to 4.54)			
Month 4 (n = 19)	2.93 (-3.22 to 11.96)			
Month 6 (n = 34)	7.13 (-2.98 to 16.24)			

Month 11 (n = 19)	3.49 (-2.29 to 13.97)			

Statistical analyses

No statistical analyses for this end point

Primary: Number of T cells in lymphocytes

End point title	Number of T cells in lymphocytes[9][10]

End point description:

The number of T cells in the lymphocyte population during DMF treatment.

End point type	Primary

End point timeframe:

Months 0, 2, 4, 6 and 11.

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: Since this is an explorative study, the endpoints were only evaluated descriptively.

[10] - The end point is not reporting statistics for all the arms in the baseline period. It is expected all the baseline period arms will be reported on when providing values for an end point on the baseline period.
Justification: Because there were not enough samples from healthy subjects, this arm was not evaluated.

End point values	Dimethyl fumarate (DMF) (RRMS patients)			
Subject group type	Reporting group			
Number of subjects analysed	34			
Units: T cells (percent of Lymphocytes)				
median (inter-quartile range (Q1-Q3))				
Month 0 (n = 34)	69.17 (56.87 to 72.39)			
Month 2 (n = 19)	66.47 (63.96 to 72.69)			
Month 4 (n = 19)	69.68 (63.21 to 71.54)			
Month 6 (n = 34)	64.53 (53.87 to 71.01)			
Month 11 (n = 19)	65.23 (59.75 to 72.86)			

Statistical analyses

No statistical analyses for this end point

Primary: Absolute change of T cells in lymphocytes

End point title	Absolute change of T cells in lymphocytes[11][12]

End point description:

Absolute change of T cells from baseline (month 0) within the lymphocytes population during DMF treatment.

End point type	Primary

End point timeframe:

Months 0, 2, 4, 6 and 11.

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: Since this is an explorative study, the endpoints were only evaluated descriptively.

[12] - The end point is not reporting statistics for all the arms in the baseline period. It is expected all the baseline period arms will be reported on when providing values for an end point on the baseline period.
Justification: Because there were not enough samples from healthy subjects, this arm was not evaluated.

End point values	Dimethyl fumarate (DMF) (RRMS patients)			
Subject group type	Reporting group			
Number of subjects analysed	34			
Units: T cells (percent of Lymphocytes)				
median (inter-quartile range (Q1-Q3))				
Month 2 (n = 19)	-0.21 (-3.65 to 3.30)			
Month 4 (n = 19)	2.61 (-2.69 to 6.68)			
Month 6 (n = 34)	-0.91 (-10.28 to 4.37)			
Month 11 (n = 19)	0.77 (-4.19 to 7.19)			

Statistical analyses

No statistical analyses for this end point

Primary: Number of CD4 T cells in T cells

End point title	Number of CD4 T cells in T cells[13][14]

End point description:

The number of CD4 T cells in the T cell population during DMF treatment.

End point type	Primary

End point timeframe:

Months 0, 2, 4, 6 and 11.

Notes:

[13] - 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: Since this is an explorative study, the endpoints were only evaluated descriptively.

[14] - The end point is not reporting statistics for all the arms in the baseline period. It is expected all the baseline period arms will be reported on when providing values for an end point on the baseline period.
Justification: Because there were not enough samples from healthy subjects, this arm was not evaluated.

End point values	Dimethyl fumarate (DMF) (RRMS patients)			
Subject group type	Reporting group			
Number of subjects analysed	34			
Units: CD4 T cells (percent of T cells)				
median (inter-quartile range (Q1-Q3))				
Month 0 (n = 34)	72.10 (67.29 to 79.42)			
Month 2 (n = 19)	74.66 (66.82 to 81.78)			
Month 4 (n = 19)	80.64 (69.42 to 86.15)			
Month 6 (n = 34)	76.47 (72.55 to 82.83)			
Month 11 (n = 19)	80.70 (69.58 to 84.73)			

Statistical analyses

No statistical analyses for this end point

Primary: Absolute change of CD4 T cells in T cells

End point title	Absolute change of CD4 T cells in T cells[15][16]

End point description:

Absolute change of CD4 T cells from baseline (month 0) within the T cell population during DMF treatment.

End point type	Primary

End point timeframe:

Months 0, 2, 4, 6 and 11.

Notes:

[15] - 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: Since this is an explorative study, the endpoints were only evaluated descriptively.

[16] - The end point is not reporting statistics for all the arms in the baseline period. It is expected all the baseline period arms will be reported on when providing values for an end point on the baseline period.
Justification: Because there were not enough samples from healthy subjects, this arm was not evaluated.

End point values	Dimethyl fumarate (DMF) (RRMS patients)			
Subject group type	Reporting group			
Number of subjects analysed	34			
Units: CD4 T cells (percent of T cells)				
median (inter-quartile range (Q1-Q3))				
Month 2 (n = 19)	0.49 (-1.61 to 2.88)			
Month 4 (n = 19)	2.60 (-1.75 to 5.52)			
Month 6 (n = 34)	4.31 (0.37 to 6.02)			

Month 11 (n = 19)	3.62 (1.65 to 9.15)			

Statistical analyses

No statistical analyses for this end point

Primary: Number of CD8 T cells in T cells

End point title	Number of CD8 T cells in T cells[17][18]

End point description:

The number of CD8 T cells in the T cell population during DMF treatment.

End point type	Primary

End point timeframe:

Months 0, 2, 4, 6 and 11.

Notes:

[17] - 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: Since this is an explorative study, the endpoints were only evaluated descriptively.

[18] - The end point is not reporting statistics for all the arms in the baseline period. It is expected all the baseline period arms will be reported on when providing values for an end point on the baseline period.
Justification: Because there were not enough samples from healthy subjects, this arm was not evaluated.

End point values	Dimethyl fumarate (DMF) (RRMS patients)			
Subject group type	Reporting group			
Number of subjects analysed	34			
Units: CD8 T cells (percent of T cells)				
median (inter-quartile range (Q1-Q3))				
Month 0 (n = 34)	17.78 (13.55 to 23.34)			
Month 2 (n = 19)	16.62 (11.03 to 25.79)			
Month 4 (n = 19)	12.96 (7.28 to 25.02)			
Month 6 (n = 34)	15.85 (9.84 to 20.16)			
Month 11 (n = 19)	12.44 (8.00 to 22.06)			

Statistical analyses

No statistical analyses for this end point

Primary: Absolute change of CD8 T cells in T cells

End point title	Absolute change of CD8 T cells in T cells[19][20]

End point description:

Absolute change of CD8 T cells from baseline (month 0) within the T cell population during DMF treatment.

End point type	Primary

End point timeframe:

Months 0, 2, 4, 6 and 11.

Notes:

[19] - 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: Since this is an explorative study, the endpoints were only evaluated descriptively.

[20] - The end point is not reporting statistics for all the arms in the baseline period. It is expected all the baseline period arms will be reported on when providing values for an end point on the baseline period.
Justification: Because there were not enough samples from healthy subjects, this arm was not evaluated.

End point values	Dimethyl fumarate (DMF) (RRMS patients)			
Subject group type	Reporting group			
Number of subjects analysed	34			
Units: CD8 T cells (percent of T cells)				
median (inter-quartile range (Q1-Q3))				
Month 2 (n = 19)	0.09 (-2.15 to 2.04)			
Month 4 (n = 19)	-2.13 (-4.01 to 0.30)			
Month 6 (n = 34)	-2.18 (-5.16 to -0.56)			
Month 11 (n = 19)	-3.63 (-8.05 to -1.22)			

Statistical analyses

No statistical analyses for this end point

Primary: Number of naive CD4 T cells in CD4 T cells

End point title	Number of naive CD4 T cells in CD4 T cells[21][22]

End point description:

The number of naive CD4 T cells in the CD4 T cell population during DMF treatment.

End point type	Primary

End point timeframe:

Months 0, 2, 4, 6 and 11.

Notes:

[21] - 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: Since this is an explorative study, the endpoints were only evaluated descriptively.

[22] - The end point is not reporting statistics for all the arms in the baseline period. It is expected all the baseline period arms will be reported on when providing values for an end point on the baseline period.
Justification: Because there were not enough samples from healthy subjects, this arm was not evaluated.

End point values	Dimethyl fumarate (DMF) (RRMS patients)			
Subject group type	Reporting group			
Number of subjects analysed	34			
Units: Cell count per µL				
median (inter-quartile range (Q1-Q3))				
Month 0 (n = 34)	94.78 (81.69 to 95.99)			
Month 2 (n = 19)	93.82 (91.63 to 96.14)			
Month 4 (n = 19)	94.59 (91.90 to 95.73)			
Month 6 (n = 34)	91.82 (81.57 to 95.73)			
Month 11 (n = 19)	94.35 (91.52 to 95.72)			

Statistical analyses

No statistical analyses for this end point

Primary: Absolute change of naive CD4 T cells in CD4 T cells

End point title	Absolute change of naive CD4 T cells in CD4 T cells[23][24]

End point description:

Absolute change of naive CD4 T cells from baseline (month 0) within the CD4 T cell population during DMF treatment.

End point type	Primary

End point timeframe:

Months 0, 2, 4, 6 and 11.

Notes:

[23] - 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: Since this is an explorative study, the endpoints were only evaluated descriptively.

[24] - The end point is not reporting statistics for all the arms in the baseline period. It is expected all the baseline period arms will be reported on when providing values for an end point on the baseline period.
Justification: Because there were not enough samples from healthy subjects, this arm was not evaluated.

End point values	Dimethyl fumarate (DMF) (RRMS patients)			
Subject group type	Reporting group			
Number of subjects analysed	34			
Units: Cell count per µL				
median (inter-quartile range (Q1-Q3))				
Month 2 (n = 19)	-0.93 (-2.61 to 0.91)			
Month 4 (n = 19)	-0.73 (-2.68 to 1.14)			
Month 6 (n = 34)	-0.16 (-5.57 to 4.72)			

Month 11 (n = 19)	-0.46 (-5.63 to 6.38)			

Statistical analyses

No statistical analyses for this end point

Primary: Number of central memory CD4 T cells in CD4 T cells

End point title	Number of central memory CD4 T cells in CD4 T cells[25][26]

End point description:

The number of central memory CD4 T cells in the CD4 T cell population during DMF treatment.

End point type	Primary

End point timeframe:

Months 0, 2, 4, 6 and 11.

Notes:

[25] - 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: Since this is an explorative study, the endpoints were only evaluated descriptively.

[26] - The end point is not reporting statistics for all the arms in the baseline period. It is expected all the baseline period arms will be reported on when providing values for an end point on the baseline period.
Justification: Because there were not enough samples from healthy subjects, this arm was not evaluated.

End point values	Dimethyl fumarate (DMF) (RRMS patients)			
Subject group type	Reporting group			
Number of subjects analysed	34			
Units: Cell count per µL				
median (inter-quartile range (Q1-Q3))				
Month 0 (n = 34)	137.04 (67.28 to 262.87)			
Month 2 (n = 19)	145.88 (77.15 to 204.24)			
Month 4 (n = 19)	88.42 (46.43 to 232.67)			
Month 6 (n = 34)	71.08 (44.93 to 168.54)			
Month 11 (n = 17)	62.28 (41.54 to 95.99)			

Statistical analyses

No statistical analyses for this end point

Primary: Absolute change of central memory CD4 T cells in CD4 T cells

End point title	Absolute change of central memory CD4 T cells in CD4 T

End point description:

Absolute change of central memory CD4 T cells from baseline (month 0) within the CD4 T cell population during DMF Treatment.

End point type	Primary

End point timeframe:

Months 0, 2, 4, 6 and 11.

Notes:

[27] - 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: Since this is an explorative study, the endpoints were only evaluated descriptively.

[28] - The end point is not reporting statistics for all the arms in the baseline period. It is expected all the baseline period arms will be reported on when providing values for an end point on the baseline period.
Justification: Since this is an explorative study, the endpoints were only evaluated descriptively.

End point values	Dimethyl fumarate (DMF) (RRMS patients)			
Subject group type	Reporting group			
Number of subjects analysed	34			
Units: Cell count per µL				
median (inter-quartile range (Q1-Q3))				
Month 2 (n = 19)	-28.74 (-57.11 to 8.29)			
Month 4 (n = 19)	-44.34 (-97.71 to 17.85)			
Month 6 (n = 34)	-69.46 (-120.78 to 9.88)			
Month 11 (n = 17)	-83.50 (-167.00 to -56.30)			

Statistical analyses

No statistical analyses for this end point

Primary: Number of effector memory CD4 T cells in CD4 T cells

End point title	Number of effector memory CD4 T cells in CD4 T cells[29][30]

End point description:

The number of effector memory CD4 T cells in the CD4 T cell population during DMF treatment.

End point type	Primary

End point timeframe:

Months 0, 2, 4, 6 and 11.

Notes:

[29] - 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: Since this is an explorative study, the endpoints were only evaluated descriptively.

[30] - The end point is not reporting statistics for all the arms in the baseline period. It is expected all the baseline period arms will be reported on when providing values for an end point on the baseline period.
Justification: Because there were not enough samples from healthy subjects, this arm was not evaluated.

End point values	Dimethyl fumarate (DMF) (RRMS patients)			
Subject group type	Reporting group			
Number of subjects analysed	34			
Units: Cell count per µL				
median (inter-quartile range (Q1-Q3))				
Month 0 (n = 34)	113.40 (53.26 to 155.11)			
Month 2 (n = 19)	126.91 (57.30 to 162.66)			
Month 4 (n = 19)	67.56 (43.60 to 128.14)			
Month 6 (n = 34)	59.14 (18.41 to 123.99)			
Month 11 (n = 17)	34.47 (17.07 to 53.70)			

Statistical analyses

No statistical analyses for this end point

Primary: Absolute change of effector memory CD4 T cells in CD4 T cells

End point title	Absolute change of effector memory CD4 T cells in CD4 T

End point description:

Absolute change of memory CD4 T cells from baseline (month 0) within the CD4 T cell population during DMF Treatment.

End point type	Primary

End point timeframe:

Months 0, 2, 4, 6 and 11.

Notes:

[31] - 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: Since this is an explorative study, the endpoints were only evaluated descriptively.

[32] - The end point is not reporting statistics for all the arms in the baseline period. It is expected all the baseline period arms will be reported on when providing values for an end point on the baseline period.
Justification: Because there were not enough samples from healthy subjects, this arm was not evaluated.

End point values	Dimethyl fumarate (DMF) (RRMS patients)			
Subject group type	Reporting group			
Number of subjects analysed	34			
Units: Cell count per µL				
median (inter-quartile range (Q1-Q3))				
Month 2 (n = 19)	12.96 (-59.83 to 32.89)			
Month 4 (n = 19)	-46.18 (-77.48 to 10.63)			
Month 6 (n = 34)	-64.68 (-94.91 to -4.67)			

Month 11 (n = 17)	-86.80 (-115.07 to -49.35)			

Statistical analyses

No statistical analyses for this end point

Primary: Number of CD4 RTEs in CD4 T cells

End point title	Number of CD4 RTEs in CD4 T cells[33][34]

End point description:

The number of CD4 RTEs (Recent Thymic Emigrants) in the CD4 T cell population during DMF treatment.

End point type	Primary

End point timeframe:

Months 0, 2, 4, 6 and 11.

Notes:

[33] - 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: Since this is an explorative study, the endpoints were only evaluated descriptively.

[34] - The end point is not reporting statistics for all the arms in the baseline period. It is expected all the baseline period arms will be reported on when providing values for an end point on the baseline period.
Justification: Because there were not enough samples from healthy subjects, this arm was not evaluated.

End point values	Dimethyl fumarate (DMF) (RRMS patients)			
Subject group type	Reporting group			
Number of subjects analysed	34			
Units: Cell count per µL				
median (inter-quartile range (Q1-Q3))				
Month 0 (n = 34)	248.37 (177.33 to 395.43)			
Month 2 (n = 19)	241.99 (186.56 to 323.91)			
Month 4 (n = 19)	245.58 (152.32 to 307.67)			
Month 6 (n = 34)	200.22 (126.39 to 332.06)			
Month 11 (n = 17)	225.50 (139.55 to 316.22)			

Statistical analyses

No statistical analyses for this end point

Primary: Absolute change of CD4 RTEs in CD4 T cells

End point title	Absolute change of CD4 RTEs in CD4 T cells[35][36]

End point description:

Absolute change of CD4 RTEs from baseline (month 0) within the CD4 T cell population during DMF treatment.

End point type	Primary

End point timeframe:

Months 0, 2, 4, 6 and 11.

Notes:

[35] - 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: Since this is an explorative study, the endpoints were only evaluated descriptively.

[36] - The end point is not reporting statistics for all the arms in the baseline period. It is expected all the baseline period arms will be reported on when providing values for an end point on the baseline period.
Justification: Because there were not enough samples from healthy subjects, this arm was not evaluated.

End point values	Dimethyl fumarate (DMF) (RRMS patients)			
Subject group type	Reporting group			
Number of subjects analysed	34			
Units: Cell count per µL				
median (inter-quartile range (Q1-Q3))				
Month 2 (n = 19)	-33.79 (-79.50 to 31.02)			
Month 4 (n = 19)	-5.73 (-110.75 to 19.93)			
Month 6 (n = 34)	-47.01 (-130.13 to 18.15)			
Month 11 (n = 17)	-39.23 (-69.11 to 10.93)			

Statistical analyses

No statistical analyses for this end point

Primary: Number of naive CD8 T cells in CD8 T cells

End point title	Number of naive CD8 T cells in CD8 T cells[37][38]

End point description:

The number of naive CD8 T cells in the CD8 T cell population during DMF treatment.

End point type	Primary

End point timeframe:

Months 0, 2, 4, 6 and 11.

Notes:

[37] - 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: Since this is an explorative study, the endpoints were only evaluated descriptively.

[38] - The end point is not reporting statistics for all the arms in the baseline period. It is expected all the baseline period arms will be reported on when providing values for an end point on the baseline period.
Justification: Because there were not enough samples from healthy subjects, this arm was not evaluated.

End point values	Dimethyl fumarate (DMF) (RRMS patients)			
Subject group type	Reporting group			
Number of subjects analysed	34			
Units: Cell count per µL				
median (inter-quartile range (Q1-Q3))				
Month 0 (n = 34)	60.85 (37.58 to 138.80)			
Month 2 (n = 19)	65.60 (22.20 to 126.16)			
Month 4 (n = 19)	40.48 (22.08 to 97.46)			
Month 6 (n = 34)	37.74 (22.53 to 77.30)			
Month 11 (n = 17)	37.70 (21.14 to 81.52)			

Statistical analyses

No statistical analyses for this end point

Primary: Absolute change of naive CD8 T cells in CD8 T cells

End point title	Absolute change of naive CD8 T cells in CD8 T cells[39][40]

End point description:

Absolute change of naive CD8 T cells from baseline (month 0) within the CD8 T cell population during DMF treatment.

End point type	Primary

End point timeframe:

Months 0, 2, 4, 6 and 11.

Notes:

[39] - 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: Since this is an explorative study, the endpoints were only evaluated descriptively.

[40] - The end point is not reporting statistics for all the arms in the baseline period. It is expected all the baseline period arms will be reported on when providing values for an end point on the baseline period.
Justification: Because there were not enough samples from healthy subjects, this arm was not evaluated.

End point values	Dimethyl fumarate (DMF) (RRMS patients)			
Subject group type	Reporting group			
Number of subjects analysed	34			
Units: Cell count per µL				
median (inter-quartile range (Q1-Q3))				

Month 2 (n = 19)	-9.70 (-31.05 to 7.18)			
Month 4 (n = 19)	-15.71 (-67.91 to 2.29)			
Month 6 (n = 34)	-18.93 (-49.83 to 0.89)			
Month 11 (n = 17)	-25.49 (-55.25 to -4.10)			

Statistical analyses

No statistical analyses for this end point

Primary: Number of central memory CD8 T cells in CD8 T cells

End point title	Number of central memory CD8 T cells in CD8 T cells[41][42]

End point description:

The number of central memory CD8 T cells in the CD8 T cell population during DMF treatment.

End point type	Primary

End point timeframe:

Months 0, 2, 4, 6 and 11.

Notes:

[41] - 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: Since this is an explorative study, the endpoints were only evaluated descriptively.

[42] - The end point is not reporting statistics for all the arms in the baseline period. It is expected all the baseline period arms will be reported on when providing values for an end point on the baseline period.
Justification: Because there were not enough samples from healthy subjects, this arm was not evaluated.

End point values	Dimethyl fumarate (DMF) (RRMS patients)			
Subject group type	Reporting group			
Number of subjects analysed	34			
Units: Cell count per µL				
median (inter-quartile range (Q1-Q3))				
Month 0 (n = 34)	1.97 (0.75 to 4.72)			
Month 2 (n = 19)	1.73 (0.67 to 2.80)			
Month 4 (n = 19)	0.89 (0.63 to 2.31)			
Month 6 (n = 34)	0.64 (0.36 to 2.25)			
Month 11 (n = 17)	0.35 (0.25 to 0.69)			

Statistical analyses

No statistical analyses for this end point

Primary: Absolute change of central memory CD8 T cells in CD8 T cells

End point title	Absolute change of central memory CD8 T cells in CD8 T

End point description:

Absolute change of central memory CD8 T cells from baseline (month 0) within the CD8 T cell population during DMF treatment.

End point type	Primary

End point timeframe:

Months 0, 2, 4, 6 and 11.

Notes:

[43] - 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: Because there were not enough samples from healthy subjects, this arm was not evaluated.
[44] - The end point is not reporting statistics for all the arms in the baseline period. It is expected all the baseline period arms will be reported on when providing values for an end point on the baseline period.
Justification: Because there were not enough samples from healthy subjects, this arm was not evaluated.

End point values	Dimethyl fumarate (DMF) (RRMS patients)			
Subject group type	Reporting group			
Number of subjects analysed	34			
Units: Cell count per µL				
median (inter-quartile range (Q1-Q3))				
Month 2 (n = 19)	-0.81 (-1.37 to 0.02)			
Month 4 (n = 19)	-0.86 (-1.91 to 0.15)			
Month 6 (n = 34)	-1.16 (-1.96 to 0.16)			
Month 11 (n = 17)	-1.22 (-2.29 to -0.52)			

Statistical analyses

No statistical analyses for this end point

Primary: Number of effector memory CD8 T cells in CD8 T cells

End point title	Number of effector memory CD8 T cells in CD8 T cells[45][46]

End point description:

The number of effector memory CD8 T cells in the CD8 T cell population during DMF treatment.

End point type	Primary

End point timeframe:

Months 0, 2, 4, 6 and 11.

Notes:

[45] - 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: Since this is an explorative study, the endpoints were only evaluated descriptively.

[46] - The end point is not reporting statistics for all the arms in the baseline period. It is expected all the baseline period arms will be reported on when providing values for an end point on the baseline period.
Justification: Because there were not enough samples from healthy subjects, this arm was not evaluated.

End point values	Dimethyl fumarate (DMF) (RRMS patients)			
Subject group type	Reporting group			
Number of subjects analysed	34			
Units: Cell count per µL				
median (inter-quartile range (Q1-Q3))				
Month 0 (n = 34)	14.19 (7.65 to 27.84)			
Month 2 (n = 19)	11.65 (6.62 to 22.08)			
Month 4 (n = 19)	6.97 (3.53 to 21.58)			
Month 6 (n = 34)	5.95 (2.60 to 14.22)			
Month 11 (n = 17)	2.30 (1.63 to 5.61)			

Statistical analyses

No statistical analyses for this end point

Primary: Absolute change of effector memory CD8 T cells in CD8 T cells

End point title	Absolute change of effector memory CD8 T cells in CD8 T

End point description:

Absolute change of effector memory CD8 T cells from baseline (month 0) within the CD8 T cell population during DMF treatment.

End point type	Primary

End point timeframe:

Months 0, 2, 4, 6 and 11.

Notes:

[47] - 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: Since this is an explorative study, the endpoints were only evaluated descriptively.

[48] - The end point is not reporting statistics for all the arms in the baseline period. It is expected all the baseline period arms will be reported on when providing values for an end point on the baseline period.
Justification: Because there were not enough samples from healthy subjects, this arm was not evaluated.

End point values	Dimethyl fumarate (DMF) (RRMS patients)			
Subject group type	Reporting group			
Number of subjects analysed	34			
Units: Cell count per µL				
median (inter-quartile range (Q1-Q3))				

Month 2 (n = 19)	-1.05 (-10.45 to 2.85)			
Month 4 (n = 19)	-4.77 (-11.87 to -1.17)			
Month 6 (n = 34)	-8.58 (-16.34 to -0.57)			
Month 11 (n = 17)	-12.49 (-24.05 to -4.54)			

Statistical analyses

No statistical analyses for this end point

Primary: Number of TEMRA in CD8 T cells

End point title	Number of TEMRA in CD8 T cells[49][50]

End point description:

The number of TEMRAs (Effector Memory RA T cells) in the CD8 T cell population during DMF treatment.

End point type	Primary

End point timeframe:

Months 0, 2, 4, 6 and 11.

Notes:

[49] - 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: Since this is an explorative study, the endpoints were only evaluated descriptively.

[50] - The end point is not reporting statistics for all the arms in the baseline period. It is expected all the baseline period arms will be reported on when providing values for an end point on the baseline period.
Justification: Because there were not enough samples from healthy subjects, this arm was not evaluated.

End point values	Dimethyl fumarate (DMF) (RRMS patients)			
Subject group type	Reporting group			
Number of subjects analysed	34			
Units: Cell count per µL				
median (inter-quartile range (Q1-Q3))				
Month 0 (n = 34)	14.01 (6.36 to 26.86)			
Month 2 (n = 19)	5.40 (4.34 to 16.98)			
Month 4 (n = 19)	5.96 (3.55 to 23.16)			
Month 6 (n = 34)	7.27 (3.55 to 11.26)			
Month 11 (n = 17)	3.14 (1.75 to 4.86)			

Statistical analyses

No statistical analyses for this end point

Primary: Absolute change of TEMRA in CD8 T cells

End point title	Absolute change of TEMRA in CD8 T cells[51][52]

End point description:

Absolute change of TEMRAs from baseline (month 0) within the CD8 T cell population during DMF treatment.

End point type	Primary

End point timeframe:

Months 0, 2, 4, 6 and 11.

Notes:

[51] - 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: Since this is an explorative study, the endpoints were only evaluated descriptively.

[52] - The end point is not reporting statistics for all the arms in the baseline period. It is expected all the baseline period arms will be reported on when providing values for an end point on the baseline period.
Justification: Because there were not enough samples from healthy subjects, this arm was not evaluated.

End point values	Dimethyl fumarate (DMF) (RRMS patients)			
Subject group type	Reporting group			
Number of subjects analysed	34			
Units: Cell count per µL				
median (inter-quartile range (Q1-Q3))				
Month 2 (n = 19)	-1.00 (-6.16 to 0.39)			
Month 4 (n = 19)	-2.30 (-8.56 to -0.41)			
Month 6 (n = 34)	-4.79 (-15.47 to 1.82)			
Month 11 (n = 17)	-6.02 (-14.17 to -2.77)			

Statistical analyses

No statistical analyses for this end point

Secondary: Number of GM-CSF-producing CD4 T cells

End point title	Number of GM-CSF-producing CD4 T cells[53]

End point description:

CD4 T cells were stimulated with leukocyte activation Cocktail for 6 hours and analyzed by flow cytometry for the intracellular amount of granulocyte-macrophage colony-stimulating factor (GM-CSF).

End point type	Secondary

End point timeframe:

Months 0, 2, 4, 6 and 11.

Notes:

[53] - The end point is not reporting statistics for all the arms in the baseline period. It is expected all the baseline period arms will be reported on when providing values for an end point on the baseline period.
Justification: Because there were not enough samples from healthy subjects, this arm was not

evaluated.

End point values	Dimethyl fumarate (DMF) (RRMS patients)			
Subject group type	Reporting group			
Number of subjects analysed	34			
Units: Cell count per µL				
median (inter-quartile range (Q1-Q3))				
Month 0 (n = 34)	1.43 (0.94 to 1.76)			
Month 2 (n = 19)	1.13 (0.89 to 1.65)			
Month 4 (n = 19)	0.97 (0.71 to 1.36)			
Month 6 (n = 34)	1.02 (0.68 to 1.56)			
Month 11 (n = 19)	0.98 (0.75 to 1.25)			

Statistical analyses

No statistical analyses for this end point

Secondary: Absolute change of GM-CSF-producing CD4 T cells

End point title	Absolute change of GM-CSF-producing CD4 T cells[54]

End point description:

CD4 T cells were stimulated with leukocyte activation Cocktail for 6 hours and analyzed by flow cytometry for the intracellular amount of granulocyte-macrophage colony-stimulating factor (GM-CSF).

End point type	Secondary

End point timeframe:

Months 0, 2, 4, 6 and 11.

Notes:

[54] - The end point is not reporting statistics for all the arms in the baseline period. It is expected all the baseline period arms will be reported on when providing values for an end point on the baseline period.
Justification: Because there were not enough samples from healthy subjects, this arm was not evaluated.

End point values	Dimethyl fumarate (DMF) (RRMS patients)			
Subject group type	Reporting group			
Number of subjects analysed	34			
Units: Cell count per µL				
median (inter-quartile range (Q1-Q3))				
Month 2 (n = 19)	-0.24 (-0.63 to 0.18)			
Month 4 (n = 19)	-0.44 (-0.87 to -0.15)			

Month 6 (n = 34)	-0.16 (-0.81 to 0.37)			
Month 11 (n = 19)	-0.47 (-0.65 to -0.11)			

Statistical analyses

No statistical analyses for this end point

Secondary: Number of IFN-gamma-producing CD4 T cells

End point title	Number of IFN-gamma-producing CD4 T cells[55]

End point description:

CD4 T cells were stimulated with leukocyte activation Cocktail for 6 hours and analyzed by flow cytometry for the intracellular amount of interferon (IFN)-gamma.

End point type	Secondary

End point timeframe:

Months 0, 2, 4, 6 and 11.

Notes:

[55] - The end point is not reporting statistics for all the arms in the baseline period. It is expected all the baseline period arms will be reported on when providing values for an end point on the baseline period.
Justification: Because there were not enough samples from healthy subjects, this arm was not evaluated.

End point values	Dimethyl fumarate (DMF) (RRMS patients)			
Subject group type	Reporting group			
Number of subjects analysed	34			
Units: Cell count per µL				
median (inter-quartile range (Q1-Q3))				
Month 0 (n = 34)	10.15 (7.02 to 13.78)			
Month 2 (n = 19)	11.25 (4.20 to 15.58)			
Month 4 (n = 19)	7.94 (2.13 to 12.24)			
Month 6 (n = 34)	6.97 (2.27 to 10.06)			
Month 11 (n = 19)	3.15 (2.04 to 8.85)			

Statistical analyses

No statistical analyses for this end point

Secondary: Absolute change of IFN-gamma-producing CD4 T cells

End point title	Absolute change of IFN-gamma-producing CD4 T cells[56]

End point description:

CD4 T cells were stimulated with leukocyte activation Cocktail for 6 hours and analyzed by flow

cytometry for the intracellular amount of interferon (IFN)-gamma.

End point type	Secondary

End point timeframe:

Months 0, 2, 4, 6 and 11.

Notes:

[56] - The end point is not reporting statistics for all the arms in the baseline period. It is expected all the baseline period arms will be reported on when providing values for an end point on the baseline period.
Justification: Because there were not enough samples from healthy subjects, this arm was not evaluated.

End point values	Dimethyl fumarate (DMF) (RRMS patients)			
Subject group type	Reporting group			
Number of subjects analysed	34			
Units: Cell count per µL				
median (inter-quartile range (Q1-Q3))				
Month 2 (n = 19)	-0.12 (-3.02 to 2.29)			
Month 4 (n = 19)	-2.34 (-5.84 to 1.50)			
Month 6 (n = 34)	-3.73 (-6.81 to -0.04)			
Month 11 (n = 19)	-4.85 (-8.34 to -1.24)			

Statistical analyses

No statistical analyses for this end point

Secondary: Number of IL-17A-producing CD4 T cells

End point title	Number of IL-17A-producing CD4 T cells[57]

End point description:

CD4 T cells were stimulated with leukocyte activation Cocktail for 6 hours and analyzed by flow cytometry for the intracellular amount of IL-17A.

End point type	Secondary

End point timeframe:

Months 0, 2, 4, 6 and 11.

Notes:

[57] - The end point is not reporting statistics for all the arms in the baseline period. It is expected all the baseline period arms will be reported on when providing values for an end point on the baseline period.
Justification: Because there were not enough samples from healthy subjects, this arm was not evaluated.

End point values	Dimethyl fumarate (DMF) (RRMS patients)			
Subject group type	Reporting group			
Number of subjects analysed	34			
Units: Cell count per µL				
median (inter-quartile range (Q1-Q3))				

Month 0 (n = 34)	0.84 (0.51 to 1.27)			
Month 2 (n = 19)	0.81 (0.49 to 1.10)			
Month 4 (n = 19)	0.75 (0.41 to 0.88)			
Month 6 (n = 34)	0.65 (0.40 to 0.96)			
Month 11 (n = 19)	0.51 (0.26 to 0.90)			

Statistical analyses

No statistical analyses for this end point

Secondary: Absolute change of IL17A-producing CD4 T cells

End point title	Absolute change of IL17A-producing CD4 T cells[58]

End point description:

CD4 T cells were stimulated with leukocyte activation Cocktail for 6 hours and analyzed by flow cytometry for the intracellular amount of IL17A.

End point type	Secondary

End point timeframe:

Months 0, 2, 4, 6 and 11.

Notes:

[58] - The end point is not reporting statistics for all the arms in the baseline period. It is expected all the baseline period arms will be reported on when providing values for an end point on the baseline period.
Justification: Because there were not enough samples from healthy subjects, this arm was not evaluated.

End point values	Dimethyl fumarate (DMF) (RRMS patients)			
Subject group type	Reporting group			
Number of subjects analysed	34			
Units: Cell count per µL				
median (inter-quartile range (Q1-Q3))				
Month 2 (n = 19)	-0.07 (-0.25 to 0.13)			
Month 4 (n = 19)	-0.06 (-0.36 to 0.01)			
Month 6 (n = 34)	-0.24 (-0.39 to 0.01)			
Month 11 (n = 19)	-0.31 (-0.52 to -0.04)			

Statistical analyses

No statistical analyses for this end point

Secondary: Number of IL-4-producing CD4 T cells

End point title	Number of IL-4-producing CD4 T cells[59]

End point description:

CD4 T cells were stimulated with leukocyte activation Cocktail for 6 hours and analyzed by flow cytometry for the intracellular amount of IL-4.

End point type	Secondary

End point timeframe:

Months 0, 2, 4, 6 and 11.

Notes:

[59] - The end point is not reporting statistics for all the arms in the baseline period. It is expected all the baseline period arms will be reported on when providing values for an end point on the baseline period.
Justification: Because there were not enough samples from healthy subjects, this arm was not evaluated.

End point values	Dimethyl fumarate (DMF) (RRMS patients)			
Subject group type	Reporting group			
Number of subjects analysed	34			
Units: Cell count per µL				
median (inter-quartile range (Q1-Q3))				
Month 0 (n = 34)	1.73 (1.28 to 2.17)			
Month 2 (n = 19)	1.50 (1.27 to 2.29)			
Month 4 (n = 19)	1.48 (1.16 to 1.94)			
Month 6 (n = 34)	1.56 (1.18 to 2.35)			
Month 11 (n = 19)	1.35 (1.10 to 1.97)			

Statistical analyses

No statistical analyses for this end point

Secondary: Absolute change of IL-4-producing CD4 T cells

End point title	Absolute change of IL-4-producing CD4 T cells[60]

End point description:

CD4 T cells were stimulated with leukocyte activation Cocktail for 6 hours and analyzed by flow cytometry for the intracellular amount of IL-4.

End point type	Secondary

End point timeframe:

Months 0, 2, 4, 6 and 11.

Notes:

[60] - The end point is not reporting statistics for all the arms in the baseline period. It is expected all the baseline period arms will be reported on when providing values for an end point on the baseline period.
Justification: Because there were not enough samples from healthy subjects, this arm was not evaluated.

End point values	Dimethyl fumarate (DMF) (RRMS patients)			
Subject group type	Reporting group			
Number of subjects analysed	34			
Units: Cell count per µL				
median (inter-quartile range (Q1-Q3))				
Month 2 (n = 19)	-0.05 (-0.36 to 0.17)			
Month 4 (n = 19)	-0.10 (-0.53 to 0.18)			
Month 6 (n = 34)	-0.05 (-0.26 to 0.17)			
Month 11 (n = 19)	-0.32 (-0.56 to 0.08)			

Statistical analyses

No statistical analyses for this end point

Secondary: Absolute change of thymus derived regulatory T cells in memory CD4 T cells

End point title	Absolute change of thymus derived regulatory T cells in memory CD4 T cells[61]

End point description:

Absolute change of thymus derived regulatory T cells (tTreg) from baseline (month 0) within the memory CD4 T cell (CD4 Mem) population during DMF treatment.

End point type	Secondary

End point timeframe:

Months 0, 2, 4, 6 and 11.

Notes:

[61] - The end point is not reporting statistics for all the arms in the baseline period. It is expected all the baseline period arms will be reported on when providing values for an end point on the baseline period.
Justification: Because there were not enough samples from healthy subjects, this arm was not evaluated.

End point values	Dimethyl fumarate (DMF) (RRMS patients)			
Subject group type	Reporting group			
Number of subjects analysed	34			
Units: tTreg (percent of CD4 Mem)				
median (inter-quartile range (Q1-Q3))				
Month 2 (n = 19)	-0.12 (-0.64 to 1.49)			
Month 4 (n = 19)	0.39 (-0.48 to 1.66)			
Month 6 (n = 34)	0.59 (-0.23 to 2.27)			
Month 11 (n = 19)	1.78 (-0.19 to 3.32)			

Statistical analyses

No statistical analyses for this end point

Secondary: Absolute change of regulatory T cells in CD4 T cells

End point title	Absolute change of regulatory T cells in CD4 T cells[62]

End point description:

Absolute change of regulatory T cells (Treg) from baseline (month 0) within the CD4 T cell population during DMF treatment.

End point type	Secondary

End point timeframe:

Months 0, 2, 4, 6 and 11.

Notes:

[62] - The end point is not reporting statistics for all the arms in the baseline period. It is expected all the baseline period arms will be reported on when providing values for an end point on the baseline period.
Justification: Because there were not enough samples from healthy subjects, this arm was not evaluated.

End point values	Dimethyl fumarate (DMF) (RRMS patients)			
Subject group type	Reporting group			
Number of subjects analysed	34			
Units: Treg (percent of CD4 T cells)				
median (inter-quartile range (Q1-Q3))				
Month 2 (n = 19)	-2.00 (-6.97 to 2.49)			
Month 4 (n = 19)	-3.96 (-9.89 to 1.32)			
Month 6 (n = 34)	-7.20 (-10.68 to 0.61)			
Month 11 (n = 19)	-8.49 (-13.64 to -6.67)			

Statistical analyses

No statistical analyses for this end point

Secondary: Absolute change of thymus derived regulatory T cells in CD4 T cells

End point title	Absolute change of thymus derived regulatory T cells in CD4 T cells[63]

End point description:

Absolute change of thymus derived regulatory T cells (tTreg) from baseline (month 0) within the CD4 T cell population during DMF Treatment.

End point type	Secondary

End point timeframe:

Months 0, 2, 4, 6 and 11.

Notes:

[63] - The end point is not reporting statistics for all the arms in the baseline period. It is expected all the baseline period arms will be reported on when providing values for an end point on the baseline period.
Justification: Because there were not enough samples from healthy subjects, this arm was not evaluated.

End point values	Dimethyl fumarate (DMF) (RRMS patients)			
Subject group type	Reporting group			
Number of subjects analysed	34			
Units: tTreg (percent of CD4 T cells)				
median (inter-quartile range (Q1-Q3))				
Month 2 (n = 19)	-0.15 (-0.39 to 0.42)			
Month 4 (n = 19)	-0.17 (-0.57 to 0.34)			
Month 6 (n = 34)	0.04 (-0.51 to 0.31)			
Month 11 (n = 19)	-0.26 (-0.88 to 0.15)			

Statistical analyses

No statistical analyses for this end point

Secondary: Absolute change of peripheral derived regulatory T cells in CD4 T cells

End point title	Absolute change of peripheral derived regulatory T cells in CD4 T cells[64]

End point description:

Absolute change of peripheral derived regulatory T cells (pTreg) from baseline (month 0) within the CD4 T cell population during DMF treatment.

End point type	Secondary

End point timeframe:

Months 0, 2, 4, 6 and 11.

Notes:

[64] - The end point is not reporting statistics for all the arms in the baseline period. It is expected all the baseline period arms will be reported on when providing values for an end point on the baseline period.
Justification: Because there were not enough samples from healthy subjects, this arm was not evaluated.

End point values	Dimethyl fumarate (DMF) (RRMS patients)			
Subject group type	Reporting group			
Number of subjects analysed	34			
Units: pTreg (percent of CD4 T cells)				
median (inter-quartile range (Q1-Q3))				

Month 2 (n = 19)	-0.02 (-0.09 to 0.05)			
Month 4 (n = 19)	-0.03 (-0.15 to 0.05)			
Month 6 (n = 34)	-0.03 (-0.10 to 0.03)			
Month 11 (n = 19)	-0.06 (-0.14 to -0.02)			

Statistical analyses

No statistical analyses for this end point

Secondary: Mitochondrial energy metabolism of unstimulated (ex vivo) CD4 T cells

End point title	Mitochondrial energy metabolism of unstimulated (ex vivo) CD4 T cells[65]

End point description:

Measurement of mitochondrial energy metabolism (i.e. oxidative phosphorylation) of unstimulated (ex vivo) CD4 T cells using seahorse agilent technology during DMF treatment.

End point type	Secondary

End point timeframe:

Months 0, 6 and 11.

Notes:

[65] - The end point is not reporting statistics for all the arms in the baseline period. It is expected all the baseline period arms will be reported on when providing values for an end point on the baseline period.
Justification: Because there were not enough samples from healthy subjects, this arm was not evaluated.

End point values	Dimethyl fumarate (DMF) (RRMS patients)			
Subject group type	Reporting group			
Number of subjects analysed	14			
Units: oxygen consumption rate in pmol/min				
median (inter-quartile range (Q1-Q3))				
Month 0 (n = 14)	60.14 (41.57 to 101.45)			
Month 6 (n = 14)	62.20 (51.39 to 92.01)			
Month 11 (n = 14)	65.18 (28.63 to 75.57)			

Statistical analyses

No statistical analyses for this end point

Secondary: Mitochondrial energy metabolism of short-term stimulated CD4 T cells

End point title	Mitochondrial energy metabolism of short-term stimulated CD4 T cells[66]

End point description:

Measurement of mitochondrial energy metabolism (i.e. oxidative phosphorylation) of short-term stimulated CD4 T cells using seahorse agilent technology during DMF treatment.

End point type	Secondary

End point timeframe:

Months 0, 6 and 11.

Notes:

[66] - The end point is not reporting statistics for all the arms in the baseline period. It is expected all the baseline period arms will be reported on when providing values for an end point on the baseline period.
Justification: Because there were not enough samples from healthy subjects, this arm was not evaluated.

End point values	Dimethyl fumarate (DMF) (RRMS patients)			
Subject group type	Reporting group			
Number of subjects analysed	14			
Units: oxygen consumption rate in pmol/min				
median (inter-quartile range (Q1-Q3))				
Month 0 (n = 14)	49.26 (38.33 to 69.60)			
Month 6 (n = 14)	34.79 (16.78 to 57.62)			
Month 11 (n = 14)	34.41 (16.44 to 44.32)			

Statistical analyses

No statistical analyses for this end point

Secondary: Mitochondrial energy metabolism of unstimulated (ex vivo) CD8 T cells

End point title	Mitochondrial energy metabolism of unstimulated (ex vivo) CD8 T cells[67]

End point description:

Measurement of mitochondrial energy metabolism (i.e. oxidative phosphorylation) of unstimulated (ex vivo) CD8 T cells using seahorse agilent technology during DMF treatment.

End point type	Secondary

End point timeframe:

Months 0, 6 and 11.

Notes:

[67] - The end point is not reporting statistics for all the arms in the baseline period. It is expected all the baseline period arms will be reported on when providing values for an end point on the baseline period.
Justification: Because there were not enough samples from healthy subjects, this arm was not evaluated.

End point values	Dimethyl fumarate (DMF) (RRMS patients)			
Subject group type	Reporting group			
Number of subjects analysed	14			
Units: oxygen consumption rate in pmol/min				
median (inter-quartile range (Q1-Q3))				
Month 0 (n = 14)	86.12 (60.22 to 132.35)			
Month 6 (n = 14)	62.07 (36.14 to 81.76)			
Month 11 (n = 14)	66.66 (34.79 to 121.96)			

Statistical analyses

No statistical analyses for this end point

Secondary: Mitochondrial energy metabolism of short-term stimulated CD8 T cells

End point title	Mitochondrial energy metabolism of short-term stimulated CD8 T cells[68]

End point description:

Measurement of mitochondrial energy metabolism (i.e. oxidative phosphorylation) of short-term stimulated CD8 T cells using seahorse agilent technology during DMF treatment.

End point type	Secondary

End point timeframe:

Months 0, 6 and 11.

Notes:

[68] - The end point is not reporting statistics for all the arms in the baseline period. It is expected all the baseline period arms will be reported on when providing values for an end point on the baseline period.
Justification: Because there were not enough samples from healthy subjects, this arm was not evaluated.

End point values	Dimethyl fumarate (DMF) (RRMS patients)			
Subject group type	Reporting group			
Number of subjects analysed	14			
Units: oxygen consumption rate in pmol/min				
median (inter-quartile range (Q1-Q3))				
Month 0 (n = 14)	34.90 (16.80 to 63.01)			
Month 6 (n = 14)	19.99 (6.75 to 38.75)			
Month 11 (n = 14)	21.90 (8.43 to 27.43)			

Statistical analyses

No statistical analyses for this end point

Secondary: Migratory capacity of CD4 T cells

End point title	Migratory capacity of CD4 T cells[69]

End point description:

Migration analysis in an in vitro model of the blood-brain-barrier of unstimulated CD4 T cells during DMF treatment.

End point type	Secondary

End point timeframe:

Months 0, 6 and 11.

Notes:

[69] - The end point is not reporting statistics for all the arms in the baseline period. It is expected all the baseline period arms will be reported on when providing values for an end point on the baseline period.
Justification: Because there were not enough samples from healthy subjects, this arm was not evaluated.

End point values	Dimethyl fumarate (DMF) (RRMS patients)			
Subject group type	Reporting group			
Number of subjects analysed	20			
Units: Percentage of migrated cells				
median (inter-quartile range (Q1-Q3))				
Month 0 (n = 20)	19.77 (1.92 to 64.27)			
Month 6 (n = 19)	19.64 (2.31 to 56.85)			
Month 11 (n = 10)	1.66 (0.82 to 2.82)			

Statistical analyses

No statistical analyses for this end point

Secondary: Migratory capacity of CD8 T cells

End point title	Migratory capacity of CD8 T cells[70]

End point description:

Migration analysis in an in vitro model of the blood-brain-barrier of unstimulated CD8 T cells during DMF treatment.

End point type	Secondary

End point timeframe:

Months 0, 6 and 11.

Notes:

[70] - The end point is not reporting statistics for all the arms in the baseline period. It is expected all the baseline period arms will be reported on when providing values for an end point on the baseline period.
Justification: Because there were not enough samples from healthy subjects, this arm was not evaluated.

End point values	Dimethyl fumarate (DMF) (RRMS patients)			
Subject group type	Reporting group			
Number of subjects analysed	20			
Units: Percentage of migrated cells				
median (inter-quartile range (Q1-Q3))				
Month 0 (n = 20)	11.50 (0.82 to 148.75)			
Month 6 (n = 19)	19.44 (0.69 to 173.56)			
Month 11 (n = 10)	0.83 (0.37 to 0.97)			

Statistical analyses

No statistical analyses for this end point

Adverse events

Adverse events information	
Timeframe for reporting adverse events:	
From enrollment in the study to the final study visit.	
Assessment type	Systematic

Dictionary used	
Dictionary name	MedDRA
Dictionary version	20.1

Reporting groups	
Reporting group title	Safety group
Reporting group description:	
RRMS patients who received at least one dose of dimethyl fumarate.	

Serious adverse events	Safety group		
Total subjects affected by serious adverse events			
subjects affected / exposed	3 / 42 (7.14%)		
number of deaths (all causes)	0		
number of deaths resulting from adverse events	0		
Investigations			
Weight decreased			
subjects affected / exposed	1 / 42 (2.38%)		
occurrences causally related to treatment / all	1 / 1		
deaths causally related to treatment / all	0 / 0		
Injury, poisoning and procedural complications			
Radius fracture			
subjects affected / exposed	1 / 42 (2.38%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Pregnancy, puerperium and perinatal conditions			
Abortion			
subjects affected / exposed	1 / 42 (2.38%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Nervous system disorders			
Cerebral ischaemia			

subjects affected / exposed	1 / 42 (2.38%)		
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	Safety group		
Total subjects affected by non-serious adverse events			
subjects affected / exposed	37 / 42 (88.10%)		
Vascular disorders			
Flushing			
subjects affected / exposed	24 / 42 (57.14%)		
occurrences (all)	28		
Hot flush			
subjects affected / exposed	1 / 42 (2.38%)		
occurrences (all)	1		
General disorders and administration site conditions			
Fatigue			
subjects affected / exposed	4 / 42 (9.52%)		
occurrences (all)	4		
Feeling hot			
subjects affected / exposed	1 / 42 (2.38%)		
occurrences (all)	1		
Oedema peripheral			
subjects affected / exposed	2 / 42 (4.76%)		
occurrences (all)	2		
Reproductive system and breast disorders			
Menopausal symptoms			
subjects affected / exposed	1 / 42 (2.38%)		
occurrences (all)	1		
Respiratory, thoracic and mediastinal disorders			
Cough			
subjects affected / exposed	1 / 42 (2.38%)		
occurrences (all)	1		
Oropharyngeal pain			

subjects affected / exposed	1 / 42 (2.38%)		
occurrences (all)	1		
Psychiatric disorders			
Depression			
subjects affected / exposed	1 / 42 (2.38%)		
occurrences (all)	1		
Investigations			
Alanine aminotransferase increased			
subjects affected / exposed	1 / 42 (2.38%)		
occurrences (all)	1		
Aspartate aminotransferase increased			
subjects affected / exposed	1 / 42 (2.38%)		
occurrences (all)	1		
Hepatic enzyme increased			
subjects affected / exposed	1 / 42 (2.38%)		
occurrences (all)	1		
Protein urine present			
subjects affected / exposed	1 / 42 (2.38%)		
occurrences (all)	1		
Injury, poisoning and procedural complications			
Cartilage injury			
subjects affected / exposed	1 / 42 (2.38%)		
occurrences (all)	1		
Foot fracture			
subjects affected / exposed	1 / 42 (2.38%)		
occurrences (all)	1		
Cardiac disorders			
Arrhythmia			
subjects affected / exposed	1 / 42 (2.38%)		
occurrences (all)	1		
Tachycardia			
subjects affected / exposed	1 / 42 (2.38%)		
occurrences (all)	1		
Nervous system disorders			
Ataxia			

subjects affected / exposed	1 / 42 (2.38%)		
occurrences (all)	1		
Dizziness			
subjects affected / exposed	1 / 42 (2.38%)		
occurrences (all)	1		
Dysgeusia			
subjects affected / exposed	1 / 42 (2.38%)		
occurrences (all)	1		
Headache			
subjects affected / exposed	4 / 42 (9.52%)		
occurrences (all)	4		
Hypertonia			
subjects affected / exposed	1 / 42 (2.38%)		
occurrences (all)	1		
Hypoaesthesia			
subjects affected / exposed	1 / 42 (2.38%)		
occurrences (all)	1		
Sensory loss			
subjects affected / exposed	1 / 42 (2.38%)		
occurrences (all)	1		
Tremor			
subjects affected / exposed	1 / 42 (2.38%)		
occurrences (all)	1		
Blood and lymphatic system disorders			
Iron deficiency anaemia			
subjects affected / exposed	1 / 42 (2.38%)		
occurrences (all)	1		
Leukopenia			
subjects affected / exposed	1 / 42 (2.38%)		
occurrences (all)	1		
Lymphopenia			
subjects affected / exposed	3 / 42 (7.14%)		
occurrences (all)	3		
Ear and labyrinth disorders			
Vertigo			

subjects affected / exposed	1 / 42 (2.38%)		
occurrences (all)	1		
Eye disorders			
Visual impairment			
subjects affected / exposed	2 / 42 (4.76%)		
occurrences (all)	2		
Gastrointestinal disorders			
Abdominal discomfort			
subjects affected / exposed	1 / 42 (2.38%)		
occurrences (all)	1		
Abdominal pain			
subjects affected / exposed	1 / 42 (2.38%)		
occurrences (all)	1		
Abdominal pain upper			
subjects affected / exposed	4 / 42 (9.52%)		
occurrences (all)	4		
Aphthous ulcer			
subjects affected / exposed	1 / 42 (2.38%)		
occurrences (all)	1		
Diarrhoea			
subjects affected / exposed	5 / 42 (11.90%)		
occurrences (all)	6		
Dry mouth			
subjects affected / exposed	1 / 42 (2.38%)		
occurrences (all)	1		
Epigastric discomfort			
subjects affected / exposed	1 / 42 (2.38%)		
occurrences (all)	1		
Flatulence			
subjects affected / exposed	3 / 42 (7.14%)		
occurrences (all)	3		
Gastric disorder			
subjects affected / exposed	3 / 42 (7.14%)		
occurrences (all)	3		
Gastrointestinal disorder			

subjects affected / exposed occurrences (all) Nausea subjects affected / exposed occurrences (all) Vomiting subjects affected / exposed occurrences (all)	3 / 42 (7.14%) 3 4 / 42 (9.52%) 4 2 / 42 (4.76%) 2		
Skin and subcutaneous tissue disorders Erythema subjects affected / exposed occurrences (all) Pruritus subjects affected / exposed occurrences (all) Skin irritation subjects affected / exposed occurrences (all) Skin warm subjects affected / exposed occurrences (all)	 4 / 42 (9.52%) 7 6 / 42 (14.29%) 7 1 / 42 (2.38%) 1 2 / 42 (4.76%) 2		
Renal and urinary disorders Proteinuria subjects affected / exposed occurrences (all)	 1 / 42 (2.38%) 1		
Musculoskeletal and connective tissue disorders Arthralgia subjects affected / exposed occurrences (all) Joint lock subjects affected / exposed occurrences (all) Muscular weakness subjects affected / exposed occurrences (all) Osteoarthritis	 2 / 42 (4.76%) 2 1 / 42 (2.38%) 1 1 / 42 (2.38%) 1		

subjects affected / exposed	1 / 42 (2.38%)		
occurrences (all)	1		
Pain in extremity			
subjects affected / exposed	1 / 42 (2.38%)		
occurrences (all)	1		
Infections and infestations			
Acute sinusitis			
subjects affected / exposed	1 / 42 (2.38%)		
occurrences (all)	1		
Bronchitis			
subjects affected / exposed	1 / 42 (2.38%)		
occurrences (all)	1		
Folliculitis			
subjects affected / exposed	1 / 42 (2.38%)		
occurrences (all)	1		
Gastric infection			
subjects affected / exposed	1 / 42 (2.38%)		
occurrences (all)	1		
Gastroenteritis			
subjects affected / exposed	2 / 42 (4.76%)		
occurrences (all)	2		
Hand-foot-and-mouth disease			
subjects affected / exposed	1 / 42 (2.38%)		
occurrences (all)	1		
Infection			
subjects affected / exposed	2 / 42 (4.76%)		
occurrences (all)	2		
Nasal herpes			
subjects affected / exposed	1 / 42 (2.38%)		
occurrences (all)	1		
Nasopharyngitis			
subjects affected / exposed	14 / 42 (33.33%)		
occurrences (all)	17		
Oral herpes			
subjects affected / exposed	1 / 42 (2.38%)		
occurrences (all)	1		

Rhinitis subjects affected / exposed occurrences (all)	1 / 42 (2.38%) 1		
Tonsillitis subjects affected / exposed occurrences (all)	1 / 42 (2.38%) 1		
Urinary tract infection subjects affected / exposed occurrences (all)	6 / 42 (14.29%) 6		
Vulvovaginal mycotic infection subjects affected / exposed occurrences (all)	1 / 42 (2.38%) 1		

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

Date	Amendment
06 October 2015	Inclusion and exclusion criteria of the protocol have been amended: • The time limit for disease-modifying treatment before the start of the trial was reduced from 6 months to one month (the procedure remained unchanged for patients who received IFN ß-1 or glatiramer acetate at the time of screening). • Previously, the test for tuberculosis, HIV and hepatitis B and C had to be performed during screening. After the amendment, test results not older than 3 months at the time of screening were also allowed. • Limit values for certain laboratory parameters have been removed. Only clinical significant deviations of the laboratory values lead to the exclusion of the patient (decision of the investigator). In addition, the following has been modified in the protocol: • In order to exclude pregnancy at the time of screening, a urine pregnancy test should now also be allowed (previously only a blood test was allowed). • The analysis of laboratory parameters (clinical chemistry) which are not recommended or obligatory according to the summary of product characteristics or the Krankheitsbezogenen Kompetenznetzes Multiple Sklerose should no longer be performed.
25 April 2017	Secondary objectives have been modified: • In order to examine the cytokine production of the cells, only the cytokines GM-CSF, IFNγ, TNF-α, IL-22 und IL-17A should be examined (the analysis of IL-2, IL-4, IL-10 and IL-21 was removed from the protocol). Secondary objectives have been removed: • Investigating the differentiation capability of T cells and the ability of regulatory T cells to suppress the effector T cell response were removed from the protocol. Secondary objectives have been added: • Evaluation of changes in mitochondrial energy metabolism was added to the protocol. Sample size / change to the power analyses: • Initially, it was planned to recruit 60 RRMS patients. Due to new external information concerning the mean change in Th17 cells, the number of RRMS patients was decreased to 50 patients and the power analysis was repeated.

Notes:

Interruptions (globally)

Were there any global interruptions to the trial? No

Limitations and caveats

None reported