Clinical trial results:
A 3-Year Open-Label, Exploratory, Single Arm Study to Describe Long Term Changes in the Visual System of Patients with Relapsing Remitting Multiple Sclerosis (RRMS) on Oral Dimethyl Fumarate

Summary

EudraCT number	2014-000395-26
Trial protocol	DE
Global end of trial date	21 October 2016

Results information

Result version number	v1 (current)
This version publication date	08 December 2017
First version publication date	08 December 2017

Trial information

Trial identification

Sponsor protocol code	GER-BGT-13-10586

Additional study identifiers

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

Notes:

Sponsors

Sponsor organisation name	Biogen
Sponsor organisation address	250 Binney Street, Cambridge, United States, 02142
Public contact	Study Director, Biogen, +1 866-633-4636, clinicaltrials@biogen.com
Scientific contact	Study Director, Biogen, +1 866-633-4636, clinicaltrials@biogen.com

Notes:

Paediatric regulatory details

Is trial part of an agreed paediatric investigation plan (PIP)	No
Does article 45 of REGULATION (EC) No 1901/2006 apply to this trial?	No
Does article 46 of REGULATION (EC) No 1901/2006 apply to this trial?	No

Notes:

Results analysis stage

Analysis stage	Final
Date of interim/final analysis	12 October 2017
Is this the analysis of the primary completion data?	Yes
Primary completion date	21 October 2016
Global end of trial reached?	Yes
Global end of trial date	21 October 2016
Was the trial ended prematurely?	Yes

Notes:

General information about the trial

Main objective of the trial:

To evaluate changes of the visual system in relapsed remitting multiple sclerosis (RRMS) patients treated with dimethyl fumarate assessed by retinal nerve fiber layer (RNFL) thickness measured by optical coherence tomography (OCT) over 36 months.

Protection of trial subjects:

Written informed consent was obtained from each subject prior to evaluations performed for eligibility. Subjects were given adequate time to review the information in the informed consent and were allowed to ask, and have answered, questions concerning all portions of the conduct of the study. Subjects were provided with a copy of the signed and dated informed consent form (ICF).

Background therapy: -

Evidence for comparator: -

Actual start date of recruitment	02 November 2015
Long term follow-up planned	No
Independent data monitoring committee (IDMC) involvement?	No

Notes:

Population of trial subjects

Subjects enrolled per country

Country: Number of subjects enrolled	Germany: 18
Worldwide total number of subjects	18
EEA total number of subjects	18

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)	18
From 65 to 84 years	0
85 years and over	0

Subject disposition

Recruitment

Recruitment details:

Subjects were recruited from 5 sites in Germany. All subjects who signed the informed consent form and who were initially considered for study participation must have been clinically stable on 240 mg dimethyl fumarate (DMF) twice daily for at least 4 and up to 20 weeks prior to the screening visit.

Pre-assignment

Screening details:

Subjects were screened for enrollment over 28 days. All screened subjects were exposed to dimethyl fumarate (DMF) for at least one day (at screening) during the study. Subjects deemed screening failures were exposed to DMF for one day (at screening) except for one subject that was on DMF for 86 days and was retrospectively deemed screening failure.

Period 1

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

Arms

Arm title	Dimethyl Fumarate

Arm description:

Adult subjects who met eligibility criteria and with a confirmed diagnosis of relapsed remitting multiple sclerosis (RRMS) defined by the current McDonald criteria and be in line with the Tecfidera® summary of product characteristics.

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

Dosage and administration details:

Administered as specified in the treatment arm.

Number of subjects in period 1[1]	Dimethyl Fumarate
Started	12
Completed	12

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: Not all subjects who signed an informed consent form and who were screened for eligibility contributed data to the baseline characteristics and study endpoints.

Baseline characteristics

Reporting groups	
Reporting group title	Dimethyl Fumarate

Reporting group description:

Adult subjects who met eligibility criteria and with a confirmed diagnosis of relapsed remitting multiple sclerosis (RRMS) defined by the current McDonald criteria and be in line with the Tecfidera® summary of product characteristics.

Reporting group values	Dimethyl Fumarate	Total	
Number of subjects	12	12	
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)	12	12	
From 65-84 years	0	0	
85 years and over	0	0	
Age Continuous Units: years			
arithmetic mean	37.4		
standard deviation	± 10.3	-	
Gender Categorical Units: Subjects			
Female	8	8	
Male	4	4	

End points

End points reporting groups

Reporting group title	Dimethyl Fumarate

Reporting group description:

Adult subjects who met eligibility criteria and with a confirmed diagnosis of relapsed remitting multiple sclerosis (RRMS) defined by the current McDonald criteria and be in line with the Tecfidera® summary of product characteristics.

Primary: Change from baseline in mean global thickness of the retinal nerve fiber layer as measured by optical coherence tomography at a circle diameter of 3.5 millimeters

End point title	Change from baseline in mean global thickness of the retinal nerve fiber layer as measured by optical coherence tomography at a circle diameter of 3.5 millimeters[1]

End point description:

Changes in retinal nerve fiber layer (RNFL) thickness were measured for both eyes at baseline and at the end of the study by using Heidelberg spectral domain (SD) optical coherence tomography (OCT). The mean duration between baseline and end-of-study assessments was 21.8±10.5 weeks (median: 17.5 weeks [range: 12.7; 46.3 weeks]). OCT scans were performed at circle diameters of 3.5 mm, 4.1 mm, and 4.7 mm. Thickness was measured globally, for the papillo macular bundle, and for the nasal, nasal/inferior, temporal/inferior, temporal, temporal/superior, and nasal/superior quadrants. In addition, the nasal/temporal ratio was calculated. A negative change from baseline indicates that retinal thickness decreased.
This outcome assessed the Full Analysis Set, defined as all enrolled patients who were successfully screened (i.e. met all eligibility criteria) and who had post-baseline measurements available.

End point type	Primary

End point timeframe:

Baseline and End-of-Study

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: Although it is generally expected that each primary endpoint will have at least one statistical analysis, statistical analyses were not performed because the study was terminated early.

End point values	Dimethyl Fumarate			
Subject group type	Reporting group			
Number of subjects analysed	8			
Units: micrometers				
arithmetic mean (standard deviation)				
Left Eye	-0.13 (± 3.14)			
Right Eye	0.38 (± 1.93)			

Statistical analyses

No statistical analyses for this end point

Primary: Change from baseline in mean thickness of the papillo macular bundle of the retinal nerve fiber layer as measured by optical coherence tomography at a circle diameter of 3.5 millimeters

End point title	Change from baseline in mean thickness of the papillo macular bundle of the retinal nerve fiber layer as measured by optical coherence tomography at a circle diameter of 3.5 millimeters[2]

End point description:

Changes in retinal nerve fiber layer (RNFL) thickness were measured for both eyes at baseline and at the end of the study by using Heidelberg spectral domain (SD) optical coherence tomography (OCT). The mean duration between baseline and end-of-study assessments was 21.8±10.5 weeks (median: 17.5 weeks [range: 12.7; 46.3 weeks]). OCT scans were performed at circle diameters of 3.5 millimeters (mm), 4.1 mm, and 4.7 mm. Thickness was measured globally, for the papillo-macular bundle, and for the nasal, nasal/inferior, temporal/inferior, temporal, temporal/superior, and nasal/superior quadrants. In addition, the nasal/temporal ratio was calculated. A negative change from baseline indicates that retinal thickness decreased.
This outcome assessed the Full Analysis Set, defined as all enrolled patients who were successfully screened (i.e. met all eligibility criteria) and who had post-baseline measurements available.

End point type	Primary

End point timeframe:

Baseline and End-of-Study

Notes:

[2] - No statistical analyses have been specified for this primary end point. It is expected there is at least one statistical analysis for each primary end point.
Justification: Although it is generally expected that each primary endpoint will have at least one statistical analysis, statistical analyses were not performed because the study was terminated early.

End point values	Dimethyl Fumarate			
Subject group type	Reporting group			
Number of subjects analysed	8			
Units: micrometers				
arithmetic mean (standard deviation)				
Left Eye	1.0 (± 2.2)			
Right Eye	0.1 (± 1.4)			

Statistical analyses

No statistical analyses for this end point

Primary: Change from baseline in mean thickness of the nasal/superior quadrant of the retinal nerve fiber layer as measured by optical coherence tomography at a circle diameter of 3.5 millimeters

End point title	Change from baseline in mean thickness of the nasal/superior quadrant of the retinal nerve fiber layer as measured by optical coherence tomography at a circle diameter of 3.5 millimeters[3]

End point description:

Changes in retinal nerve fiber layer (RNFL) thickness were measured for both eyes at baseline and at the end of the study by using Heidelberg spectral domain (SD) optical coherence tomography (OCT). The mean duration between baseline and end-of-study assessments was 21.8±10.5 weeks (median: 17.5 weeks [range: 12.7; 46.3 weeks]). OCT scans were performed at circle diameters of 3.5 mm, 4.1 mm, and 4.7 mm. Thickness was measured globally, for the papillo macular bundle, and for the nasal, nasal/inferior, temporal/inferior, temporal, temporal/superior, and nasal/superior quadrants. In addition, the nasal/temporal ratio was calculated. A negative change from baseline indicates that retinal thickness decreased.
This outcome assessed the Full Analysis Set, defined as all enrolled patients who were successfully screened (i.e. met all eligibility criteria) and who had post-baseline measurements available.

End point type	Primary

End point timeframe:

Baseline and End-of-Study

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: Although it is generally expected that each primary endpoint will have at least one statistical analysis, statistical analyses were not performed because the study was terminated early.

End point values	Dimethyl Fumarate			
Subject group type	Reporting group			
Number of subjects analysed	8			
Units: micrometers				
arithmetic mean (standard deviation)				
Left Eye	-2.3 (± 7.6)			
Right Eye	-0.1 (± 3.6)			

Statistical analyses

No statistical analyses for this end point

Primary: Change from baseline in mean thickness of the nasal quadrant of the retinal nerve fiber layer as measured by optical coherence tomography at a circle diameter of 3.5 millimeters

End point title	Change from baseline in mean thickness of the nasal quadrant of the retinal nerve fiber layer as measured by optical coherence tomography at a circle diameter of 3.5 millimeters[4]

End point description:

Changes in retinal nerve fiber layer (RNFL) thickness were measured for both eyes at baseline and at the end of the study by using Heidelberg spectral domain (SD) optical coherence tomography (OCT). The mean duration between baseline and end-of-study assessments was 21.8±10.5 weeks (median: 17.5 weeks [range: 12.7; 46.3 weeks]). OCT scans were performed at circle diameters of 3.5 mm, 4.1 mm, and 4.7 mm. Thickness was measured globally, for the papillo macular bundle, and for the nasal, nasal/inferior, temporal/inferior, temporal, temporal/superior, and nasal/superior quadrants. In addition, the nasal/temporal ratio was calculated. A negative change from baseline indicates that retinal thickness decreased.
This outcome assessed the Full Analysis Set, defined as all enrolled patients who were successfully screened (i.e. met all eligibility criteria) and who had post-baseline measurements available.

End point type	Primary

End point timeframe:

Baseline and End-of-Study

Notes:

[4] - No statistical analyses have been specified for this primary end point. It is expected there is at least one statistical analysis for each primary end point.
Justification: Although it is generally expected that each primary endpoint will have at least one statistical analysis, statistical analyses were not performed because the study was terminated early.

End point values	Dimethyl Fumarate			
Subject group type	Reporting group			
Number of subjects analysed	8			
Units: micrometers				
arithmetic mean (standard deviation)				
Left Eye	-0.3 (± 2.5)			
Right Eye	0.9 (± 3.6)			

Statistical analyses

No statistical analyses for this end point

Primary: Change from baseline in mean thickness of the nasal/inferior quadrant of the retinal nerve fiber layer as measured by optical coherence tomography at a circle diameter of 3.5 millimeters

End point title	Change from baseline in mean thickness of the nasal/inferior quadrant of the retinal nerve fiber layer as measured by optical coherence tomography at a circle diameter of 3.5 millimeters[5]

End point description:

Changes in retinal nerve fiber layer (RNFL) thickness were measured for both eyes at baseline and at the end of the study by using Heidelberg spectral domain (SD) optical coherence tomography (OCT). The mean duration between baseline and end-of-study assessments was 21.8±10.5 weeks (median: 17.5 weeks [range: 12.7; 46.3 weeks]). OCT scans were performed at circle diameters of 3.5 mm, 4.1 mm, and 4.7 mm. Thickness was measured globally, for the papillo macular bundle, and for the nasal, nasal/inferior, temporal/inferior, temporal, temporal/superior, and nasal/superior quadrants. In addition, the nasal/temporal ratio was calculated. A negative change from baseline indicates that retinal thickness decreased.
This outcome assessed the Full Analysis Set, defined as all enrolled patients who were successfully screened (i.e. met all eligibility criteria) and who had post-baseline measurements available.

End point type	Primary

End point timeframe:

Baseline and End-of-Study

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: Although it is generally expected that each primary endpoint will have at least one statistical analysis, statistical analyses were not performed because the study was terminated early.

End point values	Dimethyl Fumarate			
Subject group type	Reporting group			
Number of subjects analysed	8			
Units: micrometers				
arithmetic mean (standard deviation)				
Left Eye	1.6 (± 4.1)			
Right Eye	-0.5 (± 2.9)			

Statistical analyses

No statistical analyses for this end point

Primary: Change from baseline in mean thickness of the temporal/inferior quadrant of the retinal nerve fiber layer as measured by optical coherence tomography at a circle diameter of 3.5 millimeters

End point title	Change from baseline in mean thickness of the temporal/inferior quadrant of the retinal nerve fiber layer as

	measured by optical coherence tomography at a circle diameter of 3.5 millimeters[6]

End point description:

Changes in retinal nerve fiber layer (RNFL) thickness were measured for both eyes at baseline and at the end of the study by using Heidelberg spectral domain (SD) optical coherence tomography (OCT). The mean duration between baseline and end-of-study assessments was 21.8±10.5 weeks (median: 17.5 weeks [range: 12.7; 46.3 weeks]). OCT scans were performed at circle diameters of 3.5 mm, 4.1 mm, and 4.7 mm. Thickness was measured globally, for the papillo macular bundle, and for the nasal, nasal/inferior, temporal/inferior, temporal, temporal/superior, and nasal/superior quadrants. In addition, the nasal/temporal ratio was calculated. A negative change from baseline indicates that retinal thickness decreased.
This outcome assessed the Full Analysis Set, defined as all enrolled patients who were successfully screened (i.e. met all eligibility criteria) and who had post-baseline measurements available.

End point type	Primary

End point timeframe:

Baseline and End-of-Study

Notes:

[6] - 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: Although it is generally expected that each primary endpoint will have at least one statistical analysis, statistical analyses were not performed because the study was terminated early.

End point values	Dimethyl Fumarate			
Subject group type	Reporting group			
Number of subjects analysed	8			
Units: micrometers				
arithmetic mean (standard deviation)				
Left Eye	1.9 (± 6.8)			
Right Eye	-0.5 (± 1.0)			

Statistical analyses

No statistical analyses for this end point

Primary: Change from baseline in mean thickness of the temporal quadrant of the retinal nerve fiber layer as measured by optical coherence tomography at a circle diameter of 3.5 millimeters

End point title	Change from baseline in mean thickness of the temporal quadrant of the retinal nerve fiber layer as measured by optical coherence tomography at a circle diameter of 3.5 millimeters[7]

End point description:

Changes in retinal nerve fiber layer (RNFL) thickness were measured for both eyes at baseline and at the end of the study by using Heidelberg spectral domain (SD) optical coherence tomography (OCT). The mean duration between baseline and end-of-study assessments was 21.8±10.5 weeks (median: 17.5 weeks [range: 12.7; 46.3 weeks]). OCT scans were performed at circle diameters of 3.5 mm, 4.1 mm, and 4.7 mm. Thickness was measured globally, for the papillo macular bundle, and for the nasal, nasal/inferior, temporal/inferior, temporal, temporal/superior, and nasal/superior quadrants. In addition, the nasal/temporal ratio was calculated. A negative change from baseline indicates that retinal thickness decreased.
This outcome assessed the Full Analysis Set, defined as all enrolled patients who were successfully screened (i.e. met all eligibility criteria) and who had post-baseline measurements available.

End point type	Primary

End point timeframe:

Baseline and End-of-Study

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: Although it is generally expected that each primary endpoint will have at least one statistical analysis, statistical analyses were not performed because the study was terminated early.

End point values	Dimethyl Fumarate			
Subject group type	Reporting group			
Number of subjects analysed	8			
Units: micrometers				
arithmetic mean (standard deviation)				
Left Eye	-0.5 (± 2.2)			
Right Eye	0.4 (± 1.4)			

Statistical analyses

No statistical analyses for this end point

Primary: Change from baseline in mean thickness of the temporal/superior quadrant of the retinal nerve fiber layer as measured by optical coherence tomography at a circle diameter of 3.5 millimeters

End point title	Change from baseline in mean thickness of the temporal/superior quadrant of the retinal nerve fiber layer as measured by optical coherence tomography at a circle diameter of 3.5 millimeters[8]

End point description:

Changes in retinal nerve fiber layer (RNFL) thickness were measured for both eyes at baseline and at the end of the study by using Heidelberg spectral domain (SD) optical coherence tomography (OCT). The mean duration between baseline and end-of-study assessments was 21.8±10.5 weeks (median: 17.5 weeks [range: 12.7; 46.3 weeks]). OCT scans were performed at circle diameters of 3.5 mm, 4.1 mm, and 4.7 mm. Thickness was measured globally, for the papillo macular bundle, and for the nasal, nasal/inferior, temporal/inferior, temporal, temporal/superior, and nasal/superior quadrants. In addition, the nasal/temporal ratio was calculated. A negative change from baseline indicates that retinal thickness decreased.
This outcome assessed the Full Analysis Set, defined as all enrolled patients who were successfully screened (i.e. met all eligibility criteria) and who had post-baseline measurements available.

End point type	Primary

End point timeframe:

Baseline and End-of-Study

Notes:

[8] - 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: Although it is generally expected that each primary endpoint will have at least one statistical analysis, statistical analyses were not performed because the study was terminated early.

End point values	Dimethyl Fumarate			
Subject group type	Reporting group			
Number of subjects analysed	8			
Units: micrometers				
arithmetic mean (standard deviation)				
Left Eye	-0.4 (± 4.2)			
Right Eye	1.0 (± 1.8)			

Statistical analyses

No statistical analyses for this end point

Primary: Change from baseline in the ratio of the mean thickness of the nasal and temporal quadrants of the retinal nerve fiber layer as measured by optical coherence tomography at a circle diameter of 3.5 millimeters

End point title	Change from baseline in the ratio of the mean thickness of the nasal and temporal quadrants of the retinal nerve fiber layer as measured by optical coherence tomography at a circle diameter of 3.5 millimeters[9]

End point description:

Changes in retinal nerve fiber layer (RNFL) thickness were measured for both eyes at baseline and at the end of the study by using Heidelberg spectral domain (SD) optical coherence tomography (OCT). The mean duration between baseline and end-of-study assessments was 21.8±10.5 weeks (median: 17.5 weeks [range: 12.7; 46.3 weeks]). OCT scans were performed at circle diameters of 3.5 mm, 4.1 mm, and 4.7 mm. Thickness was measured globally, for the papillo macular bundle, and for the nasal, nasal/inferior, temporal/inferior, temporal, temporal/superior, and nasal/superior quadrants. In addition, the nasal/temporal ratio was calculated. A negative change from baseline indicates that retinal thickness decreased.
This outcome assessed the Full Analysis Set, defined as all enrolled patients who were successfully screened (i.e. met all eligibility criteria) and who had post-baseline measurements available.

End point type	Primary

End point timeframe:

Baseline and End-of-Study

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: Although it is generally expected that each primary endpoint will have at least one statistical analysis, statistical analyses were not performed because the study was terminated early.

End point values	Dimethyl Fumarate			
Subject group type	Reporting group			
Number of subjects analysed	8			
Units: micrometers				
arithmetic mean (standard deviation)				
Left Eye	0.001 (± 0.041)			
Right Eye	0.006 (± 0.042)			

Statistical analyses

No statistical analyses for this end point

Primary: Change from baseline in mean global thickness of the retinal nerve fiber layer in the left eye as measured by optical coherence tomography at a circle

diameter of 4.1 millimeters

End point title	Change from baseline in mean global thickness of the retinal nerve fiber layer in the left eye as measured by optical coherence tomography at a circle diameter of 4.1 millimeters[10]

End point description:

Changes in retinal nerve fiber layer (RNFL) thickness were measured for both eyes at baseline and at the end of the study by using Heidelberg spectral domain (SD) optical coherence tomography (OCT). The mean duration between baseline and end-of-study assessments was 21.8±10.5 weeks (median: 17.5 weeks [range: 12.7; 46.3 weeks]). OCT scans were performed at circle diameters of 3.5 mm, 4.1 mm, and 4.7 mm. Thickness was measured globally, for the papillo macular bundle, and for the nasal, nasal/inferior, temporal/inferior, temporal, temporal/superior, and nasal/superior quadrants. In addition, the nasal/temporal ratio was calculated. A negative change from baseline indicates that retinal thickness decreased.
This outcome assessed the Full Analysis Set, defined as all enrolled patients who were successfully screened (i.e. met all eligibility criteria) and who had post-baseline measurements available.

End point type	Primary

End point timeframe:

Baseline and End-of-Study

Notes:

[10] - 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: Although it is generally expected that each primary endpoint will have at least one statistical analysis, statistical analyses were not performed because the study was terminated early.

End point values	Dimethyl Fumarate			
Subject group type	Reporting group			
Number of subjects analysed	7			
Units: micrometers				
arithmetic mean (standard deviation)				
Left Eye	-0.71 (± 2.37)			

Statistical analyses

No statistical analyses for this end point

Primary: Change from baseline in mean global thickness of the retinal nerve fiber layer in the right eye as measured by optical coherence tomography at a circle diameter of 4.1 millimeters

End point title	Change from baseline in mean global thickness of the retinal nerve fiber layer in the right eye as measured by optical coherence tomography at a circle diameter of 4.1 millimeters[11]

End point description:

Changes in retinal nerve fiber layer (RNFL) thickness were measured for both eyes at baseline and at the end of the study by using Heidelberg spectral domain (SD) optical coherence tomography (OCT). The mean duration between baseline and end-of-study assessments was 21.8±10.5 weeks (median: 17.5 weeks [range: 12.7; 46.3 weeks]). OCT scans were performed at circle diameters of 3.5 mm, 4.1 mm, and 4.7 mm. Thickness was measured globally, for the papillo macular bundle, and for the nasal, nasal/inferior, temporal/inferior, temporal, temporal/superior, and nasal/superior quadrants. In addition, the nasal/temporal ratio was calculated. A negative change from baseline indicates that retinal thickness decreased.
This outcome assessed the Full Analysis Set, defined as all enrolled patients who were successfully screened (i.e. met all eligibility criteria) and who had post-baseline measurements available.

End point type	Primary

End point timeframe:

Baseline and End-of-Study

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: Although it is generally expected that each primary endpoint will have at least one statistical analysis, statistical analyses were not performed because the study was terminated early.

End point values	Dimethyl Fumarate			
Subject group type	Reporting group			
Number of subjects analysed	8			
Units: micrometers				
arithmetic mean (standard deviation)				
Right Eye	0.25 (± 1.85)			

Statistical analyses

No statistical analyses for this end point

Primary: Change from baseline in mean thickness of the papillo macular bundle of the retinal nerve fiber layer in the left eye as measured by optical coherence tomography at a circle diameter of 4.1 millimeters

End point title	Change from baseline in mean thickness of the papillo macular bundle of the retinal nerve fiber layer in the left eye as measured by optical coherence tomography at a circle diameter of 4.1 millimeters[12]

End point description:

Changes in retinal nerve fiber layer (RNFL) thickness were measured for both eyes at baseline and at the end of the study by using Heidelberg spectral domain (SD) optical coherence tomography (OCT). The mean duration between baseline and end-of-study assessments was 21.8±10.5 weeks (median: 17.5 weeks [range: 12.7; 46.3 weeks]). OCT scans were performed at circle diameters of 3.5 mm, 4.1 mm, and 4.7 mm. Thickness was measured globally, for the papillo macular bundle, and for the nasal, nasal/inferior, temporal/inferior, temporal, temporal/superior, and nasal/superior quadrants. In addition, the nasal/temporal ratio was calculated. A negative change from baseline indicates that retinal thickness decreased.
This outcome assessed the Full Analysis Set, defined as all enrolled patients who were successfully screened (i.e. met all eligibility criteria) and who had post-baseline measurements available.

End point type	Primary

End point timeframe:

Baseline and End-of-Study

Notes:

[12] - 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: Although it is generally expected that each primary endpoint will have at least one statistical analysis, statistical analyses were not performed because the study was terminated early.

End point values	Dimethyl Fumarate			
Subject group type	Reporting group			
Number of subjects analysed	7			
Units: micrometers				
arithmetic mean (standard deviation)				
Left Eye	-0.4 (± 1.0)			

Statistical analyses

No statistical analyses for this end point

Primary: Change from baseline in mean thickness of the papillo macular bundle of the retinal nerve fiber layer in the right eye as measured by optical coherence tomography at a circle diameter of 4.1 millimeters

End point title	Change from baseline in mean thickness of the papillo macular bundle of the retinal nerve fiber layer in the right eye as measured by optical coherence tomography at a circle diameter of 4.1 millimeters[13]

End point description:

Changes in retinal nerve fiber layer (RNFL) thickness were measured for both eyes at baseline and at the end of the study by using Heidelberg spectral domain (SD) optical coherence tomography (OCT). The mean duration between baseline and end-of-study assessments was 21.8±10.5 weeks (median: 17.5 weeks [range: 12.7; 46.3 weeks]). OCT scans were performed at circle diameters of 3.5 mm, 4.1 mm, and 4.7 mm. Thickness was measured globally, for the papillo macular bundle, and for the nasal, nasal/inferior, temporal/inferior, temporal, temporal/superior, and nasal/superior quadrants. In addition, the nasal/temporal ratio was calculated. A negative change from baseline indicates that retinal thickness decreased.
This outcome assessed the Full Analysis Set, defined as all enrolled patients who were successfully screened (i.e. met all eligibility criteria) and who had post-baseline measurements available.

End point type	Primary

End point timeframe:

Baseline and End-of-Study

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: Although it is generally expected that each primary endpoint will have at least one statistical analysis, statistical analyses were not performed because the study was terminated early.

End point values	Dimethyl Fumarate			
Subject group type	Reporting group			
Number of subjects analysed	8			
Units: micrometers				
arithmetic mean (standard deviation)				
Right Eye	1.1 (± 2.5)			

Statistical analyses

No statistical analyses for this end point

Primary: Change from baseline in mean thickness of the nasal/superior quadrant of the retinal nerve fiber layer in the left eye as measured by optical coherence tomography at a circle diameter of 4.1 millimeters

End point title	Change from baseline in mean thickness of the nasal/superior quadrant of the retinal nerve fiber layer in the left eye as

	measured by optical coherence tomography at a circle diameter of 4.1 millimeters[14]

End point description:

Changes in retinal nerve fiber layer (RNFL) thickness were measured for both eyes at baseline and at the end of the study by using Heidelberg spectral domain (SD) optical coherence tomography (OCT). The mean duration between baseline and end-of-study assessments was 21.8±10.5 weeks (median: 17.5 weeks [range: 12.7; 46.3 weeks]). OCT scans were performed at circle diameters of 3.5 mm, 4.1 mm, and 4.7 mm. Thickness was measured globally, for the papillo macular bundle, and for the nasal, nasal/inferior, temporal/inferior, temporal, temporal/superior, and nasal/superior quadrants. In addition, the nasal/temporal ratio was calculated. A negative change from baseline indicates that retinal thickness decreased.
This outcome assessed the Full Analysis Set, defined as all enrolled patients who were successfully screened (i.e. met all eligibility criteria) and who had post-baseline measurements available.

End point type	Primary

End point timeframe:

Baseline and End-of-Study

Notes:

[14] - 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: Although it is generally expected that each primary endpoint will have at least one statistical analysis, statistical analyses were not performed because the study was terminated early.

End point values	Dimethyl Fumarate			
Subject group type	Reporting group			
Number of subjects analysed	7			
Units: micrometers				
arithmetic mean (standard deviation)				
Left Eye	-1.0 (± 5.0)			

Statistical analyses

No statistical analyses for this end point

Primary: Change from baseline in mean thickness of the nasal/superior quadrant of the retinal nerve fiber layer in the right eye as measured by optical coherence tomography at a circle diameter of 4.1 millimeters

End point title	Change from baseline in mean thickness of the nasal/superior quadrant of the retinal nerve fiber layer in the right eye as measured by optical coherence tomography at a circle diameter of 4.1 millimeters[15]

End point description:

Changes in retinal nerve fiber layer (RNFL) thickness were measured for both eyes at baseline and at the end of the study by using Heidelberg spectral domain (SD) optical coherence tomography (OCT). The mean duration between baseline and end-of-study assessments was 21.8±10.5 weeks (median: 17.5 weeks [range: 12.7; 46.3 weeks]). OCT scans were performed at circle diameters of 3.5 mm, 4.1 mm, and 4.7 mm. Thickness was measured globally, for the papillo macular bundle, and for the nasal, nasal/inferior, temporal/inferior, temporal, temporal/superior, and nasal/superior quadrants. In addition, the nasal/temporal ratio was calculated. A negative change from baseline indicates that retinal thickness decreased.
This outcome assessed the Full Analysis Set, defined as all enrolled patients who were successfully screened (i.e. met all eligibility criteria) and who had post-baseline measurements available.

End point type	Primary

End point timeframe:

Baseline and End-of-Study

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: Although it is generally expected that each primary endpoint will have at least one statistical analysis, statistical analyses were not performed because the study was terminated early.

End point values	Dimethyl Fumarate			
Subject group type	Reporting group			
Number of subjects analysed	8			
Units: micrometers				
arithmetic mean (standard deviation)				
Right Eye	0.4 (± 2.5)			

Statistical analyses

No statistical analyses for this end point

Primary: Change from baseline in mean thickness of the nasal quadrant of the retinal nerve fiber layer in the left eye as measured by optical coherence tomography at a circle diameter of 4.1 millimeters

End point title	Change from baseline in mean thickness of the nasal quadrant of the retinal nerve fiber layer in the left eye as measured by optical coherence tomography at a circle diameter of 4.1 millimeters[16]

End point description:

Changes in retinal nerve fiber layer (RNFL) thickness were measured for both eyes at baseline and at the end of the study by using Heidelberg spectral domain (SD) optical coherence tomography (OCT). The mean duration between baseline and end-of-study assessments was 21.8±10.5 weeks (median: 17.5 weeks [range: 12.7; 46.3 weeks]). OCT scans were performed at circle diameters of 3.5 mm, 4.1 mm, and 4.7 mm. Thickness was measured globally, for the papillo macular bundle, and for the nasal, nasal/inferior, temporal/inferior, temporal, temporal/superior, and nasal/superior quadrants. In addition, the nasal/temporal ratio was calculated. A negative change from baseline indicates that retinal thickness decreased.
This outcome assessed the Full Analysis Set, defined as all enrolled patients who were successfully screened (i.e. met all eligibility criteria) and who had post-baseline measurements available.

End point type	Primary

End point timeframe:

Baseline and End-of-Study

Notes:

[16] - 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: Although it is generally expected that each primary endpoint will have at least one statistical analysis, statistical analyses were not performed because the study was terminated early.

End point values	Dimethyl Fumarate			
Subject group type	Reporting group			
Number of subjects analysed	7			
Units: micrometers				
arithmetic mean (standard deviation)				
Left Eye	-0.9 (± 2.4)			

Statistical analyses

No statistical analyses for this end point

Primary: Change from baseline in mean thickness of the nasal quadrant of the retinal nerve fiber layer in the right eye as measured by optical coherence tomography at a circle diameter of 4.1 millimeters

End point title	Change from baseline in mean thickness of the nasal quadrant of the retinal nerve fiber layer in the right eye as measured by optical coherence tomography at a circle diameter of 4.1 millimeters[17]

End point description:

Changes in retinal nerve fiber layer (RNFL) thickness were measured for both eyes at baseline and at the end of the study by using Heidelberg spectral domain (SD) optical coherence tomography (OCT). The mean duration between baseline and end-of-study assessments was 21.8±10.5 weeks (median: 17.5 weeks [range: 12.7; 46.3 weeks]). OCT scans were performed at circle diameters of 3.5 mm, 4.1 mm, and 4.7 mm. Thickness was measured globally, for the papillo macular bundle, and for the nasal, nasal/inferior, temporal/inferior, temporal, temporal/superior, and nasal/superior quadrants. In addition, the nasal/temporal ratio was calculated. A negative change from baseline indicates that retinal thickness decreased.
This outcome assessed the Full Analysis Set, defined as all enrolled patients who were successfully screened (i.e. met all eligibility criteria) and who had post-baseline measurements available.

End point type	Primary

End point timeframe:

Baseline and End-of-Study

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: Although it is generally expected that each primary endpoint will have at least one statistical analysis, statistical analyses were not performed because the study was terminated early.

End point values	Dimethyl Fumarate			
Subject group type	Reporting group			
Number of subjects analysed	8			
Units: micrometers				
arithmetic mean (standard deviation)				
Right Eye	0.8 (± 2.9)			

Statistical analyses

No statistical analyses for this end point

Primary: Change from baseline in mean thickness of the nasal/inferior quadrant of the retinal nerve fiber layer in the left eye as measured by optical coherence tomography at a circle diameter of 4.1 millimeters

End point title	Change from baseline in mean thickness of the nasal/inferior quadrant of the retinal nerve fiber layer in the left eye as measured by optical coherence tomography at a circle diameter of 4.1 millimeters[18]

End point description:

Changes in retinal nerve fiber layer (RNFL) thickness were measured for both eyes at baseline and at the end of the study by using Heidelberg spectral domain (SD) optical coherence tomography (OCT). The mean duration between baseline and end-of-study assessments was 21.8±10.5 weeks (median: 17.5 weeks [range: 12.7; 46.3 weeks]). OCT scans were performed at circle diameters of 3.5 mm, 4.1 mm, and 4.7 mm. Thickness was measured globally, for the papillo macular bundle, and for the nasal, nasal/inferior, temporal/inferior, temporal, temporal/superior, and nasal/superior quadrants. In addition,

the nasal/temporal ratio was calculated. A negative change from baseline indicates that retinal thickness decreased.
This outcome assessed the Full Analysis Set, defined as all enrolled patients who were successfully screened (i.e. met all eligibility criteria) and who had post-baseline measurements available.

End point type	Primary

End point timeframe:

Baseline and End-of-Study

Notes:

[18] - 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: Although it is generally expected that each primary endpoint will have at least one statistical analysis, statistical analyses were not performed because the study was terminated early.

End point values	Dimethyl Fumarate			
Subject group type	Reporting group			
Number of subjects analysed	7			
Units: micrometers				
arithmetic mean (standard deviation)				
Left Eye	0.6 (± 2.1)			

Statistical analyses

No statistical analyses for this end point

Primary: Change from baseline in mean thickness of the nasal/inferior quadrant of the retinal nerve fiber layer in the right eye as measured by optical coherence tomography at a circle diameter of 4.1 millimeters

End point title	Change from baseline in mean thickness of the nasal/inferior quadrant of the retinal nerve fiber layer in the right eye as measured by optical coherence tomography at a circle diameter of 4.1 millimeters[19]

End point description:

Changes in retinal nerve fiber layer (RNFL) thickness were measured for both eyes at baseline and at the end of the study by using Heidelberg spectral domain (SD) optical coherence tomography (OCT). The mean duration between baseline and end-of-study assessments was 21.8±10.5 weeks (median: 17.5 weeks [range: 12.7; 46.3 weeks]). OCT scans were performed at circle diameters of 3.5 mm, 4.1 mm, and 4.7 mm. Thickness was measured globally, for the papillo macular bundle, and for the nasal, nasal/inferior, temporal/inferior, temporal, temporal/superior, and nasal/superior quadrants. In addition, the nasal/temporal ratio was calculated. A negative change from baseline indicates that retinal thickness decreased.
This outcome assessed the Full Analysis Set, defined as all enrolled patients who were successfully screened (i.e. met all eligibility criteria) and who had post-baseline measurements available.

End point type	Primary

End point timeframe:

Baseline and End-of-Study

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: Although it is generally expected that each primary endpoint will have at least one statistical analysis, statistical analyses were not performed because the study was terminated early.

End point values	Dimethyl Fumarate			
Subject group type	Reporting group			
Number of subjects analysed	8			
Units: micrometers				
arithmetic mean (standard deviation)				
Right Eye	0.4 (± 3.1)			

Statistical analyses

No statistical analyses for this end point

Primary: Change from baseline in mean thickness of the temporal/inferior quadrant of the retinal nerve fiber layer in the left eye as measured by optical coherence tomography at a circle diameter of 4.1 millimeters

End point title	Change from baseline in mean thickness of the temporal/inferior quadrant of the retinal nerve fiber layer in the left eye as measured by optical coherence tomography at a circle diameter of 4.1 millimeters[20]

End point description:

Changes in retinal nerve fiber layer (RNFL) thickness were measured for both eyes at baseline and at the end of the study by using Heidelberg spectral domain (SD) optical coherence tomography (OCT). The mean duration between baseline and end-of-study assessments was 21.8±10.5 weeks (median: 17.5 weeks [range: 12.7; 46.3 weeks]). OCT scans were performed at circle diameters of 3.5 mm, 4.1 mm, and 4.7 mm. Thickness was measured globally, for the papillo macular bundle, and for the nasal, nasal/inferior, temporal/inferior, temporal, temporal/superior, and nasal/superior quadrants. In addition, the nasal/temporal ratio was calculated. A negative change from baseline indicates that retinal thickness decreased.
This outcome assessed the Full Analysis Set, defined as all enrolled patients who were successfully screened (i.e. met all eligibility criteria) and who had post-baseline measurements available.

End point type	Primary

End point timeframe:

Baseline and End-of-Study

Notes:

[20] - 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: Although it is generally expected that each primary endpoint will have at least one statistical analysis, statistical analyses were not performed because the study was terminated early.

End point values	Dimethyl Fumarate			
Subject group type	Reporting group			
Number of subjects analysed	7			
Units: micrometers				
arithmetic mean (standard deviation)				
Left Eye	-0.7 (± 3.0)			

Statistical analyses

No statistical analyses for this end point

Primary: Change from baseline in mean thickness of the temporal/inferior quadrant

of the retinal nerve fiber layer in the right eye as measured by optical coherence tomography at a circle diameter of 4.1 millimeters

End point title	Change from baseline in mean thickness of the temporal/inferior quadrant of the retinal nerve fiber layer in the right eye as measured by optical coherence tomography at a circle diameter of 4.1 millimeters[21]

End point description:

Changes in retinal nerve fiber layer (RNFL) thickness were measured for both eyes at baseline and at the end of the study by using Heidelberg spectral domain (SD) optical coherence tomography (OCT). The mean duration between baseline and end-of-study assessments was 21.8±10.5 weeks (median: 17.5 weeks [range: 12.7; 46.3 weeks]). OCT scans were performed at circle diameters of 3.5 mm, 4.1 mm, and 4.7 mm. Thickness was measured globally, for the papillo macular bundle, and for the nasal, nasal/inferior, temporal/inferior, temporal, temporal/superior, and nasal/superior quadrants. In addition, the nasal/temporal ratio was calculated. A negative change from baseline indicates that retinal thickness decreased.
This outcome assessed the Full Analysis Set, defined as all enrolled patients who were successfully screened (i.e. met all eligibility criteria) and who had post-baseline measurements available.

End point type	Primary

End point timeframe:

Baseline and End-of-Study

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: Although it is generally expected that each primary endpoint will have at least one statistical analysis, statistical analyses were not performed because the study was terminated early.

End point values	Dimethyl Fumarate			
Subject group type	Reporting group			
Number of subjects analysed	8			
Units: micrometers				
arithmetic mean (standard deviation)				
Right Eye	-0.4 (± 1.7)			

Statistical analyses

No statistical analyses for this end point

Primary: Change from baseline in mean thickness of the temporal quadrant of the retinal nerve fiber layer in the left eye as measured by optical coherence tomography at a circle diameter of 4.1 millimeters

End point title	Change from baseline in mean thickness of the temporal quadrant of the retinal nerve fiber layer in the left eye as measured by optical coherence tomography at a circle diameter of 4.1 millimeters[22]

End point description:

Changes in retinal nerve fiber layer (RNFL) thickness were measured for both eyes at baseline and at the end of the study by using Heidelberg spectral domain (SD) optical coherence tomography (OCT). The mean duration between baseline and end-of-study assessments was 21.8±10.5 weeks (median: 17.5 weeks [range: 12.7; 46.3 weeks]). OCT scans were performed at circle diameters of 3.5 mm, 4.1 mm, and 4.7 mm. Thickness was measured globally, for the papillo macular bundle, and for the nasal, nasal/inferior, temporal/inferior, temporal, temporal/superior, and nasal/superior quadrants. In addition, the nasal/temporal ratio was calculated. A negative change from baseline indicates that retinal thickness decreased.
This outcome assessed the Full Analysis Set, defined as all enrolled patients who were successfully screened (i.e. met all eligibility criteria) and who had post-baseline measurements available.

End point type	Primary

End point timeframe:

Baseline and End-of-Study

Notes:

[22] - 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: Although it is generally expected that each primary endpoint will have at least one statistical analysis, statistical analyses were not performed because the study was terminated early.

End point values	Dimethyl Fumarate			
Subject group type	Reporting group			
Number of subjects analysed	7			
Units: micrometers				
arithmetic mean (standard deviation)				
Left Eye	-0.6 (± 1.8)			

Statistical analyses

No statistical analyses for this end point

Primary: Change from baseline in mean thickness of the temporal quadrant of the retinal nerve fiber layer in the right eye as measured by optical coherence tomography at a circle diameter of 4.1 millimeters

End point title	Change from baseline in mean thickness of the temporal quadrant of the retinal nerve fiber layer in the right eye as measured by optical coherence tomography at a circle diameter of 4.1 millimeters[23]

End point description:

Changes in retinal nerve fiber layer (RNFL) thickness were measured for both eyes at baseline and at the end of the study by using Heidelberg spectral domain (SD) optical coherence tomography (OCT). The mean duration between baseline and end-of-study assessments was 21.8±10.5 weeks (median: 17.5 weeks [range: 12.7; 46.3 weeks]). OCT scans were performed at circle diameters of 3.5 mm, 4.1 mm, and 4.7 mm. Thickness was measured globally, for the papillo macular bundle, and for the nasal, nasal/inferior, temporal/inferior, temporal, temporal/superior, and nasal/superior quadrants. In addition, the nasal/temporal ratio was calculated. A negative change from baseline indicates that retinal thickness decreased.
This outcome assessed the Full Analysis Set, defined as all enrolled patients who were successfully screened (i.e. met all eligibility criteria) and who had post-baseline measurements available.

End point type	Primary

End point timeframe:

Baseline and End-of-Study

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: Although it is generally expected that each primary endpoint will have at least one statistical analysis, statistical analyses were not performed because the study was terminated early.

End point values	Dimethyl Fumarate			
Subject group type	Reporting group			
Number of subjects analysed	8			
Units: micrometers				
arithmetic mean (standard deviation)				
Right Eye	-0.5 (± 3.5)			

Statistical analyses

No statistical analyses for this end point

Primary: Change from baseline in mean thickness of the temporal/superior quadrant of the retinal nerve fiber layer in the left eye as measured by optical coherence tomography at a circle diameter of 4.1 millimeters

End point title	Change from baseline in mean thickness of the temporal/superior quadrant of the retinal nerve fiber layer in the left eye as measured by optical coherence tomography at a circle diameter of 4.1 millimeters[24]

End point description:

Changes in retinal nerve fiber layer (RNFL) thickness were measured for both eyes at baseline and at the end of the study by using Heidelberg spectral domain (SD) optical coherence tomography (OCT). The mean duration between baseline and end-of-study assessments was 21.8±10.5 weeks (median: 17.5 weeks [range: 12.7; 46.3 weeks]). OCT scans were performed at circle diameters of 3.5 mm, 4.1 mm, and 4.7 mm. Thickness was measured globally, for the papillo macular bundle, and for the nasal, nasal/inferior, temporal/inferior, temporal, temporal/superior, and nasal/superior quadrants. In addition, the nasal/temporal ratio was calculated. A negative change from baseline indicates that retinal thickness decreased.
This outcome assessed the Full Analysis Set, defined as all enrolled patients who were successfully screened (i.e. met all eligibility criteria) and who had post-baseline measurements available.

End point type	Primary

End point timeframe:

Baseline and End-of-Study

Notes:

[24] - 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: Although it is generally expected that each primary endpoint will have at least one statistical analysis, statistical analyses were not performed because the study was terminated early.

End point values	Dimethyl Fumarate			
Subject group type	Reporting group			
Number of subjects analysed	7			
Units: micrometers				
arithmetic mean (standard deviation)				
Left Eye	-0.9 (± 4.2)			

Statistical analyses

No statistical analyses for this end point

Primary: Change from baseline in mean thickness of the temporal/superior quadrant of the retinal nerve fiber layer in the right eye as measured by optical coherence tomography at a circle diameter of 4.1 millimeters

End point title	Change from baseline in mean thickness of the temporal/superior quadrant of the retinal nerve fiber layer in

	the right eye as measured by optical coherence tomography at a circle diameter of 4.1 millimeters[25]

End point description:

Changes in retinal nerve fiber layer (RNFL) thickness were measured for both eyes at baseline and at the end of the study by using Heidelberg spectral domain (SD) optical coherence tomography (OCT). The mean duration between baseline and end-of-study assessments was 21.8±10.5 weeks (median: 17.5 weeks [range: 12.7; 46.3 weeks]). OCT scans were performed at circle diameters of 3.5 mm, 4.1 mm, and 4.7 mm. Thickness was measured globally, for the papillo macular bundle, and for the nasal, nasal/inferior, temporal/inferior, temporal, temporal/superior, and nasal/superior quadrants. In addition, the nasal/temporal ratio was calculated. A negative change from baseline indicates that retinal thickness decreased.
This outcome assessed the Full Analysis Set, defined as all enrolled patients who were successfully screened (i.e. met all eligibility criteria) and who had post-baseline measurements available.

End point type	Primary

End point timeframe:

Baseline and End-of-Study

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: Although it is generally expected that each primary endpoint will have at least one statistical analysis, statistical analyses were not performed because the study was terminated early.

End point values	Dimethyl Fumarate			
Subject group type	Reporting group			
Number of subjects analysed	8			
Units: micrometers				
arithmetic mean (standard deviation)				
Right Eye	-1.9 (± 5.0)			

Statistical analyses

No statistical analyses for this end point

Primary: Change from baseline in the ratio of the mean thickness of the nasal and temporal quadrants of the retinal nerve fiber layer in the left eye as measured by optical coherence tomography at a circle diameter of 4.1 millimeters

End point title	Change from baseline in the ratio of the mean thickness of the nasal and temporal quadrants of the retinal nerve fiber layer in the left eye as measured by optical coherence tomography at a circle diameter of 4.1 millimeters[26]

End point description:

Changes in retinal nerve fiber layer (RNFL) thickness were measured for both eyes at baseline and at the end of the study by using Heidelberg spectral domain (SD) optical coherence tomography (OCT). The mean duration between baseline and end-of-study assessments was 21.8±10.5 weeks (median: 17.5 weeks [range: 12.7; 46.3 weeks]). OCT scans were performed at circle diameters of 3.5 mm, 4.1 mm, and 4.7 mm. Thickness was measured globally, for the papillo macular bundle, and for the nasal, nasal/inferior, temporal/inferior, temporal, temporal/superior, and nasal/superior quadrants. In addition, the nasal/temporal ratio was calculated. A negative change from baseline indicates that retinal thickness decreased.
This outcome assessed the Full Analysis Set, defined as all enrolled patients who were successfully screened (i.e. met all eligibility criteria) and who had post-baseline measurements available.

End point type	Primary

End point timeframe:

Baseline and End-of-Study

Notes:

[26] - 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: Although it is generally expected that each primary endpoint will have at least one statistical analysis, statistical analyses were not performed because the study was terminated early.

End point values	Dimethyl Fumarate			
Subject group type	Reporting group			
Number of subjects analysed	7			
Units: micrometers				
arithmetic mean (standard deviation)				
Left Eye	-0.003 (± 0.036)			

Statistical analyses

No statistical analyses for this end point

Primary: Change from baseline in the ratio of the mean thickness of the nasal and temporal quadrants of the retinal nerve fiber layer in the right eye as measured by optical coherence tomography at a circle diameter of 4.1 millimeters

End point title	Change from baseline in the ratio of the mean thickness of the nasal and temporal quadrants of the retinal nerve fiber layer in the right eye as measured by optical coherence tomography at a circle diameter of 4.1 millimeters[27]

End point description:

Changes in retinal nerve fiber layer (RNFL) thickness were measured for both eyes at baseline and at the end of the study by using Heidelberg spectral domain (SD) optical coherence tomography (OCT). The mean duration between baseline and end-of-study assessments was 21.8±10.5 weeks (median: 17.5 weeks [range: 12.7; 46.3 weeks]). OCT scans were performed at circle diameters of 3.5 mm, 4.1 mm, and 4.7 mm. Thickness was measured globally, for the papillo macular bundle, and for the nasal, nasal/inferior, temporal/inferior, temporal, temporal/superior, and nasal/superior quadrants. In addition, the nasal/temporal ratio was calculated. A negative change from baseline indicates that retinal thickness decreased.
This outcome assessed the Full Analysis Set, defined as all enrolled patients who were successfully screened (i.e. met all eligibility criteria) and who had post-baseline measurements available.

End point type	Primary

End point timeframe:

Baseline and End-of-Study

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: Although it is generally expected that each primary endpoint will have at least one statistical analysis, statistical analyses were not performed because the study was terminated early.

End point values	Dimethyl Fumarate			
Subject group type	Reporting group			
Number of subjects analysed	8			
Units: micrometers				
arithmetic mean (standard deviation)				
Right Eye	0.029 (± 0.088)			

Statistical analyses

No statistical analyses for this end point

Primary: Change from baseline in mean global thickness of the retinal nerve fiber layer as measured by optical coherence tomography at a circle diameter of 4.7 millimeters

End point title	Change from baseline in mean global thickness of the retinal nerve fiber layer as measured by optical coherence tomography at a circle diameter of 4.7 millimeters[28]

End point description:

Changes in retinal nerve fiber layer (RNFL) thickness were measured for both eyes at baseline and at the end of the study by using Heidelberg spectral domain (SD) optical coherence tomography (OCT). The mean duration between baseline and end-of-study assessments was 21.8±10.5 weeks (median: 17.5 weeks [range: 12.7; 46.3 weeks]). OCT scans were performed at circle diameters of 3.5 mm, 4.1 mm, and 4.7 mm. Thickness was measured globally, for the papillo macular bundle, and for the nasal, nasal/inferior, temporal/inferior, temporal, temporal/superior, and nasal/superior quadrants. In addition, the nasal/temporal ratio was calculated. A negative change from baseline indicates that retinal thickness decreased.
This outcome assessed the Full Analysis Set, defined as all enrolled patients who were successfully screened (i.e. met all eligibility criteria) and who had post-baseline measurements available.

End point type	Primary

End point timeframe:

Baseline and End-of-Study

Notes:

[28] - 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: Although it is generally expected that each primary endpoint will have at least one statistical analysis, statistical analyses were not performed because the study was terminated early.

End point values	Dimethyl Fumarate			
Subject group type	Reporting group			
Number of subjects analysed	7			
Units: micrometers				
arithmetic mean (standard deviation)				
Left Eye	-0.14 (± 0.99)			
Right Eye	0.29 (± 2.91)			

Statistical analyses

No statistical analyses for this end point

Primary: Change from baseline in mean thickness of the papillo macular bundle of the retinal nerve fiber layer as measured by optical coherence tomography at a circle diameter of 4.7 millimeters

End point title	Change from baseline in mean thickness of the papillo macular bundle of the retinal nerve fiber layer as measured by optical

	coherence tomography at a circle diameter of 4.7

End point description:

Changes in retinal nerve fiber layer (RNFL) thickness were measured for both eyes at baseline and at the end of the study by using Heidelberg spectral domain (SD) optical coherence tomography (OCT). The mean duration between baseline and end-of-study assessments was 21.8±10.5 weeks (median: 17.5 weeks [range: 12.7; 46.3 weeks]). OCT scans were performed at circle diameters of 3.5 mm, 4.1 mm, and 4.7 mm. Thickness was measured globally, for the papillo macular bundle, and for the nasal, nasal/inferior, temporal/inferior, temporal, temporal/superior, and nasal/superior quadrants. In addition, the nasal/temporal ratio was calculated. A negative change from baseline indicates that retinal thickness decreased.
This outcome assessed the Full Analysis Set, defined as all enrolled patients who were successfully screened (i.e. met all eligibility criteria) and who had post-baseline measurements available.

End point type	Primary

End point timeframe:

Baseline and End-of-Study

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: Although it is generally expected that each primary endpoint will have at least one statistical analysis, statistical analyses were not performed because the study was terminated early.

End point values	Dimethyl Fumarate			
Subject group type	Reporting group			
Number of subjects analysed	7			
Units: micrometers				
arithmetic mean (standard deviation)				
Left Eye	0.4 (± 1.8)			
Right Eye	1.3 (± 2.7)			

Statistical analyses

No statistical analyses for this end point

Primary: Change from baseline in mean thickness of the nasal/superior quadrant of the retinal nerve fiber layer as measured by optical coherence tomography at a circle diameter of 4.7 millimeters

End point title	Change from baseline in mean thickness of the nasal/superior quadrant of the retinal nerve fiber layer as measured by optical coherence tomography at a circle diameter of 4.7 millimeters[30]

End point description:

Changes in retinal nerve fiber layer (RNFL) thickness were measured for both eyes at baseline and at the end of the study by using Heidelberg spectral domain (SD) optical coherence tomography (OCT). The mean duration between baseline and end-of-study assessments was 21.8±10.5 weeks (median: 17.5 weeks [range: 12.7; 46.3 weeks]). OCT scans were performed at circle diameters of 3.5 mm, 4.1 mm, and 4.7 mm. Thickness was measured globally, for the papillo macular bundle, and for the nasal, nasal/inferior, temporal/inferior, temporal, temporal/superior, and nasal/superior quadrants. In addition, the nasal/temporal ratio was calculated. A negative change from baseline indicates that retinal thickness decreased.
This outcome assessed the Full Analysis Set, defined as all enrolled patients who were successfully screened (i.e. met all eligibility criteria) and who had post-baseline measurements available.

End point type	Primary

End point timeframe:

Baseline and End-of-Study

Notes:

[30] - 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: Although it is generally expected that each primary endpoint will have at least one statistical analysis, statistical analyses were not performed because the study was terminated early.

End point values	Dimethyl Fumarate			
Subject group type	Reporting group			
Number of subjects analysed	7			
Units: micrometers				
arithmetic mean (standard deviation)				
Left Eye	0.9 (± 2.5)			
Right Eye	-0.1 (± 3.0)			

Statistical analyses

No statistical analyses for this end point

Primary: Change from baseline in mean thickness of the nasal quadrant of the retinal nerve fiber layer as measured by optical coherence tomography at a circle diameter of 4.7

End point title	Change from baseline in mean thickness of the nasal quadrant of the retinal nerve fiber layer as measured by optical coherence tomography at a circle diameter of 4.7[31]

End point description:

Changes in retinal nerve fiber layer (RNFL) thickness were measured for both eyes at baseline and at the end of the study by using Heidelberg spectral domain (SD) optical coherence tomography (OCT).The mean duration between baseline and end-of-study assessments was 21.8±10.5 weeks (median: 17.5 weeks [range: 12.7; 46.3 weeks]). OCT scans were performed at circle diameters of 3.5 mm, 4.1 mm, and 4.7 mm. Thickness was measured globally, for the papillo macular bundle, and for the nasal, nasal/inferior, temporal/inferior, temporal, temporal/superior, and nasal/superior quadrants. In addition, the nasal/temporal ratio was calculated. A negative change from baseline indicates that retinal thickness decreased.
This outcome assessed the Full Analysis Set, defined as all enrolled patients who were successfully screened (i.e. met all eligibility criteria) and who had post-baseline measurements available.

End point type	Primary

End point timeframe:

Baseline and End-of-Study

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: Although it is generally expected that each primary endpoint will have at least one statistical analysis, statistical analyses were not performed because the study was terminated early.

End point values	Dimethyl Fumarate			
Subject group type	Reporting group			
Number of subjects analysed	7			
Units: micrometers				
arithmetic mean (standard deviation)				
Left Eye	-1.0 (± 2.3)			
Right Eye	0.1 (± 2.9)			

Statistical analyses

No statistical analyses for this end point

Primary: Change from baseline in mean thickness of the nasal/inferior quadrant of the retinal nerve fiber layer as measured by optical coherence tomography at a circle diameter of 4.7 millimeters

End point title	Change from baseline in mean thickness of the nasal/inferior quadrant of the retinal nerve fiber layer as measured by optical coherence tomography at a circle diameter of 4.7 millimeters[32]

End point description:

Changes in retinal nerve fiber layer (RNFL) thickness were measured for both eyes at baseline and at the end of the study by using Heidelberg spectral domain (SD) optical coherence tomography (OCT). The mean duration between baseline and end-of-study assessments was 21.8±10.5 weeks (median: 17.5 weeks [range: 12.7; 46.3 weeks]). OCT scans were performed at circle diameters of 3.5 mm, 4.1 mm, and 4.7 mm. Thickness was measured globally, for the papillo macular bundle, and for the nasal, nasal/inferior, temporal/inferior, temporal, temporal/superior, and nasal/superior quadrants. In addition, the nasal/temporal ratio was calculated. A negative change from baseline indicates that retinal thickness decreased.
This outcome assessed the Full Analysis Set, defined as all enrolled patients who were successfully screened (i.e. met all eligibility criteria) and who had post-baseline measurements available.

End point type	Primary

End point timeframe:

Baseline and End-of-Study

Notes:

[32] - 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: Although it is generally expected that each primary endpoint will have at least one statistical analysis, statistical analyses were not performed because the study was terminated early.

End point values	Dimethyl Fumarate			
Subject group type	Reporting group			
Number of subjects analysed	7			
Units: micrometers				
arithmetic mean (standard deviation)				
Left Eye	1.0 (± 1.8)			
Right Eye	0.0 (± 6.0)			

Statistical analyses

No statistical analyses for this end point

Primary: Change from baseline in mean thickness of the temporal/inferior quadrant of the retinal nerve fiber layer as measured by optical coherence tomography at a circle diameter of 4.7 millimeters

End point title	Change from baseline in mean thickness of the

	temporal/inferior quadrant of the retinal nerve fiber layer as measured by optical coherence tomography at a circle diameter of 4.7 millimeters[33]

End point description:

Changes in retinal nerve fiber layer (RNFL) thickness were measured for both eyes at baseline and at the end of the study by using Heidelberg spectral domain (SD) optical coherence tomography (OCT). The mean duration between baseline and end-of-study assessments was 21.8±10.5 weeks (median: 17.5 weeks [range: 12.7; 46.3 weeks]). OCT scans were performed at circle diameters of 3.5 mm, 4.1 mm, and 4.7 mm. Thickness was measured globally, for the papillo macular bundle, and for the nasal, nasal/inferior, temporal/inferior, temporal, temporal/superior, and nasal/superior quadrants. In addition, the nasal/temporal ratio was calculated. A negative change from baseline indicates that retinal thickness decreased.
This outcome assessed the Full Analysis Set, defined as all enrolled patients who were successfully screened (i.e. met all eligibility criteria) and who had post-baseline measurements available.

End point type	Primary

End point timeframe:

Baseline and End-of-Study

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: Although it is generally expected that each primary endpoint will have at least one statistical analysis, statistical analyses were not performed because the study was terminated early.

End point values	Dimethyl Fumarate			
Subject group type	Reporting group			
Number of subjects analysed	7			
Units: micrometers				
arithmetic mean (standard deviation)				
Left Eye	-0.3 (± 2.1)			
Right Eye	-0.4 (± 3.2)			

Statistical analyses

No statistical analyses for this end point

Primary: Change from baseline in mean thickness of the temporal quadrant of the retinal nerve fiber layer as measured by optical coherence tomography at a circle diameter of 4.7 millimeters

End point title	Change from baseline in mean thickness of the temporal quadrant of the retinal nerve fiber layer as measured by optical coherence tomography at a circle diameter of 4.7 millimeters[34]

End point description:

Changes in retinal nerve fiber layer (RNFL) thickness were measured for both eyes at baseline and at the end of the study by using Heidelberg spectral domain (SD) optical coherence tomography (OCT). The mean duration between baseline and end-of-study assessments was 21.8±10.5 weeks (median: 17.5 weeks [range: 12.7; 46.3 weeks]). OCT scans were performed at circle diameters of 3.5 mm, 4.1 mm, and 4.7 mm. Thickness was measured globally, for the papillo macular bundle, and for the nasal, nasal/inferior, temporal/inferior, temporal, temporal/superior, and nasal/superior quadrants. In addition, the nasal/temporal ratio was calculated. A negative change from baseline indicates that retinal thickness decreased.
This outcome assessed the Full Analysis Set, defined as all enrolled patients who were successfully screened (i.e. met all eligibility criteria) and who had post-baseline measurements available.

End point type	Primary

End point timeframe:

Baseline and End-of-Study

Notes:

[34] - 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: Although it is generally expected that each primary endpoint will have at least one statistical analysis, statistical analyses were not performed because the study was terminated early.

End point values	Dimethyl Fumarate			
Subject group type	Reporting group			
Number of subjects analysed	7			
Units: micrometers				
arithmetic mean (standard deviation)				
Left Eye	-0.1 (± 0.6)			
Right Eye	0.9 (± 2.2)			

Statistical analyses

No statistical analyses for this end point

Primary: Change from baseline in mean thickness of the temporal/superior quadrant of the retinal nerve fiber layer as measured by optical coherence tomography at a circle diameter of 4.7 millimeters

End point title	Change from baseline in mean thickness of the temporal/superior quadrant of the retinal nerve fiber layer as measured by optical coherence tomography at a circle diameter of 4.7 millimeters[35]

End point description:

Changes in retinal nerve fiber layer (RNFL) thickness were measured for both eyes at baseline and at the end of the study by using Heidelberg spectral domain (SD) optical coherence tomography (OCT). The mean duration between baseline and end-of-study assessments was 21.8±10.5 weeks (median: 17.5 weeks [range: 12.7; 46.3 weeks]). OCT scans were performed at circle diameters of 3.5 mm, 4.1 mm, and 4.7 mm. Thickness was measured globally, for the papillo macular bundle, and for the nasal, nasal/inferior, temporal/inferior, temporal, temporal/superior, and nasal/superior quadrants. In addition, the nasal/temporal ratio was calculated. A negative change from baseline indicates that retinal thickness decreased.
This outcome assessed the Full Analysis Set, defined as all enrolled patients who were successfully screened (i.e. met all eligibility criteria) and who had post-baseline measurements available.

End point type	Primary

End point timeframe:

Baseline and End-of-Study

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: Although it is generally expected that each primary endpoint will have at least one statistical analysis, statistical analyses were not performed because the study was terminated early.

End point values	Dimethyl Fumarate			
Subject group type	Reporting group			
Number of subjects analysed	7			
Units: micrometers				
arithmetic mean (standard deviation)				
Left Eye	-0.4 (± 1.8)			
Right Eye	-1.1 (± 3.0)			

Statistical analyses

No statistical analyses for this end point

Primary: Change from baseline in the ratio of the mean thickness of the nasal and temporal quadrants of the retinal nerve fiber layer as measured by optical coherence tomography at a circle diameter of 4.7 millimeters

End point title	Change from baseline in the ratio of the mean thickness of the nasal and temporal quadrants of the retinal nerve fiber layer as measured by optical coherence tomography at a circle diameter of 4.7 millimeters[36]

End point description:

Changes in retinal nerve fiber layer (RNFL) thickness were measured for both eyes at baseline and at the end of the study by using Heidelberg spectral domain (SD) optical coherence tomography (OCT). The mean duration between baseline and end-of-study assessments was 21.8±10.5 weeks (median: 17.5 weeks [range: 12.7; 46.3 weeks]). OCT scans were performed at circle diameters of 3.5 mm, 4.1 mm, and 4.7 mm. Thickness was measured globally, for the papillo macular bundle, and for the nasal, nasal/inferior, temporal/inferior, temporal, temporal/superior, and nasal/superior quadrants. In addition, the nasal/temporal ratio was calculated. A negative change from baseline indicates that retinal thickness decreased.
This outcome assessed the Full Analysis Set, defined as all enrolled patients who were successfully screened (i.e. met all eligibility criteria) and who had post-baseline measurements available.

End point type	Primary

End point timeframe:

micrometers

Notes:

[36] - 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: Although it is generally expected that each primary endpoint will have at least one statistical analysis, statistical analyses were not performed because the study was terminated early.

End point values	Dimethyl Fumarate			
Subject group type	Reporting group			
Number of subjects analysed	7			
Units: Baseline and End-of-Study				
arithmetic mean (standard deviation)				
Left Eye	-0.017 (± 0.049)			
Right Eye	0.001 (± 0.052)			

Statistical analyses

No statistical analyses for this end point

Adverse events

Adverse events information	
Timeframe for reporting adverse events:	
Screening to End-of-Study; maximum 50.3 weeks	
Adverse event reporting additional description:	
The mean time of study participation of the safety population from screening to End-of-Study was 14.0±13.2 weeks (median: 13.1 weeks; [range: 0.1; 50.3]).	
Assessment type	Systematic

Dictionary used	
Dictionary name	MedDRA
Dictionary version	19.1

Reporting groups	
Reporting group title	Safety Population
Reporting group description:	
All enrolled subjects who received dimethyl fumarate (DMF) are included in safety population. As eligible subjects must have been treated with 240 mg DMF twice daily for at least four weeks and up to 20 weeks prior to screening, all enrolled subjects (i.e. with a signed informed consent form) were included in the safety population.	

Serious adverse events	Safety Population		
Total subjects affected by serious adverse events			
subjects affected / exposed	1 / 18 (5.56%)		
number of deaths (all causes)	0		
number of deaths resulting from adverse events	0		
Nervous system disorders			
Optic neuritis			
subjects affected / exposed	1 / 18 (5.56%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		

Frequency threshold for reporting non-serious adverse events: 5 %

Non-serious adverse events	Safety Population		
Total subjects affected by non-serious adverse events			
subjects affected / exposed	6 / 18 (33.33%)		
Vascular disorders			
Flushing			
subjects affected / exposed	1 / 18 (5.56%)		
occurrences (all)	1		
Nervous system disorders			

Cervicogenic headache subjects affected / exposed occurrences (all) Hypoaesthesia subjects affected / exposed occurrences (all) Multiple sclerosis relapse subjects affected / exposed occurrences (all) Paraesthesia subjects affected / exposed occurrences (all) Somnolence subjects affected / exposed occurrences (all)	 1 / 18 (5.56%) 1 1 / 18 (5.56%) 2 1 / 18 (5.56%) 1 1 / 18 (5.56%) 2 1 / 18 (5.56%) 1		
General disorders and administration site conditions Facial pain subjects affected / exposed occurrences (all)	 1 / 18 (5.56%) 1		
Gastrointestinal disorders Dyspepsia subjects affected / exposed occurrences (all) Haemorrhoids thrombosed subjects affected / exposed occurrences (all)	 1 / 18 (5.56%) 2 1 / 18 (5.56%) 1		
Respiratory, thoracic and mediastinal disorders Cough subjects affected / exposed occurrences (all)	 1 / 18 (5.56%) 1		
Renal and urinary disorders Micturition urgency subjects affected / exposed occurrences (all)	 1 / 18 (5.56%) 1		
Musculoskeletal and connective tissue disorders			

Temporomandibular joint syndrome subjects affected / exposed occurrences (all)	1 / 18 (5.56%) 1		
Infections and infestations Nasopharyngitis subjects affected / exposed occurrences (all)	1 / 18 (5.56%) 1		

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

Date	Amendment
16 May 2014	The amendment included the following main changes: Protocol amendment to further define and specify the objectives and parameters of the clinical trial. The description of statistical analysis was edited. The exclusion criteria as well as study stopping rules were amended, the specifications for pregnancy testing were enhanced and some inconsistencies within the protocol were clarified.
07 July 2015	The amendment was triggered by the Ethic Committee review and included the following changes of the protocol: study title, the primary outcome, primary endpoint, exclusion criteria, primary contact point, and optical coherence tomography section.
10 May 2016	The amendment included the following changes of the protocol: primary contact point, lymphocyte monitoring, adding PLM information to the profile of previous experience, exclusion criteria, discontinuation of the Study treatment, and pregnancy section.

Notes:

Interruptions (globally)

Were there any global interruptions to the trial? No

Limitations and caveats

Limitations of the trial such as small numbers of subjects analysed or technical problems leading to unreliable data.

This study was terminated early, and the number of subjects who participated was low. As such, the data reported here may not be suitable to draw conclusions regarding the outcomes of the study.

Notes: