EU Clinical Trials Register

Clinical trial results:
Dimethyl fumarate treatment of primary progressive multiple sclerosis

Summary

EudraCT number	2016-000283-41
Trial protocol	DK
Global end of trial date	09 December 2020

Results information

Result version number	v1 (current)
This version publication date	20 March 2022
First version publication date	20 March 2022
Summary attachment (see zip file)	Dimethyl Fumarate Treatment in Patients With Primary Progressive Multiple Sclerosis A Randomized, Controlled Trial (Dimethyl Fumarate Treatment in Patients With Primary Progressive Multiple Sclerosis.pdf)

Trial information

Trial identification

Sponsor protocol code	FUMAPMS2016

Additional study identifiers

ISRCTN number	-
ClinicalTrials.gov id (NCT number)	NCT02959658
WHO universal trial number (UTN)	-

Notes:

Sponsors

Sponsor organisation name	Danish Multiple Sclerosis Center
Sponsor organisation address	Valdemar Hansens Vej 13, Entrance 5, 7th floor, Glostrup, Denmark, 2600
Public contact	Finn Sellebjerg, Copenhagen University Hospital, Rigshospitalet Glostrup Danish Multiple Sclerosis Center , finn.thorup.sellebjerg@regionh.dk
Scientific contact	Finn Sellebjerg, Copenhagen University Hospital, Rigshospitalet Glostrup Danish Multiple Sclerosis Center , +45 38633236, finn.thorup.sellebjerg@regionh.dk

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	22 December 2020
Is this the analysis of the primary completion data?	No

Global end of trial reached?	Yes
Global end of trial date	09 December 2020
Was the trial ended prematurely?	No

Notes:

General information about the trial

Main objective of the trial:

The trial investigates the use of dimethyl fumarate treatment in patients with primary progressive multiple sclerosis (PPMS).

Protection of trial subjects:

Local anesthesia before lumbar puncture and sedative in tablet form if requested by the participant before lumbar puncture and or MRI

Background therapy: -

Evidence for comparator: -

Actual start date of recruitment	01 September 2016
Long term follow-up planned	No
Independent data monitoring committee (IDMC) involvement?	Yes

Notes:

Population of trial subjects

Subjects enrolled per country

Country: Number of subjects enrolled	Denmark: 54
Worldwide total number of subjects	54
EEA total number of subjects	54

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)	54

From 65 to 84 years	0
85 years and over	0

Subject disposition

Recruitment

Recruitment details:

Randomized-controlled phase inclusion: December 6, 2016 – January 16, 2019
Open-label phase inclusion: January 25, 2018 – December 17, 2019

Pre-assignment

Screening details:

Inclusion criteria: Age 18 to 65 years, PPMS according to the McDonald (2010) and Lublin (2014) criteria, Disease duration at least one year, EDSS ≤6.5, No other signs of significant disease judged by the investigator, Eligible for randomisation to active treatment or placebo as assessed by CSF NFL levels above 380 ng/L.

Pre-assignment period milestones

Number of subjects started	54
Number of subjects completed	54

Period 1

Period 1 title	Baseline
Is this the baseline period?	Yes
Allocation method	Randomised - controlled
Blinding used	Double blind
Roles blinded	Subject, Investigator, Monitor, Data analyst, Carer, Assessor

Arms

Are arms mutually exclusive?	Yes
Arm title	Arm 1, DMF

Arm description: -

Arm type	Experimental
Investigational medicinal product name	dimethyl fumarate
Investigational medicinal product code	
Other name	BG-12
Pharmaceutical forms	Coated tablet
Routes of administration	Oral use

Dosage and administration details:

Tablets, 120 mg each
2 tablets (240 mg), twice daily, eg. 480 mg daily.

Arm title	Arm 2, placebo

Arm description: -

Arm type	Placebo
Investigational medicinal product name	Placebo
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Film-coated tablet
Routes of administration	Oral use

Dosage and administration details:

Placebo tbl, 2 tblts twice daily

Number of subjects in period 1	Arm 1, DMF	Arm 2, placebo
Started	27	27
Completed	27	27

Period 2

Period 2 title	Phase 1
Is this the baseline period?	No
Allocation method	Randomised - controlled
Blinding used	Double blind
Roles blinded	Subject, Investigator, Monitor, Data analyst, Carer, Assessor

Arms

Are arms mutually exclusive?	Yes
Arm title	Arm 1, DMF

Arm description: -

Arm type	Placebo
Investigational medicinal product name	dimethyl fumarate
Investigational medicinal product code	
Other name	BG-12
Pharmaceutical forms	Coated tablet
Routes of administration	Oral use

Dosage and administration details:

Tablets, 120 mg each
2 tablets (240 mg), twice daily, e.i. 480 mg daily.

Arm title	Arm 2, placebo

Arm description: -

Arm type	Placebo
Investigational medicinal product name	Placebo
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Film-coated tablet
Routes of administration	Oral use

Dosage and administration details:

2 tbl, twice daily.

Number of subjects in period 2	Arm 1, DMF	Arm 2, placebo
Started	27	27
Completed	26	24
Not completed	1	3
Consent withdrawn by subject	-	3
Adverse event, non-fatal	1	-

Period 3

Period 3 title	Phase 2, open label
Is this the baseline period?	No
Allocation method	Not applicable
Blinding used	Not blinded

Arms

Are arms mutually exclusive?	Yes
Arm title	Arm 1, DMF/DMF

Arm description:

Patients who recevied DMF in Phase 1 and continued DMF treatment in the open-label-phase.

Arm type	Experimental
Investigational medicinal product name	dimethyl fumarate
Investigational medicinal product code	
Other name	BG-12
Pharmaceutical forms	Coated tablet
Routes of administration	Oral use

Dosage and administration details:

Tablets, 120 mg each
2 tablets (240 mg), twice daily, eg. 480 mg daily.

Arm title	Arm 2, UNT/DMF

Arm description:

Patients who received Placebo in Phase 1 and were included in the open-label-phase receiving DMF.

Arm type	Experimental
Investigational medicinal product name	dimethyl fumarate
Investigational medicinal product code	
Other name	BG-12
Pharmaceutical forms	Coated tablet
Routes of administration	Oral use

Dosage and administration details:

Tablets, 120 mg each
2 tablets (240 mg), twice daily, eg. 480 mg daily.

Number of subjects in period 3	Arm 1, DMF/DMF	Arm 2, UNT/DMF
Started	26	24
Completed	17	16
Not completed	9	8
Consent withdrawn by subject	6	2
Adverse event, non-fatal	3	6

Baseline characteristics

Reporting groups

Reporting group title	Arm 1, DMF
Reporting group description: -	
Reporting group title	Arm 2, placebo

Reporting group description: -

Reporting group values	Arm 1, DMF	Arm 2, placebo	Total
Number of subjects	27	27	54
Age categorical			
Units: Subjects			
In utero			0
Preterm newborn infants (gestational age < 37 wks)			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)			0
From 65-84 years			0
85 years and over			0
Age continuous			
Units: years			
arithmetic mean	55.7	54.0	
standard deviation	± 5.5	± 6.6	-
Gender categorical			
Units: Subjects			
Female	10	11	21
Male	17	16	33
Cell Count			
Subjects with CSF cell count			
Units: Subjects			
>4 cells/uL	8	4	12
<5 cells/uL	19	23	42
Oligoclonal bands			
Units: Subjects			
Oligoclonal bands, Yes	25	23	48
Oligoclonal bands, No	2	4	6
Gd-enhancing lesions			
Gadolinium-enhancing lesions			
Units: Subjects			
1 Gd enhancing lesions	3	2	5
0 Gd enhancing lesions	24	23	47
NA	0	2	2
Disease duration			
Units: years			
arithmetic mean	14.3	13.8	

standard deviation	± 9.4	± 9.7	-

End points

End points reporting groups

Reporting group title	Arm 1, DMF
Reporting group description: -	
Reporting group title	Arm 2, placebo
Reporting group description: -	
Reporting group title	Arm 1, DMF
Reporting group description: -	
Reporting group title	Arm 2, placebo
Reporting group description: -	
Reporting group title	Arm 1, DMF/DMF
Reporting group description:	
Patients who recevied DMF in Phase 1 and continued DMF treatment in the open-label-phase.	
Reporting group title	Arm 2, UNT/DMF
Reporting group description:	
Patients who received Placebo in Phase 1 and were included in the open-label-phase receiving DMF.	

Primary: Neurofilament light chain (cerebrospinal fluid)

End point title	Neurofilament light chain (cerebrospinal fluid)
End point description:	
End point type	Primary
End point timeframe:	
Screening, week 48	

End point values	Arm 1, DMF	Arm 2, placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	26	24		
Units: ng/L				
arithmetic mean (standard deviation)	-73 (± 190)	35 (± 1002)		

Statistical analyses

Statistical analysis title	Generalized linear model
Statistical analysis description:	
ANCOVA adjusted for baseline value.	
Comparison groups	Arm 1, DMF v Arm 2, placebo

Number of subjects included in analysis	50
Analysis specification	Pre-specified
Analysis type	equivalence
P-value	= 0.61
Method	ANCOVA
Parameter estimate	Mean difference (net)
Point estimate	99
Confidence interval	
level	95 %
sides	2-sided
lower limit	-292
upper limit	490

Secondary: Myelin basic protein (cerebrospinal fluid)

End point title	Myelin basic protein (cerebrospinal fluid)
End point description:	
End point type	Secondary
End point timeframe:	
Screening, week 48	

End point values	Arm 1, DMF	Arm 2, placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	26	24		
Units: ng/L				
arithmetic mean (standard deviation)	-206 (± 461)	18 (± 200)		

Statistical analyses

Statistical analysis title	generalized linear model
Statistical analysis description:	
ANCOVA adjusted for baseline value.	
Comparison groups	Arm 1, DMF v Arm 2, placebo
Number of subjects included in analysis	50
Analysis specification	Pre-specified
Analysis type	equivalence
P-value	= 0.01 [1]
Method	ANCOVA
Parameter estimate	Mean difference (net)
Point estimate	-182

Confidence interval	
level	95 %
sides	2-sided
lower limit	-323
upper limit	-41

Notes:

[1] - Conducted with multiple imputation of missing values.

Secondary: Soluble CD27 (cerebrospinal fluid)

End point title	Soluble CD27 (cerebrospinal fluid)

End point description:

End point type	Secondary

End point timeframe:

Screening, week 48

End point values	Arm 1, DMF	Arm 2, placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	26	24		
Units: ng/L				
arithmetic mean (standard deviation)	-188 (± 321)	-307 (± 481)		

Statistical analyses

Statistical analysis title	Generalized linear model

Statistical analysis description:

ANCOVA adjusted for baseline value.

Comparison groups	Arm 1, DMF v Arm 2, placebo
Number of subjects included in analysis	50
Analysis specification	Pre-specified
Analysis type	equivalence
P-value	= 0.2
Method	ANCOVA
Parameter estimate	Mean difference (net)
Point estimate	-107
Confidence interval	
level	95 %
sides	2-sided
lower limit	-274
upper limit	60

Secondary: Soluble B cell maturation antigen (cerebrospinal fluid)

End point title	Soluble B cell maturation antigen (cerebrospinal fluid)

End point description:

End point type	Secondary

End point timeframe:

Screening, week 48

End point values	Arm 1, DMF	Arm 2, placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	26	24		
Units: ng/L				
arithmetic mean (standard deviation)	-96 (± 204)	-57 (± 146)		

Statistical analyses

Statistical analysis title	Generalized linear model
Statistical analysis description:	

ANCOVA adjusted for baseline value.

Comparison groups	Arm 1, DMF v Arm 2, placebo
Number of subjects included in analysis	50
Analysis specification	Pre-specified
Analysis type	equivalence
P-value	= 0.41
Method	ANCOVA
Parameter estimate	Mean difference (net)
Point estimate	-30
Confidence interval	
level	95 %
sides	2-sided
lower limit	-103
upper limit	42

Secondary: Soluble CD14 (cerebrospinal fluid)

End point title	Soluble CD14 (cerebrospinal fluid)
End point description:	

End point type	Secondary

End point timeframe:

Screening, week 48

End point values	Arm 1, DMF	Arm 2, placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	26	24		
Units: ng/ml				
arithmetic mean (standard deviation)	7 (± 24)	5 (± 17)		

Statistical analyses

Statistical analysis title	Generalized linear model
Statistical analysis description:	
ANCOVA adjusted for baseline value.	
Comparison groups	Arm 1, DMF v Arm 2, placebo
Number of subjects included in analysis	50
Analysis specification	Pre-specified
Analysis type	equivalence
P-value	= 0.54
Method	ANCOVA
Parameter estimate	Mean difference (net)
Point estimate	3
Confidence interval	
level	95 %
sides	2-sided
lower limit	-8
upper limit	15

Secondary: Soluble chitinase-3-like-1 (cerebrospinal fluid)

End point title	Soluble chitinase-3-like-1 (cerebrospinal fluid)
End point description:	
End point type	Secondary
End point timeframe:	
Screening visit, week 48	

End point values	Arm 1, DMF	Arm 2, placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	26	24		
Units: ng/ml				
arithmetic mean (standard deviation)	-17 (± 47)	-7 (± 27)		

Statistical analyses

Statistical analysis title	Generalized linear model
Statistical analysis description:	
ANCOVA adjusted for baseline value.	
Comparison groups	Arm 2, placebo v Arm 1, DMF
Number of subjects included in analysis	50
Analysis specification	Pre-specified
Analysis type	equivalence
P-value	= 0.91
Method	ANCOVA
Parameter estimate	Mean difference (net)
Point estimate	1
Confidence interval	
level	95 %
sides	2-sided
lower limit	-18
upper limit	20

Secondary: IgG-index

End point title	IgG-index
End point description:	
End point type	Secondary
End point timeframe:	
Screening visit, week 48	

End point values	Arm 1, DMF	Arm 2, placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	26	24		
Units: index				
arithmetic mean (standard deviation)	-0.03 (± 0.08)	-0.03 (± 0.12)		

Statistical analyses

Statistical analysis title	Generalized linear model
Comparison groups	Arm 1, DMF v Arm 2, placebo
Number of subjects included in analysis	50
Analysis specification	Pre-specified
Analysis type	equivalence
P-value	= 0.82
Method	ANCOVA
Parameter estimate	Mean difference (net)
Point estimate	-0.01

Confidence interval	
level	95 %
sides	2-sided
lower limit	-0.07
upper limit	0.06

Secondary: Albumin quotient

End point title	Albumin quotient

End point description:

End point type	Secondary

End point timeframe:

Screening visit, week 48

End point values	Arm 1, DMF	Arm 2, placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	26	24		
Units: index				
arithmetic mean (standard deviation)	-0.8 (± 1.7)	0.1 (± 1.0)		

Statistical analyses

Statistical analysis title	Generalized linear model
Statistical analysis description:	
ANCOVA adjusted for baseline value.	
Comparison groups	Arm 1, DMF v Arm 2, placebo
Number of subjects included in analysis	50
Analysis specification	Pre-specified
Analysis type	equivalence
P-value	= 0.1
Method	ANCOVA
Parameter estimate	Mean difference (net)
Point estimate	-0.6
Confidence interval	
level	95 %
sides	2-sided
lower limit	-1.4
upper limit	0.1

Secondary: Fractional anisotropy in normal appearing white matter

End point title	Fractional anisotropy in normal appearing white matter

End point description:	

End point type	Secondary
End point timeframe:	
Screening visit, week 48, week 96	

End point values	Arm 1, DMF	Arm 2, placebo	Arm 1, DMF/DMF	Arm 2, UNT/DMF
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	26	24	17	16
Units: FA				
arithmetic mean (standard deviation)	0.000 (± 0.01)	-0.001 (± 0.014)	-0.003 (± 0.009)	0.002 (± 0.008)

Statistical analyses

Statistical analysis title	Generalized linear model
Statistical analysis description:	
ANCOVA adjusted for baseline value.	
Comparison groups	Arm 1, DMF v Arm 2, placebo
Number of subjects included in analysis	50
Analysis specification	Pre-specified
Analysis type	equivalence
P-value	= 0.89
Method	ANCOVA
Parameter estimate	Mean difference (net)
Point estimate	-0.001
Confidence interval	
level	95 %
sides	2-sided
lower limit	-0.01
upper limit	0.01

Secondary: T2 lesion volume

End point title	T2 lesion volume
End point description:	

End point type	Secondary
End point timeframe:	
screening visit to week 48, week 48 to week 96	

End point values	Arm 1, DMF	Arm 2, placebo	Arm 1, DMF/DMF	Arm 2, UNT/DMF
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	26	24	17	16
Units: millilitre(s)				
arithmetic mean (standard deviation)	0.7 (± 1.1)	0.6 (± 1.4)	0.3 (± 0.2)	0.1 (± 0.6)

Statistical analyses

Statistical analysis title	Generalized linear model
Statistical analysis description:	
ANCOVA adjusted for baseline value.	
Comparison groups	Arm 1, DMF v Arm 2, placebo
Number of subjects included in analysis	50
Analysis specification	Pre-specified
Analysis type	equivalence
P-value	= 0.64
Method	ANCOVA
Parameter estimate	Mean difference (net)
Point estimate	0.2
Confidence interval	
level	95 %
sides	2-sided
lower limit	-0.5
upper limit	0.8
Variability estimate	Standard deviation

Secondary: Magnetization transfer ratio of lesions

End point title	Magnetization transfer ratio of lesions
End point description:	
End point type	Secondary
End point timeframe:	
Screening visit, week 48, week 96	

End point values	Arm 1, DMF	Arm 2, placebo	Arm 1, DMF/DMF	Arm 2, UNT/DMF
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	26	24	17	16
Units: MTR				
arithmetic mean (standard deviation)	0.2 (± 1.3)	0.4 (± 1.5)	0.1 (± 0.5)	0.7 (± 0.7)

Statistical analyses

Statistical analysis title	Generalized linear model
Statistical analysis description:	
ANCOVA adjusted for baseline value.	
Comparison groups	Arm 1, DMF v Arm 2, placebo
Number of subjects included in analysis	50
Analysis specification	Pre-specified
Analysis type	equivalence
P-value	= 0.8
Method	ANCOVA
Parameter estimate	Mean difference (net)
Point estimate	-0.1
Confidence interval	
level	95 %
sides	2-sided
lower limit	-0.8
upper limit	0.6

Secondary: Expanded disability status scale, change

End point title	Expanded disability status scale, change
End point description:	
End point type	Secondary
End point timeframe:	
Screening visit, week 24, week 48, week 72, week 96	

End point values	Arm 1, DMF	Arm 2, placebo	Arm 1, DMF/DMF	Arm 2, UNT/DMF
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	26	24	17	16
Units: EDSS				
arithmetic mean (standard deviation)	0.2 (± 0.7)	0.0 (± 1.0)	0.0 (± 0.43)	0.22 (± 0.60)

Statistical analyses

Statistical analysis title	Generalized linear model
Statistical analysis description:	
ANCOVA adjusted for baseline value.	
Comparison groups	Arm 2, placebo v Arm 1, DMF

Number of subjects included in analysis	50
Analysis specification	Pre-specified
Analysis type	equivalence
P-value	= 0.16
Method	ANCOVA
Parameter estimate	Mean difference (net)
Point estimate	0.29
Confidence interval	
level	95 %
sides	2-sided
lower limit	-0.1
upper limit	0.7

Secondary: Timed 25-foot walk

End point title	Timed 25-foot walk
End point description:	
End point type	Secondary
End point timeframe:	

Screening, baseline, 24 weeks, 48 weeks, 96 weeks

End point values	Arm 1, DMF	Arm 2, placebo	Arm 1, DMF/DMF	Arm 2, UNT/DMF
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	26	24	17	16
Units: second				
arithmetic mean (standard deviation)	0.9 (± 2.7)	-0.1 (± 1.4)	-0.48 (± 3.44)	0.43 (± 1.35)

Statistical analyses

Statistical analysis title	Generalized linear model
Statistical analysis description:	
ANCOVA adjusted for baseline value.	
Comparison groups	Arm 2, placebo v Arm 1, DMF
Number of subjects included in analysis	50
Analysis specification	Pre-specified
Analysis type	equivalence
P-value	= 0.12
Method	ANCOVA
Parameter estimate	Mean difference (net)
Point estimate	0.9

Confidence interval	
level	95 %
sides	2-sided
lower limit	0
upper limit	2.1

Secondary: 9-hole peg test

End point title	9-hole peg test
End point description:	

End point type	Secondary

End point timeframe:

Screening, baseline, 24 weeks, 48 weeks, 96 weeks.

End point values	Arm 1, DMF	Arm 2, placebo	Arm 1, DMF/DMF	Arm 2, UNT/DMF
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	26	24	17	16
Units: second				
arithmetic mean (standard deviation)				
Dominant hand	1.9 (± 9)	-1.4 (± 6)	2.1 (± 7.2)	1.0 (± 3.9)
Nondominant hand	0 (± 28)	5 (± 24)	3.4 (± 4.2)	2.3 (± 4.5)

Statistical analyses

Statistical analysis title	Generalized linear model
Statistical analysis description:	
ANCOVA adjusted for baseline value.	
Comparison groups	Arm 1, DMF v Arm 2, placebo
Number of subjects included in analysis	50
Analysis specification	Pre-specified
Analysis type	equivalence
P-value	= 0.26
Method	ANCOVA
Parameter estimate	Mean difference (net)
Point estimate	-2.4
Confidence interval	
level	95 %
sides	2-sided
lower limit	-6.6
upper limit	1.8

Secondary: Symbol digit modalities test

End point title	Symbol digit modalities test
End point description:	
End point type	Secondary
End point timeframe:	
screening, baseline, week 48, week 96.	

End point values	Arm 1, DMF	Arm 2, placebo	Arm 1, DMF/DMF	Arm 2, UNT/DMF
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	26	24	17	16
Units: numbers correct				
arithmetic mean (standard deviation)	2.5 (± 6.1)	3.7 (± 5.3)	-1.2 (± 6.3)	-1.4 (± 7.3)

Statistical analyses

Statistical analysis title	Generalized linear model
Statistical analysis description:	
ANCOVA adjusted for baseline value.	
Comparison groups	Arm 1, DMF v Arm 2, placebo
Number of subjects included in analysis	50
Analysis specification	Pre-specified
Analysis type	equivalence
P-value	= 0.45
Method	ANCOVA
Parameter estimate	Mean difference (net)
Point estimate	-1.2
Confidence interval	
level	95 %
sides	2-sided
lower limit	-4.3
upper limit	1.9

Secondary: Percentage brain volume change

End point title	Percentage brain volume change
End point description:	
End point type	Secondary
End point timeframe:	
Screening to week 48	

End point values	Arm 1, DMF	Arm 2, placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	26	24		
Units: percent volume/volume				
arithmetic mean (standard deviation)	-0.5 (± 0.8)	-0.2 (± 0.8)		

Statistical analyses

Statistical analysis title	Generalized linear model
Statistical analysis description: ANCOVA adjusted for baseline value.	
Comparison groups	Arm 1, DMF v Arm 2, placebo
Number of subjects included in analysis	50
Analysis specification	Pre-specified
Analysis type	equivalence
P-value	= 0.1
Method	ANCOVA
Parameter estimate	Mean difference (net)
Point estimate	-0.6
Confidence interval	
level	95 %
sides	2-sided
lower limit	-1.4
upper limit	0.1
Variability estimate	Standard deviation

Secondary: New or enlarging lesions

End point title	New or enlarging lesions
End point description:	
End point type	Secondary
End point timeframe: Screening to week 48	

End point values	Arm 1, DMF	Arm 2, placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	26	24		
Units: no.	3	3		

Statistical analyses

Statistical analysis title	New or enlarging lesions
Statistical analysis description:	
negative binomial regression adjusted for number of T2-lesions at screening.	
Comparison groups	Arm 1, DMF v Arm 2, placebo
Number of subjects included in analysis	50
Analysis specification	Pre-specified
Analysis type	equivalence
P-value	= 0.49
Method	Negative binomial regression
Parameter estimate	Mean difference (net)
Point estimate	0
Confidence interval	
level	95 %
sides	2-sided
lower limit	-1
upper limit	0

Post-hoc: New lesions

End point title	New lesions
End point description:	
No statistics performed	
End point type	Post-hoc
End point timeframe:	
Week 48 - week 96	

End point values	Arm 1, DMF/DMF	Arm 2, UNT/DMF		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	17	16		
Units: no.	2	3		

Statistical analyses

No statistical analyses for this end point

Post-hoc: Enlarging lesions

End point title	Enlarging lesions
End point description:	
No statistics performed	
End point type	Post-hoc
End point timeframe:	
Week 48 - week 96	

End point values	Arm 1, DMF/DMF	Arm 2, UNT/DMF		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	17	16		
Units: no.	1	0		

Statistical analyses

No statistical analyses for this end point

Adverse events

Adverse events information

Timeframe for reporting adverse events:	
Screening to week 48 and Week 48 to week 96 (open label phase)	
Assessment type	Systematic

Dictionary used

Dictionary name	CTCAE
Dictionary version	4

Reporting groups

Reporting group title	Treatment group - phase 1
Reporting group description: -	
Reporting group title	Placebo group - phase 1
Reporting group description: -	
Reporting group title	Open label phase
Reporting group description: From week 48 to week 96	

Serious adverse events	Treatment group - phase 1	Placebo group - phase 1	Open label phase
Total subjects affected by serious adverse events			
subjects affected / exposed	3 / 27 (11.11%)	3 / 27 (11.11%)	5 / 42 (11.90%)
number of deaths (all causes)	0	0	0
number of deaths resulting from adverse events	0	0	0
Neoplasms benign, malignant and unspecified (incl cysts and polyps)			
Testicular seminoma (pure)			
subjects affected / exposed	1 / 27 (3.70%)	0 / 27 (0.00%)	0 / 42 (0.00%)
occurrences causally related to treatment / all	1 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Ear and labyrinth disorders			
Vertigo			
subjects affected / exposed	0 / 27 (0.00%)	1 / 27 (3.70%)	0 / 42 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Gastrointestinal disorders			
Gastroenteritis			

subjects affected / exposed	0 / 27 (0.00%)	1 / 27 (3.70%)	0 / 42 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0

Dyspepsia

subjects affected / exposed	0 / 27 (0.00%)	0 / 27 (0.00%)	1 / 42 (2.38%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0

Nausea

subjects affected / exposed	0 / 27 (0.00%)	0 / 27 (0.00%)	1 / 42 (2.38%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0

Hepatobiliary disorders
Gallbladder disorder

subjects affected / exposed	1 / 27 (3.70%)	0 / 27 (0.00%)	0 / 42 (0.00%)
occurrences causally related to treatment / all	1 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0

Skin and subcutaneous tissue disorders
Basal cell carcinoma

subjects affected / exposed	0 / 27 (0.00%)	0 / 27 (0.00%)	1 / 42 (2.38%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0

Renal and urinary disorders
Urinary tract infection

subjects affected / exposed	0 / 27 (0.00%)	1 / 27 (3.70%)	0 / 42 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0

Urinary retention

subjects affected / exposed	0 / 27 (0.00%)	0 / 27 (0.00%)	1 / 42 (2.38%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0

Infections and infestations
Sepsis

subjects affected / exposed	1 / 27 (3.70%)	0 / 27 (0.00%)	1 / 42 (2.38%)
occurrences causally related to treatment / all	1 / 1	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0

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

Non-serious adverse events	Treatment group - phase 1	Placebo group - phase 1	Open label phase
Total subjects affected by non-serious adverse events			
subjects affected / exposed	21 / 27 (77.78%)	13 / 27 (48.15%)	37 / 42 (88.10%)
Vascular disorders			
Lymphedema			
subjects affected / exposed	0 / 27 (0.00%)	0 / 27 (0.00%)	2 / 42 (4.76%)
occurrences (all)	0	0	2
General disorders and administration site conditions			
Headache			
subjects affected / exposed	2 / 27 (7.41%)	0 / 27 (0.00%)	6 / 42 (14.29%)
occurrences (all)	2	0	6
Creatinine renal clearance abnormal			
subjects affected / exposed	0 / 27 (0.00%)	0 / 27 (0.00%)	1 / 42 (2.38%)
occurrences (all)	0	0	1
Hypokalaemia			
subjects affected / exposed	0 / 27 (0.00%)	0 / 27 (0.00%)	1 / 42 (2.38%)
occurrences (all)	0	0	1
Dry mouth			
subjects affected / exposed	1 / 27 (3.70%)	1 / 27 (3.70%)	0 / 42 (0.00%)
occurrences (all)	1	1	0
Fatigue			
subjects affected / exposed	0 / 27 (0.00%)	1 / 27 (3.70%)	0 / 42 (0.00%)
occurrences (all)	0	1	0
Immune system disorders			
Lymphocyte count decreased			
subjects affected / exposed	13 / 27 (48.15%)	1 / 27 (3.70%)	14 / 42 (33.33%)
occurrences (all)	13	1	14
Reproductive system and breast disorders			

Epididymitis			
subjects affected / exposed	1 / 27 (3.70%)	0 / 27 (0.00%)	0 / 42 (0.00%)
occurrences (all)	1	0	0
Gynaecomastia			
subjects affected / exposed	0 / 27 (0.00%)	1 / 27 (3.70%)	0 / 42 (0.00%)
occurrences (all)	0	1	0
Spermatic cord hemorrhage			
subjects affected / exposed	0 / 27 (0.00%)	1 / 27 (3.70%)	0 / 42 (0.00%)
occurrences (all)	0	1	0
Uterine polyp			
subjects affected / exposed	0 / 27 (0.00%)	1 / 27 (3.70%)	0 / 42 (0.00%)
occurrences (all)	0	0	0
Ovarian cyst			
subjects affected / exposed	0 / 27 (0.00%)	1 / 27 (3.70%)	0 / 42 (0.00%)
occurrences (all)	0	1	0
Lung cyst			
subjects affected / exposed	0 / 27 (0.00%)	1 / 27 (3.70%)	0 / 42 (0.00%)
occurrences (all)	0	1	0
Respiratory, thoracic and mediastinal disorders			
Upper respiratory tract infection			
subjects affected / exposed	5 / 27 (18.52%)	4 / 27 (14.81%)	5 / 42 (11.90%)
occurrences (all)	5	4	5
Chronic obstructive pulmonary disease			
subjects affected / exposed	0 / 27 (0.00%)	1 / 27 (3.70%)	0 / 42 (0.00%)
occurrences (all)	0	0	0
Psychiatric disorders			
NIghtmares			
subjects affected / exposed	0 / 27 (0.00%)	1 / 27 (3.70%)	1 / 42 (2.38%)
occurrences (all)	0	1	1
Depression			
subjects affected / exposed	0 / 27 (0.00%)	1 / 27 (3.70%)	0 / 42 (0.00%)
occurrences (all)	0	1	0
Injury, poisoning and procedural complications			
Fall			

subjects affected / exposed	2 / 27 (7.41%)	0 / 27 (0.00%)	3 / 42 (7.14%)
occurrences (all)	2	0	3
Fracture			
subjects affected / exposed	0 / 27 (0.00%)	2 / 27 (7.41%)	0 / 42 (0.00%)
occurrences (all)	0	2	0
Ankle distortion			
subjects affected / exposed	0 / 27 (0.00%)	0 / 27 (0.00%)	1 / 42 (2.38%)
occurrences (all)	0	0	1
Wound			
subjects affected / exposed	0 / 27 (0.00%)	0 / 27 (0.00%)	1 / 42 (2.38%)
occurrences (all)	0	0	1
Pain in extremity			
subjects affected / exposed	0 / 27 (0.00%)	1 / 27 (3.70%)	0 / 42 (0.00%)
occurrences (all)	0	1	0
Cardiac disorders			
Syncope			
subjects affected / exposed	0 / 27 (0.00%)	2 / 27 (7.41%)	0 / 42 (0.00%)
occurrences (all)	0	2	0
Hypertension			
subjects affected / exposed	0 / 27 (0.00%)	0 / 27 (0.00%)	1 / 42 (2.38%)
occurrences (all)	0	0	1
Palpitations			
subjects affected / exposed	1 / 27 (3.70%)	0 / 27 (0.00%)	0 / 42 (0.00%)
occurrences (all)	1	0	0
Nervous system disorders			
Paresthesia			
subjects affected / exposed	0 / 27 (0.00%)	0 / 27 (0.00%)	1 / 42 (2.38%)
occurrences (all)	0	0	1
Vertigo positional			
subjects affected / exposed	1 / 27 (3.70%)	1 / 27 (3.70%)	1 / 42 (2.38%)
occurrences (all)	1	1	1
Dysaesthesia pharynx			
subjects affected / exposed	0 / 27 (0.00%)	1 / 27 (3.70%)	0 / 42 (0.00%)
occurrences (all)	0	1	0
Blood and lymphatic system disorders			

Epistaxis			
subjects affected / exposed	0 / 27 (0.00%)	1 / 27 (3.70%)	0 / 42 (0.00%)
occurrences (all)	0	0	0
Ear and labyrinth disorders			
Tinnitus			
subjects affected / exposed	0 / 27 (0.00%)	0 / 27 (0.00%)	1 / 42 (2.38%)
occurrences (all)	0	0	1
Gastrointestinal disorders			
Gastrointestinal pain			
subjects affected / exposed	6 / 27 (22.22%)	0 / 27 (0.00%)	7 / 42 (16.67%)
occurrences (all)	6	0	7
Nausea			
subjects affected / exposed	3 / 27 (11.11%)	3 / 27 (11.11%)	4 / 42 (9.52%)
occurrences (all)	3	3	4
Diarrhoea			
subjects affected / exposed	4 / 27 (14.81%)	5 / 27 (18.52%)	6 / 42 (14.29%)
occurrences (all)	4	5	6
Vomiting			
subjects affected / exposed	2 / 27 (7.41%)	0 / 27 (0.00%)	1 / 42 (2.38%)
occurrences (all)	2	0	1
Dyspepsia			
subjects affected / exposed	1 / 27 (3.70%)	0 / 27 (0.00%)	2 / 42 (4.76%)
occurrences (all)	1	0	2
Constipation			
subjects affected / exposed	0 / 27 (0.00%)	0 / 27 (0.00%)	1 / 42 (2.38%)
occurrences (all)	0	0	1
Gastric ulcer			
subjects affected / exposed	0 / 27 (0.00%)	0 / 27 (0.00%)	1 / 42 (2.38%)
occurrences (all)	0	0	1
Flatulence			
subjects affected / exposed	1 / 27 (3.70%)	0 / 27 (0.00%)	1 / 42 (2.38%)
occurrences (all)	1	0	1
Anal haemorrhage			
subjects affected / exposed	1 / 27 (3.70%)	0 / 27 (0.00%)	0 / 42 (0.00%)
occurrences (all)	1	0	0
Skin and subcutaneous tissue disorders			

Flushing			
subjects affected / exposed	16 / 27 (59.26%)	1 / 27 (3.70%)	15 / 42 (35.71%)
occurrences (all)	16	1	15
Eczema			
subjects affected / exposed	1 / 27 (3.70%)	2 / 27 (7.41%)	1 / 42 (2.38%)
occurrences (all)	1	2	1
Dry skin			
subjects affected / exposed	1 / 27 (3.70%)	0 / 27 (0.00%)	1 / 42 (2.38%)
occurrences (all)	1	0	1
Pruritus			
subjects affected / exposed	1 / 27 (3.70%)	0 / 27 (0.00%)	1 / 42 (2.38%)
occurrences (all)	1	0	1
Alopecia			
subjects affected / exposed	1 / 27 (3.70%)	0 / 27 (0.00%)	1 / 42 (2.38%)
occurrences (all)	1	0	1
Night sweats			
subjects affected / exposed	1 / 27 (3.70%)	0 / 27 (0.00%)	0 / 42 (0.00%)
occurrences (all)	1	0	0
Renal and urinary disorders			
Urinary tract infection			
subjects affected / exposed	3 / 27 (11.11%)	2 / 27 (7.41%)	5 / 42 (11.90%)
occurrences (all)	3	2	5
Musculoskeletal and connective tissue disorders			
Back pain			
subjects affected / exposed	2 / 27 (7.41%)	3 / 27 (11.11%)	3 / 42 (7.14%)
occurrences (all)	2	3	3
Arthralgia			
subjects affected / exposed	0 / 27 (0.00%)	1 / 27 (3.70%)	2 / 42 (4.76%)
occurrences (all)	0	1	2
Radicular pain			
subjects affected / exposed	0 / 27 (0.00%)	1 / 27 (3.70%)	1 / 42 (2.38%)
occurrences (all)	0	1	1
Infections and infestations			
Flu like symptoms			
subjects affected / exposed	5 / 27 (18.52%)	2 / 27 (7.41%)	1 / 42 (2.38%)
occurrences (all)	5	2	1

Fever			
subjects affected / exposed	2 / 27 (7.41%)	1 / 27 (3.70%)	2 / 42 (4.76%)
occurrences (all)	2	1	2
Tooth infection			
subjects affected / exposed	2 / 27 (7.41%)	0 / 27 (0.00%)	2 / 42 (4.76%)
occurrences (all)	2	0	2
gum infection			
subjects affected / exposed	0 / 27 (0.00%)	0 / 27 (0.00%)	1 / 42 (2.38%)
occurrences (all)	0	0	1
Lung infection			
subjects affected / exposed	0 / 27 (0.00%)	0 / 27 (0.00%)	1 / 42 (2.38%)
occurrences (all)	0	0	1
Borrelia infection			
subjects affected / exposed	0 / 27 (0.00%)	0 / 27 (0.00%)	1 / 42 (2.38%)
occurrences (all)	0	0	1
Cough			
subjects affected / exposed	0 / 27 (0.00%)	0 / 27 (0.00%)	1 / 42 (2.38%)
occurrences (all)	0	0	1

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

Date	Amendment
27 April 2017	Age criterion increased from 60 to 65 years of age.
24 September 2018	New principal investigator and extension of study phase
18 February 2020	Removal of secondary endpoint (LCVA) and changes in statistical analysis plan

Notes:

Interruptions (globally)

Were there any global interruptions to the trial? No

Limitations and caveats

None reported