



Clinical trial results:

Effect of MD1003 in chronic visual loss related to optic neuritis in multiple sclerosis: a pivotal randomized double masked placebo controlled study

Summary

EudraCT number	2013-002112-27
Trial protocol	FR GB
Global end of trial date	01 August 2019

Results information

Result version number	v1 (current)
This version publication date	12 November 2020
First version publication date	12 November 2020

Trial information

Trial identification

Sponsor protocol code	MD1003CT2013-01MS-ON
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Additional study identifiers

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

Notes:

Sponsors

Sponsor organisation name	Medday pharmaceuticals SA
Sponsor organisation address	24-26 rue de la Pépinière, Paris, France, Paris, France, 75008
Public contact	Frédéric Sedel, MEDDAY PHARMACEUTICALS,, Medday pharmaceuticals SA, +33 1 80 40 14 40, frederic.sedel@medday-pharma.com
Scientific contact	Frédéric Sedel, MEDDAY PHARMACEUTICALS,, Medday pharmaceuticals SA, +33 1 80 40 14 40, frederic.sedel@medday-pharma.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	01 August 2019
Is this the analysis of the primary completion data?	Yes
Primary completion date	01 August 2019
Global end of trial reached?	Yes
Global end of trial date	01 August 2019
Was the trial ended prematurely?	No

Notes:

General information about the trial

Main objective of the trial:

To demonstrate the superiority of biotin 300 mg/day over placebo in the visual improvement of patients suffering from chronic visual loss after optic neuritis related to multiple sclerosis

Protection of trial subjects:

This protocol complied with the principal laid down by the 18th World Medical Assembly (Helsinki, 1964 and following amendments) and all applicable amendments laid down by the World Medical Assemblies, as well as the International Conference on Harmonization (ICH) Good Clinical Practice (GCP) guidelines. The trial complied with the laws and regulations of the country in which the study was performed, and any applicable guidelines.

Background therapy: -

Evidence for comparator: -

Actual start date of recruitment	08 October 2013
Long term follow-up planned	Yes
Long term follow-up rationale	Safety
Long term follow-up duration	54 Months
Independent data monitoring committee (IDMC) involvement?	No

Notes:

Population of trial subjects

Subjects enrolled per country

Country: Number of subjects enrolled	United Kingdom: 4
Country: Number of subjects enrolled	France: 89
Worldwide total number of subjects	93
EEA total number of subjects	93

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)	92
From 65 to 84 years	1
85 years and over	0

Subject disposition

Recruitment

Recruitment details:

no specific requirements

Pre-assignment

Screening details: -

Pre-assignment period milestones

Number of subjects started	117 ^[1]
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Number of subjects completed	93
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Pre-assignment subject non-completion reasons

Reason: Number of subjects	inclusion/exclusion criteria: 24
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Notes:

[1] - The number of subjects reported to have started the pre-assignment period are not the same as the worldwide number enrolled in the trial. It is expected that these numbers will be the same.

Justification: the difference is the number of screen failures

Period 1

Period 1 title	Double Blind (M0-M6)
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Is this the baseline period?	Yes
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Allocation method	Randomised - controlled
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Blinding used	Double blind
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Roles blinded	Subject, Investigator, Monitor
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Arms

Are arms mutually exclusive?	Yes
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Arm title	MD1003
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Arm description:

MD1003

Arm type	Experimental
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Investigational medicinal product name	MD1003
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Investigational medicinal product code	
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Other name	
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Pharmaceutical forms	Capsule
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Routes of administration	Oral use
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Dosage and administration details:

300mg / day (100mg 3 times day - tid)

Arm title	Placebo
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Arm description:

Placebo

Arm type	Placebo
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Investigational medicinal product name	Placebo
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Investigational medicinal product code	
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Other name	
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Pharmaceutical forms	Capsule
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Routes of administration	Oral use
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Dosage and administration details:

300mg / day (100mg 3 times day - tid)

Number of subjects in period 1	MD1003	Placebo
Started	65	28
Completed	64	28
Not completed	1	0
Adverse event, non-fatal	1	-

Period 2

Period 2 title	Extension Phase (M6 - M66)
Is this the baseline period?	No
Allocation method	Not applicable
Blinding used	Not blinded

Arms

Arm title	MD1003
Arm description: MD1003	
Arm type	Experimental
Investigational medicinal product name	MD1003
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Capsule
Routes of administration	Oral use

Dosage and administration details:

300mg a day

Number of subjects in period 2	MD1003
Started	92
Completed	65
Not completed	27
Consent withdrawn by subject	5
Physician decision	5
Adverse event, non-fatal	2
other	13
Lack of efficacy	1
Protocol deviation	1

Baseline characteristics

Reporting groups

Reporting group title	MD1003
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Reporting group description:

MD1003

Reporting group title	Placebo
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Reporting group description:

Placebo

Reporting group values	MD1003	Placebo	Total
Number of subjects	65	28	93
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	41.6	41.1	
standard deviation	± 10.5	± 10.6	-
Gender categorical Units: Subjects			
Female	35	15	50
Male	30	13	43

End points

End points reporting groups

Reporting group title	MD1003
Reporting group description:	MD1003
Reporting group title	Placebo
Reporting group description:	Placebo
Reporting group title	MD1003
Reporting group description:	MD1003

Primary: Change from baseline of the best corrected visual acuity at 100% contrast

End point title	Change from baseline of the best corrected visual acuity at 100% contrast
End point description:	Best corrected visual acuity using the ETDRS logMar chart at 100% contrast
End point type	Primary
End point timeframe:	M0-M6

End point values	MD1003	Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	64	28		
Units: percentage of corrected visual acuity				
arithmetic mean (standard deviation)	-0.061 (\pm 0.206)	-0.036 (\pm 0.184)		

Statistical analyses

Statistical analysis title	MeanChange in Log Mar
Comparison groups	MD1003 v Placebo
Number of subjects included in analysis	92
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.7487
Method	Wilcoxon (Mann-Whitney)

Secondary: Number of Patients With Improved Visual Acuity From Baseline

End point title	Number of Patients With Improved Visual Acuity From Baseline
End point description:	
End point type	Secondary
End point timeframe:	
M0-M6	

End point values	MD1003	Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	65	28		
Units: patients	6	2		

Statistical analyses

No statistical analyses for this end point

Secondary: Optical Coherence Tomography

End point title	Optical Coherence Tomography
End point description:	
End point type	Secondary
End point timeframe:	
M0-M6	

End point values	MD1003	Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	65	28		
Units: micrometer				
arithmetic mean (standard deviation)	-0.5 (± 2.6)	-0.3 (± 2.7)		

Statistical analyses

No statistical analyses for this end point

Adverse events

Adverse events information

Timeframe for reporting adverse events:

M0-M66

Assessment type	Systematic
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Dictionary used

Dictionary name	MedDRA
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Dictionary version	16
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Reporting groups

Reporting group title	MD1003 double blind
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Reporting group description:

MD1003

Reporting group title	Placebo double blind
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Reporting group description:

Placebo

Reporting group title	MD1003 extension phase
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Reporting group description: -

Reporting group title	Placebo extension phase
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Reporting group description: -

Serious adverse events	MD1003 double blind	Placebo double blind	MD1003 extension phase
Total subjects affected by serious adverse events			
subjects affected / exposed	9 / 65 (13.85%)	3 / 28 (10.71%)	21 / 64 (32.81%)
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)			
Chronic myeloid leukaemia			
subjects affected / exposed	0 / 65 (0.00%)	0 / 28 (0.00%)	0 / 64 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Transitional cell carcinoma			
subjects affected / exposed	0 / 65 (0.00%)	0 / 28 (0.00%)	0 / 64 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Vascular disorders			
Hypertension			

subjects affected / exposed	0 / 65 (0.00%)	0 / 28 (0.00%)	1 / 64 (1.56%)
occurrences causally related to treatment / all	0 / 0	0 / 0	1 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Surgical and medical procedures			
Colectomy			
subjects affected / exposed	0 / 65 (0.00%)	1 / 28 (3.57%)	0 / 64 (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
Orchidectomy			
subjects affected / exposed	0 / 65 (0.00%)	0 / 28 (0.00%)	1 / 64 (1.56%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Shoulder operation			
subjects affected / exposed	0 / 65 (0.00%)	0 / 28 (0.00%)	1 / 64 (1.56%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Thyroidectomy			
subjects affected / exposed	0 / 65 (0.00%)	0 / 28 (0.00%)	1 / 64 (1.56%)
occurrences causally related to treatment / all	0 / 0	0 / 0	1 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Urostomy			
subjects affected / exposed	0 / 65 (0.00%)	0 / 28 (0.00%)	1 / 64 (1.56%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Nervous system disorders			
Multiple sclerosis			
subjects affected / exposed	0 / 65 (0.00%)	1 / 28 (3.57%)	2 / 64 (3.13%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 2
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Multiple sclerosis relapse			
subjects affected / exposed	9 / 65 (13.85%)	1 / 28 (3.57%)	11 / 64 (17.19%)
occurrences causally related to treatment / all	0 / 9	0 / 1	2 / 14
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Cervicobrachial syndrome			

subjects affected / exposed	0 / 65 (0.00%)	0 / 28 (0.00%)	1 / 64 (1.56%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Headache			
subjects affected / exposed	0 / 65 (0.00%)	0 / 28 (0.00%)	0 / 64 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
General disorders and administration site conditions			
Chest pain			
subjects affected / exposed	0 / 65 (0.00%)	0 / 28 (0.00%)	0 / 64 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Condition aggravated			
subjects affected / exposed	0 / 65 (0.00%)	0 / 28 (0.00%)	1 / 64 (1.56%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Discomfort			
subjects affected / exposed	0 / 65 (0.00%)	0 / 28 (0.00%)	1 / 64 (1.56%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Gait disturbance			
subjects affected / exposed	0 / 65 (0.00%)	0 / 28 (0.00%)	1 / 64 (1.56%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
General physical health deterioration			
subjects affected / exposed	0 / 65 (0.00%)	0 / 28 (0.00%)	1 / 64 (1.56%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Immune system disorders			
Hypersensitivity			
subjects affected / exposed	0 / 65 (0.00%)	0 / 28 (0.00%)	1 / 64 (1.56%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0

Eye disorders			
Retinal artery occlusion			
subjects affected / exposed	1 / 65 (1.54%)	0 / 28 (0.00%)	0 / 64 (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
Gastrointestinal disorders			
Anal fissure			
subjects affected / exposed	0 / 65 (0.00%)	0 / 28 (0.00%)	1 / 64 (1.56%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Volvulus			
subjects affected / exposed	0 / 65 (0.00%)	0 / 28 (0.00%)	1 / 64 (1.56%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Reproductive system and breast disorders			
Benign prostatic hyperplasia			
subjects affected / exposed	0 / 65 (0.00%)	0 / 28 (0.00%)	1 / 64 (1.56%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Epididymitis			
subjects affected / exposed	0 / 65 (0.00%)	0 / 28 (0.00%)	1 / 64 (1.56%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Endocrine disorders			
Hyperthyroidism			
subjects affected / exposed	1 / 65 (1.54%)	0 / 28 (0.00%)	0 / 64 (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
Infections and infestations			
Diverticulitis			
subjects affected / exposed	0 / 65 (0.00%)	1 / 28 (3.57%)	0 / 64 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 2	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0

Serious adverse events	Placebo extension phase		
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Total subjects affected by serious adverse events			
subjects affected / exposed	12 / 28 (42.86%)		
number of deaths (all causes)	0		
number of deaths resulting from adverse events	0		
Neoplasms benign, malignant and unspecified (incl cysts and polyps)			
Chronic myeloid leukaemia			
subjects affected / exposed	1 / 28 (3.57%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Transitional cell carcinoma			
subjects affected / exposed	1 / 28 (3.57%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Vascular disorders			
Hypertension			
subjects affected / exposed	0 / 28 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Surgical and medical procedures			
Colectomy			
subjects affected / exposed	0 / 28 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Orchidectomy			
subjects affected / exposed	0 / 28 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Shoulder operation			
subjects affected / exposed	0 / 28 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Thyroidectomy			
subjects affected / exposed	0 / 28 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		

Urostomy			
subjects affected / exposed	0 / 28 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Nervous system disorders			
Multiple sclerosis			
subjects affected / exposed	1 / 28 (3.57%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Multiple sclerosis relapse			
subjects affected / exposed	10 / 28 (35.71%)		
occurrences causally related to treatment / all	3 / 16		
deaths causally related to treatment / all	0 / 0		
Cervicobrachial syndrome			
subjects affected / exposed	0 / 28 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Headache			
subjects affected / exposed	1 / 28 (3.57%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
General disorders and administration site conditions			
Chest pain			
subjects affected / exposed	1 / 28 (3.57%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Condition aggravated			
subjects affected / exposed	0 / 28 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Discomfort			
subjects affected / exposed	0 / 28 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		

Gait disturbance			
subjects affected / exposed	0 / 28 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
General physical health deterioration			
subjects affected / exposed	0 / 28 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Immune system disorders			
Hypersensitivity			
subjects affected / exposed	0 / 28 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Eye disorders			
Retinal artery occlusion			
subjects affected / exposed	0 / 28 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Gastrointestinal disorders			
Anal fissure			
subjects affected / exposed	0 / 28 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Volvulus			
subjects affected / exposed	0 / 28 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Reproductive system and breast disorders			
Benign prostatic hyperplasia			
subjects affected / exposed	0 / 28 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Epididymitis			

subjects affected / exposed	0 / 28 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Endocrine disorders			
Hyperthyroidism			
subjects affected / exposed	0 / 28 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Infections and infestations			
Diverticulitis			
subjects affected / exposed	0 / 28 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		

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

Non-serious adverse events	MD1003 double blind	Placebo double blind	MD1003 extension phase
Total subjects affected by non-serious adverse events			
subjects affected / exposed	27 / 65 (41.54%)	17 / 28 (60.71%)	47 / 64 (73.44%)
Injury, poisoning and procedural complications			
Fall			
subjects affected / exposed	0 / 65 (0.00%)	0 / 28 (0.00%)	1 / 64 (1.56%)
occurrences (all)	0	0	1
Cardiac disorders			
Oedema peripheral			
subjects affected / exposed	0 / 65 (0.00%)	0 / 28 (0.00%)	1 / 64 (1.56%)
occurrences (all)	0	0	1
Nervous system disorders			
Multiple sclerosis relapse			
subjects affected / exposed	9 / 65 (13.85%)	1 / 28 (3.57%)	13 / 64 (20.31%)
occurrences (all)	9	1	16
Headache			
subjects affected / exposed	3 / 65 (4.62%)	3 / 28 (10.71%)	4 / 64 (6.25%)
occurrences (all)	3	3	4
Multiple sclerosis			

subjects affected / exposed occurrences (all)	0 / 65 (0.00%) 0	0 / 28 (0.00%) 0	4 / 64 (6.25%) 5
General disorders and administration site conditions			
Asthenia			
subjects affected / exposed	2 / 65 (3.08%)	2 / 28 (7.14%)	3 / 64 (4.69%)
occurrences (all)	2	7	3
Dizziness			
subjects affected / exposed	0 / 65 (0.00%)	2 / 28 (7.14%)	0 / 64 (0.00%)
occurrences (all)	0	2	0
Anxiety			
subjects affected / exposed	0 / 65 (0.00%)	2 / 28 (7.14%)	0 / 64 (0.00%)
occurrences (all)	0	2	0
Gastrointestinal disorders			
Gastroenteritis			
subjects affected / exposed	1 / 65 (1.54%)	3 / 28 (10.71%)	0 / 64 (0.00%)
occurrences (all)	1	4	0
Respiratory, thoracic and mediastinal disorders			
Bronchitis			
subjects affected / exposed	0 / 65 (0.00%)	0 / 28 (0.00%)	9 / 64 (14.06%)
occurrences (all)	0	0	11
Nasopharyngitis			
subjects affected / exposed	8 / 65 (12.31%)	1 / 28 (3.57%)	6 / 64 (9.38%)
occurrences (all)	8	1	9
Oropharyngeal pain			
subjects affected / exposed	0 / 65 (0.00%)	0 / 28 (0.00%)	0 / 64 (0.00%)
occurrences (all)	0	0	0
Skin and subcutaneous tissue disorders			
Eczema			
subjects affected / exposed	0 / 65 (0.00%)	0 / 28 (0.00%)	1 / 64 (1.56%)
occurrences (all)	0	0	1
Psychiatric disorders			
Depression			
subjects affected / exposed	0 / 65 (0.00%)	2 / 28 (7.14%)	1 / 64 (1.56%)
occurrences (all)	0	2	1
Depressive symptom			

subjects affected / exposed occurrences (all)	0 / 65 (0.00%) 0	0 / 28 (0.00%) 0	1 / 64 (1.56%) 1
Musculoskeletal and connective tissue disorders Ligament sprain subjects affected / exposed occurrences (all)	0 / 65 (0.00%) 0	0 / 28 (0.00%) 0	1 / 64 (1.56%) 1
Infections and infestations Urinary tract infection subjects affected / exposed occurrences (all)	4 / 65 (6.15%) 4	1 / 28 (3.57%) 1	5 / 64 (7.81%) 10
Influenza subjects affected / exposed occurrences (all)	0 / 65 (0.00%) 0	0 / 28 (0.00%) 0	2 / 64 (3.13%) 2

Non-serious adverse events	Placebo extension phase		
Total subjects affected by non-serious adverse events subjects affected / exposed	20 / 28 (71.43%)		
Injury, poisoning and procedural complications Fall subjects affected / exposed occurrences (all)	3 / 28 (10.71%) 3		
Cardiac disorders Oedema peripheral subjects affected / exposed occurrences (all)	2 / 28 (7.14%) 2		
Nervous system disorders Multiple sclerosis relapse subjects affected / exposed occurrences (all)	11 / 28 (39.29%) 17		
Headache subjects affected / exposed occurrences (all)	4 / 28 (14.29%) 5		
Multiple sclerosis subjects affected / exposed occurrences (all)	1 / 28 (3.57%) 2		
General disorders and administration site conditions			

Asthenia subjects affected / exposed occurrences (all)	2 / 28 (7.14%) 2		
Dizziness subjects affected / exposed occurrences (all)	0 / 28 (0.00%) 0		
Anxiety subjects affected / exposed occurrences (all)	0 / 28 (0.00%) 0		
Gastrointestinal disorders Gastroenteritis subjects affected / exposed occurrences (all)	0 / 28 (0.00%) 0		
Respiratory, thoracic and mediastinal disorders Bronchitis subjects affected / exposed occurrences (all) Nasopharyngitis subjects affected / exposed occurrences (all) Oropharyngeal pain subjects affected / exposed occurrences (all)	1 / 28 (3.57%) 2 0 / 28 (0.00%) 0 4 / 28 (14.29%) 5		
Skin and subcutaneous tissue disorders Eczema subjects affected / exposed occurrences (all)	2 / 28 (7.14%) 2		
Psychiatric disorders Depression subjects affected / exposed occurrences (all) Depressive symptom subjects affected / exposed occurrences (all)	2 / 28 (7.14%) 2 2 / 28 (7.14%) 2		
Musculoskeletal and connective tissue disorders			

Ligament sprain subjects affected / exposed occurrences (all)	2 / 28 (7.14%) 3		
Infections and infestations Urinary tract infection subjects affected / exposed occurrences (all) Influenza subjects affected / exposed occurrences (all)	1 / 28 (3.57%) 1 2 / 28 (7.14%) 3		

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

Date	Amendment
24 September 2013	100mg dose arm replaced by 300mg dose arm (due to first efficacy results) in accordance with ANSM/EMA. Addition of one investigator site (Pr Alain Vighetto).
22 January 2014	Modification of the primary endpoint in accordance with CHMP/SAWG/EMA. Enlargement of the inclusion criteria. Deletion of some exclusion criteria. DSMB creation.
02 July 2014	Due to recruiting delay, opening of 2 new investigator sites (FR & UK).
13 October 2014	Addition of M18 visit.
15 January 2015	Due to non-clinical study results (effect teratogenic on rabbits) contraceptive measures have been added. Biotin & metabolites analysed at M12. Awareness of subjects regarding teratogenics' risks and laboratory interference.
27 May 2015	Extension of the study duration until end of EMA registration (i.e 36 months).

Notes:

Interruptions (globally)

Were there any global interruptions to the trial? No

Limitations and caveats

None reported