# 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 |

### 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 an 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] |
| Number of subjects completed | 93 |

### Pre-assignment subject non-completion reasons

| | |
|---|---|
| Reason: Number of subjects | inclusion/exclusion criteria: 24 |

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) |
| Is this the baseline period? | Yes |
| Allocation method | Randomised - controlled |
| Blinding used | Double blind |
| Roles blinded | Subject, Investigator, Monitor |

### Arms

| | |
|---|---|
| Are arms mutually exclusive? | Yes |
| **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 / day ( 100mg 3 times day - tid)

| | |
|---|---|
| **Arm title** | Placebo |

Arm description:

Placebo

| | |
|---|---|
| Arm type | Placebo |
| Investigational medicinal product name | Placebo |
| Investigational medicinal product code | |
| Other name | |
| Pharmaceutical forms | Capsule |
| Routes of administration | Oral use |

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

| Reporting group values | MD1003 | Placebo | Total |
|---|---|---|---|
| Number of subjects | 65 | 28 | 93 |
| Age categorical<br>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<br>Units: years | | | |
| arithmetic mean | 41.6 | 41.1 | |
| standard deviation | ± 10.5 | ± 10.6 | - |
| Gender categorical<br>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 (± 0.206) | -0.036 (± 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 |

| Dictionary used | |
|---|---|
| Dictionary name | MedDRA |
| Dictionary version | 16 |

| Reporting groups | |
|---|---|
| Reporting group title | MD1003 double blind |
| Reporting group description: MD1003 | |
| Reporting group title | Placebo double blind |
| Reporting group description: Placebo | |
| Reporting group title | MD1003 extension phase |
| Reporting group description: - | |
| Reporting group title | Placebo extension phase |
| 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 | | |
|---|---|---|---|

| | | | |
|---|---|---|---|
| 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 | 0 / 65 (0.00%) | 0 / 28 (0.00%) | 4 / 64 (6.25%) |
| occurrences (all) | 0 | 0 | 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 | 0 / 65 (0.00%) | 0 / 28 (0.00%) | 1 / 64 (1.56%) |
| occurrences (all) | 0 | 0 | 1 |
| Musculoskeletal and connective tissue disorders | | | |
| Ligament sprain | | | |
| subjects affected / exposed | 0 / 65 (0.00%) | 0 / 28 (0.00%) | 1 / 64 (1.56%) |
| occurrences (all) | 0 | 0 | 1 |
| Infections and infestations | | | |
| Urinary tract infection | | | |
| subjects affected / exposed | 4 / 65 (6.15%) | 1 / 28 (3.57%) | 5 / 64 (7.81%) |
| occurrences (all) | 4 | 1 | 10 |
| Influenza | | | |
| subjects affected / exposed | 0 / 65 (0.00%) | 0 / 28 (0.00%) | 2 / 64 (3.13%) |
| occurrences (all) | 0 | 0 | 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 | 3 / 28 (10.71%) | | |
| occurrences (all) | 3 | | |
| Cardiac disorders | | | |
| Oedema peripheral | | | |
| subjects affected / exposed | 2 / 28 (7.14%) | | |
| occurrences (all) | 2 | | |
| Nervous system disorders | | | |
| Multiple sclerosis relapse | | | |
| subjects affected / exposed | 11 / 28 (39.29%) | | |
| occurrences (all) | 17 | | |
| Headache | | | |
| subjects affected / exposed | 4 / 28 (14.29%) | | |
| occurrences (all) | 5 | | |
| Multiple sclerosis | | | |
| subjects affected / exposed | 1 / 28 (3.57%) | | |
| occurrences (all) | 2 | | |
| General disorders and administration site conditions | | | |

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

| | | | |
|---|---|---|---|
| Ligament sprain<br>subjects affected / exposed<br>occurrences (all) | 2 / 28 (7.14%)<br>3 | | |
| Infections and infestations<br>Urinary tract infection<br>subjects affected / exposed<br>occurrences (all)<br><br>Influenza<br>subjects affected / exposed<br>occurrences (all) | <br><br>1 / 28 (3.57%)<br>1<br><br><br>2 / 28 (7.14%)<br>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.<br>Addition of one investigator site (Pr Alain Vighetto). |
| 22 January 2014 | Modification of the primary endpoint in accordance with CHMP/SAWG/EMA.<br>Enlargement of the inclusion criteria.<br>Deletion of some exclusion criteria.<br>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.<br>Biotin & metabolites analysed at M12.<br>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